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Complete List of Authors:	Yin, Xuan; Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai Dong, Bo; Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai Liang, Tingting; Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, acupuncture Yin, Ping; Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai Li, Xia; Shanghai Mental Health Center, Shanghai Jiaotong University of Medicine, Shanghai 200013, China Lin, Xiang; Shanghai Mental Health Center, Shanghai Jiaotong University of Medicine, Shanghai 200013, China Zhou, Shuang; Changhai Hospital, Second Military Medical University, Shanghai 200433, China Qian, Xiao-lu; Changhai Hospital, Second Military Medical University, Shanghai 200433, China Lao, Li-xing; School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong Xu, Shifen; Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, Shanghai University of TCM, Shanghai 200071, China
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The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

Xuan Yin[1], Bo Dong[1], Tingting Liang[1], Ping Yin[1], Xia Li[2], Xiang Lin[2], Shuang Zhou[3], Xiaolu Qian[3], Lixing Lao[4,5], Shifen Xu[1]

1 Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, Shanghai University of TCM, Shanghai 200071, China

2 Shanghai Mental Health Center, Shanghai Jiaotong University of Medicine, Shanghai 200013, China

3 Changhai Hospital, Second Military Medical University, Shanghai 200433, China

4 School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong

5 Center for Integrative Medicine, School of Medicine, University of Maryland, Baltimore, MD 21201, USA

Correspondence should be addressed to ShifenXu; xu_teacher2006@126.com and Lixing Lao; lxlao1@hku.hk

Abstract

Introduction

Sleep disorders including insomnia occur frequently in depressive patients. Acupuncture is a widely recognized therapy to treat depression and sleep disorders in clinical practice. This multicenter randomized controlled trial is aimed to investigate the efficacy and safety of electroacupunture in the treatment of depression patients with insomnia, compared with sham acupuncture and standard medical care.

Methods and analysis

We describe a protocol for a multicenter randomized controlled trial. A total of 270 eligible patients in three different healthcare centers in Shanghai will be randomly assigned to one of these three groups: Treatment group (electroacupuncture + standard care), Control A group (sham electroacupuncture + standard care) and Control B group (standard care). Treatment will be given three times per week for 8 consecutive weeks. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI). The secondary outcomes are sleep parameters recorded in the Actigraphy, Hamilton Rating Scale for Depression (HAMD) score and Self-rating Anxiety Scale (SAS) score. Daily dose of patients' antidepressant and sedative-hypnotic medication will be recorded in the dairy. All adverse effects will be assessed by the Treatment Emergent Symptom Scale (TESS). Outcomes will be evaluated at baseline, 4 weeks post-treatment and 8 weeks post-treatment, as well as at 1 month, 3 months and 6 months follow-up.

Ethics and dissemination

The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai, China (2017SHL-KY-04). Written informed consent will be obtained from all participants. The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: NCT03122080

Key words: Depression; Insomnia; Electroacupuncture; Randomized Controlled Trial

Strengths and limitations of this study

- This multicenter randomized controlled trial is the first study in mainland China to evaluate the efficacy and safety of electroacupuncture as an alternative treatment for insomnia in depressive patients.
- The study will use sleep indicators recorded in the wrist actigraphy as objective outcomes reflecting the patients' sleep quality.
- The acupuncturists in this study can't blinded to the group assignment due to the operation of acupuncture and sham acupuncture, so it can't be designed as a double-blinded trial which may minimize the bias.
- Individualized acupuncture treatment based on syndrome differentiation can be applied in future study to provide more pragmatic evidence for treating sleep disturbances in depressive patients.

Introduction

Depression and its related sleep disorders are becoming serious public health problems affecting people worldwide. Sleeping disorders including insomnia, hypersomnia and pavor nocturnus occur frequently in patients with depression [1]. Insomnia may occur in 60-80% of patients with major depressive disorders [2]; it is one of the most frequent residual symptoms of depression [3], and may persist even after depressive mood symptoms have been relieved [4].

Insomnia is characterized by persistent dissatisfaction with sleep quantity or quality for at least 4 weeks, with specific complaints of difficulty falling asleep, frequent nighttime awakenings, and/or awakening earlier in the morning than desired [5]. Insomnia may be triggered by different factors including psychiatric disorders, organic diseases and the intake of drugs or alcohol [6]. In fact, depressive symptoms are the largest and most consistent risk factors for insomnia because it affects the normal sleep-wake cycle [7 8]. Although selective serotonin reuptake inhibitors (SSRIs) and barbiturates have considerably improved the efficacy and prognosis in the treatment

of comorbid depression with insomnia, their side effects such as nausea, vomiting, tolerance, addiction, excessive sedation and neurological toxicity cannot be ignored [9-11]. What makes the pharmacotherapy more difficult is that some antidepressant drugs may worsen insomnia or cause daytime sleepiness [12], and high hypnotic dosages for insomnia is closely associated with worsened depressive outcomes [13]. In these cases, a drug-free alternative intervention is urgently needed as an effective and safe therapeutic approach for treating insomnia and depression.

Our previous study about acupuncture for primary insomnia demonstrated that acupuncture is an effective treatment to improve patients' sleep efficacy, prolong total sleep time and relieve patients' depressive mood [14]. The preliminary result of our pilot study [15] about the effect of electroacupuncture (EA) for depression related insomnia showed that the Pittsburgh Sleep Quality Index (PSQI) score in depression patients with electroacupuncture treatment obviously decreased (from 16.47±1.89 to 9.83±3.11), and there was significant difference between EA and sham EA ($p<0.001$). Meta-analysis also suggested that acupuncture combined with SSRIs is an effective and well-tolerated therapy for depression and adverse effects of antidepressants [16]. However, other studies showed that acupuncture is not significantly effective in relieving residual insomnia associated with depression [17 18]. As a result, randomized clinical trials in high quality are needed to evaluate the clinical effects and long-term effectiveness of acupuncture in the treatment of depression related insomnia.

We planned this single-blinded, multi-center, randomized and controlled trial with a sufficient observation period in three healthcare centers in Shanghai, China. All interventions will be administrated by licensed acupuncturists and psychiatrists under the supervision of an independent Data and Safety Monitoring Board (DSMB). We hope to provide conclusive evidence to prove the hypothesis that acupuncture would be superior than sham acupuncture or standard medical care in treating depression related insomnia.

Methods and analysis

Design

This is a multi-center, patient-assessor-blinded, randomized and controlled trial, aimed at evaluating the efficacy and safety of electroacupuncture for insomnia in depression patients and comparing the effects between electroacupuncture, sham acupuncture and standard medication care.

The trial will be performed in three healthcare centers in Shanghai: the acupuncture department in Shanghai Municipal Hospital of Traditional Chinese Medicine, the acupuncture department in Changhai Hospital of Shanghai and the therapeutic department in Shanghai Mental Health Center. We will recruit 270 patients who meet the inclusion criteria and randomly assign them to one of 3 groups, receiving eletroacupuncture, sham acupuncture and/or standard medical care. After a week baseline, participants will enter an 8-month observation period in this trial. All treatments will be given 3 times a week (every other day) for 8 weeks. Participants will be assessed at the following time points: the baseline (1 week before treatment), the middle of the treatment (4 weeks after treatment starts), the end of the treatment (8 weeks after treatment starts) and follow-up (1 month, 3 months and 6 months after treatment finishes). All participants will complete the assessments by the PSQI, Actigraphy, HAMD, SAS and TESS (detailed trial process seen in Figure 1 and Table 1). We will follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [19] throughout the trial.

Patients

The study will include 270 depression patients with insomnia. To ensure the precision of the results, we developed the following eligibility criteria.

Inclusion criteria

Participants meeting the following criteria will be included:

1. Male or female participants aged 18-70;

2. Participants who meet the diagnostic criteria of depression according to the

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [20];

3. Participants whose HAMD score is 20-35 (mild to moderate depression);

4. Participants who have taken the same antidepressants for more than 4 weeks or have not taken antidepressants;

5. Participants who complained about insomnia during their first visit to the doctor;

6. Participants whose PSQI score is more than 7;

7. Participants who have not received acupuncture treatment for at least one year;

8. Participants who voluntarily agree with the investigation and sign a written informed consent form for the clinical trial.

Exclusion criteria

Participants who report any of the following conditions will be excluded:

1. Participants with secondary depressive disorders caused by organic diseases, medicine, or psychotic disorders;

2. Participants who are in the depressive episode of bipolar disorder, or suffering from dysthymia, reactive depression and depressive syndrome caused by other diseases;

3. Participants who had severe diseases of the cardiovascular or hematopoietic systems, or had severe hepatic or renal insufficiency;

4. Participants with a history of alcohol abuse or drug dependence;

5. Participants who refuse to wear the actigraphy during the trial;

6. Pregnant or lactating women.

Recruitment

The participants will be recruited through hospital-based advertisements from outpatient clinics and from official websites of all three healthcare centers. If depression patients have interest in participating in the trial, they can take the phone screening first and then will be asked for face-to-face screening in any of the three healthcare centers where they need to fill in some forms with guidance from psychologists or doctors with professional training. Participants then will be asked to wear a wrist actigraphy to monitor their sleep quality for 3 days. Once the participants

meet the inclusion criteria, they will be asked to sign the written informed consent form before intervention begins.

Sample size calculation

The sample calculation is based on changes in the primary outcome of this trial, the PSQI score. In our previous trial, we also used PSQI score as the primary outcome to evaluate and compare the effects between acupuncture, superficial acupuncture at sham points and sham acupuncture on treating depression related insomnia [15]. According to the preliminary results, the PSQI score of the acupuncture group at the end of the 8 weeks' intervention was 9.83±3.11 and that of the sham acupuncture group was 13.93±3.22. We used the following formula to calculate the sample size in this trial:

$$n = \Psi^2 \left(\sum \left(S_i^2 \right) / K \right) / \left[\sum \left(\bar{X}i - \bar{X} \right)^2 / \left(K-1 \right) \right]$$

Since there will be a comparison between the Treatment group and the Control A group as well as a comparison between the Treatment group and the Control B group, a sample size of 14 in each group will have a power of 90% to detect the difference at an α-value of 0.025 and a β-value of 0.1. Assuming a 20% dropout rate, a sample size of 17 for each group is needed. We have appropriately expanded the recruiting sample size to 30 for each group in each healthcare center to ensure that there will be enough participants taking part in the trial. As a result, the total number of participants needed to be randomized is 270.

Randomization and blinding

An online random allocation system will be designed by the central randomization system with a 1:1:1 ratio, using the Pocock and Simon minimization method [21]. Staff of Shanghai BioGuider Medicinal Technology Co. Ltd (No. 2277 Zuchongzhi Road, Pudong New District, Shanghai) established the DAS for the EDC 5.0 system and prepared the randomization database. They offered technical support for the central randomization service and are not connected with the study. The system is based on

the IIS (Internet Information Server) 5.0 as the Web Server, the SQL Server 2000 as the Database server and the ASP (Active Server Page) as the scripting language [22]. Central randomization has strict limits of authority; only researchers and the specialists from the Data and Safety Monitoring Board in this trial have access to the system. If the participant meets the inclusion criteria and agrees to join in the trial, a researcher who is not involved in the intervention in each healthcare center will login in to the central randomization system with his own username and password, enter the participant's personal information, and then get the randomized number and the group assignment.

We will conduct a patient-assessor-blinded trial where participants are not aware of their group assignments and acupuncturists will not be involved in the outcome assessment or data analysis. Participants will be informed that they have an equal chance of allocation to the three groups. Participants who are assigned to the electroacupuncture (EA) or sham electroacupuncture (SA) will be treated in a closed unit to avoid communication. Furthermore, they will be asked to wear eye masks before and during the trial. Since there are inserted needles around participants' wrist joints, they will not be able to move their hands easily and cannot take off the eye masks. With these methods, participants will not be aware of the difference between EA and SA. To test the success of blinding, all participants in three centers will be asked by their acupuncturists whether they received EA or SA treatment at the end of treatment. Except the acupuncturists, other researchers including the statisticians, outcome assessors and data analysts are all blinded to the group assignments. All researchers will receive training on the specifications of this research method before the trial and strictly adhere to the task separation principle.

Intervention

Participants in Treatment group and Control A group will receive EA or SA treatment. Participants in these two groups will receive 24 sessions of different treatments, 3 times a week for 8 consecutive weeks. EA or SA treatment will be performed after

skin cleansing, with patients wearing eye masks and lying supine. Each treatment will last for 30 minutes. The temperature of the treatment room cannot be lower than 25°C.

Considering the participants' psychological state, participants in all three groups can continue regular administration of antidepressants, sedatives, hypnotics or anxiolytics during the trial. They must record the dose, especially when they reduce the amount; and dose escalation will not be allowed.

Treatment group

Participants in the Treatment group will receive electroacupuncture (EA) treatment. The acupuncture method of each acupoint is shown in Table 2. The regular acupuncture method will be applied at Baihui (GV20), Shenting (GV24), Yintang (GV29), bilateral Anmian (EX-HN22), Shenmen (HT7), Neiguan (PC6) and SanYinjiao (SP6). After needle insertion, rotating manipulation or lifting-thrusting manipulation will be applied for "Deqi" sensation. The EA apparatus (CMNS6-1, Wuxi Jiajian Medical Device CO., LTD, China) will be connected to the needles at Baihui (GV20) and Yintang (GV29) for 30 minutes and deliver a continuous wave to the patients. The frequency will be set to 30 Hz with a current intensity of 0.1 to 1 mA during the treatment, based on the tolerance of each patient.

Control A group

Participants in the Control A group will receive sham electroacupuncture treatment at the same acupoints as the Treatment group. Sham acupuncture will be applied with the placebo needles (Streitberger Placebo needle, asia-med GmbH&Co.KG, seen in Figure2) [23] that have been successfully used in our previous study [14 15]. When the tip of the blunt needles touches to the skin, the patient will get a pricking sensation but there is no real needle inserted into the skin. The EA apparatus will be set beside the patients and connected to the needles at Baihui (GV20) and Yintang (GV29). Acupuncturists will turn on the EA apparatus, but all the indicators will be set to "0". Participants will be informed when removing the needles after 30 minutes.

Acupuncturists will use dry cotton balls to press the acupoints so that patients can feel the withdrawal of the 'needles'.

Control B group

Standard care (also known as treatment-as-usual or routine care) in RCTs is frequently employed as the control condition to establish if the intervention is a significant improvement over existing practice [24]. In this trial, we set Control B group as the standard care group to investigate the differences between EA treatment group and the blank control group so that the effects of EA for insomnia and depression will be observed more clearly. All 90 participants in three healthcare centers in Control B group will continue taking in their routine antidepressants and/or sedative-hypnotics as before from baseline to 8 weeks. After finishing all the required scales and actigraphy records, they will get 10 sessions of free acupuncture treatment for insomnia.

Outcome Measurement

Primary outcome

The is a widely-used questionnaire with 19 items to assess sleep quality and disturbances over a one-month interval [25]. Four open-ended questions are followed by closed-ended questions that are rated on a 4-point Likert scale. The scores include the following indicators: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication, and daytime dysfunction. The accumulated scores of the seven indicators constitute the total score (ranging from 0–21). A higher score indicates worse sleep quality and more severe sleep disorders.

Secondary outcomes

1. The actigraphy (wActiSleep-BT. LLC, Pensacola, USA) worn on the patient's wrist can monitor the sleep quality, such as sleep onset, sleep latency, duration, awakenings during the night, etc. The software ActiLife6 (Version 6.8.1, ActiGraph,

LLC) will be used to analyze every participant's sleep condition recorded in the actigraphy. The indicators used in our trial will be sleep efficiency (SE), sleep awakenings (SA) and total sleep time (TST).

2. The Hamilton Rating Scale for Depression (HAMD) is an observer-rating questionnaire with 17 items used to assess the symptoms of patients diagnosed as suffering from depressive states [26]. Each item is rated in 3- or 5-point scales. A higher total score indicates a higher depression level.

3. The Self-rating Anxiety Scale (SAS) is primarily used as a measure of somatic symptoms associated with anxiety [27]. In using the scale, the participant will be asked to rate each item from 0-3 points according to how it applies to him or her within the past week. The standard score is the sum of the integer part of 1.25 times the raw score of the 20 items. A standard score of more than 50 points means the subject has anxious symptoms. A higher score indicates a more serious case of anxiety.

4. The dose dairy is a notebook where participants will be required to record their daily dose of antidepressants or sedative-hypnotics from baseline to 6 months follow-up, as well as the dosage time.

Adverse events

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring during the trial) related to the intervention or administration of antidepressant and sedative-hypnotics must be reported by patients and practitioners. These adverse events will be assessed by the Treatment Emergent Symptom Scale (TESS) which is mainly used as an associated indicator to evaluate the safety of acupuncture treatment in this trial [28].

Statistical analysis

The statistical analyst will be blinded to the participants' personal information and their group assignment during the trial. All analyses will be performed on the intention-to-treat (ITT) population of participants who have at least one treatment. Data analyses will be performed with the use of the statistical software SPSS20.0. The *t*-test will be used to compare the measurement data between either two groups from the baseline to 10 months follow-up; the rank sum test will be used for ranked data while the χ^2 test will be used to analyze categorical data. The significance level that will be used for statistical analysis with 2-tailed testing will be 2.5%. Data values will mainly be presented as Mean±SD.

Ethics and dissemination

All acupuncturists are licensed doctors with 3-5 years of experience in acupuncture treatment; and they will join in the clinical training before the intervention to ensure the standard real and sham acupuncture operation in three centers. The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai, China (2017SHL-KY-04) and is registered with ClinicalTrials.gov (NCT03122080).

To guarantee the quality of the study, this trial will be carried out under the supervision of an independent DSMB. The DSMB consists of three experts from different fields: Professor Bingshun Wang in medical statistics from the School of medicine at Shanghai Jiaotong University, Dr. Lin Sun in psychology from the Department of Geriatrics at Shanghai Mental Health Center, and Professor Xueyong Shen in acupuncture from the Acupuncture College at Shanghai University of Traditional Chinese Medicine. The DSMB works to identify problems in the project, examine collected data, and control bias. Researchers in each healthcare center will promptly input data on the website (https://ecdm2.drugchina.net/crct2/) so that members in the DSMB can supervise the process at any time. Once they find problems or serious adverse events during the intervention, they can raise objections directly and even stop the trial until the problem has been resolved. Meanwhile, a

qualified clinical trial expert (Lixing Lao) will be invited to monitor this study.

The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Discussion

Acupuncture has been used to treat insomnia and some mental disorders since antiquity in China. According to the theory of traditional Chinese medicine, acupuncture provides balance to the body by stimulating specific acupoints, helping the body to achieve a state of relative equilibrium (the harmony of *"yin-yang")*, thereby restoring the normal sleep-wake cycle. Recent systematic reviews indicate that acupuncture could be an alternative therapy to medication for treating insomnia but needs further studies using large samples and a rigorous study design to confirm its role [29 30].

Previous RCTs always focus on either the acupuncture treatment for insomnia or that for depression, ignoring the relationship between these two diseases. Insomnia has been identified as the most common sleep disorder comorbid to depressive disorders [31]; so a reasonable acupuncture treatment program should be developed to normalize sleep disturbance and to relieve depressive mood as well. At the time of this writing, there are no similar RCTs about acupuncture for insomnia in depression patients that included a large sample size and were conducted in multiple healthcare centers. Our trial intends to present a strictly designed trial to study the effects of EA on insomnia in depression patients and to overcome some existing limitations, including illogical design, imperfect blinding method and practical difficulties in previous acupuncture clinical researches. With a long follow-up period, we will be able to explore the persistent effects of acupuncture for insomnia and determine for how long the therapeutic effect will last.

Considering the complicated mental state of depression patients with insomnia, we will apply standard medication instead of unified antidepressants or sedative-hypnotics in this trial. Participants in all groups will continue taking in their

individual routine dosage from baseline to 6 months follow-up. If their conditions obviously change during the study, they will be free to consult our psychologists from Shanghai Mental Health Center to adjust the dose. The use of standard care control groups has been the subject of much debate, with some pointing out that what constitutes standard care is unclear [32 33]. For better implementation of the standard care, researchers in our trial will try to carry out proper health education for all patients and supervise them in recording their daily medication dosage.

As a multi-center RCT conducted in a first-tier city, our study can provide more representative results about the role and value of acupuncture as a complementary and alternative therapy for insomnia and depressive moods than other single-center RCTs. Considering the high prevalence of insomnia and depression in rural areas in China [34 35], the correlated heavy economic burden and serious public health problems cannot be underestimated. In future studies, the focus might be on the acupuncture treatment for insomnia in nationwide healthcare centers.

Trial Status

This clinical trial is now recruiting participants.

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Abbreviations

EA: Electroacupuncture;

SA: Sham electroacupuncture;

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture;

PSQI: Pittsburgh Sleep Quality Index;

HAMD: Hamilton Rating Scale for Depression;

SAS: Self-Rating Anxiety Scale;

TESS: Treatment Emergent Symptom Scale;

ITT: Intention-To-Treat Set;

GV: Governor Vessel;

EX-HN: Extra acupoints on head;

SI: Small intestine meridian of hand taiyang;

SJ: Sanjiao meridian of hand shaoyang;

SP: Spleen meridian of foot taiyin;

HT: Heart meridian of hand shaoyin;

PC: Pericardium meridian of hand jueyin;

CRF: Case Report Form

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

SFX is the main researcher who provided conception, design of the study and contributed to the final approval of the manuscript. LXL is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XY contributed to the design of the protocol, writing and review of the manuscript. BD, TTL and Xiang Lin contributed to the manuscript draft. PY and XLQ contributed to the statistical design. Xia Li and SZ are the project managers for the design of the randomization. All authors read and approved the final manuscript.

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Table 1 Trial process chart

	Baseline	Treatment phase			Follow-up phase		
	Week -1	Week 0	Week 4	Week 8	Month 1	Month 3	Month 6
Patients							
Enrollment	×						
Signed informed consent		×					
Medical history	×						
Merger disease	×						
Randomization		×					
Intervention			×	×			
Primary outcomes							
PSQI	×		×	×	×	×	×
Secondary outcomes							
Actigraphy	×		×	×			
HAMD	×		×	×	×	×	×
SAS	×		×	×			
TESS			×	×	×	×	×
Drug dose record	×		×	×	×	×	×
Patients' compliance			×	×	×	×	×

PSQI: Pittsburgh Sleep Quality Index

SAS: Self-Rating Anxiety Scale;

HAMD: Hamilton Rating Scale for Depression

TESS: Treatment Emergent Symptom Scale

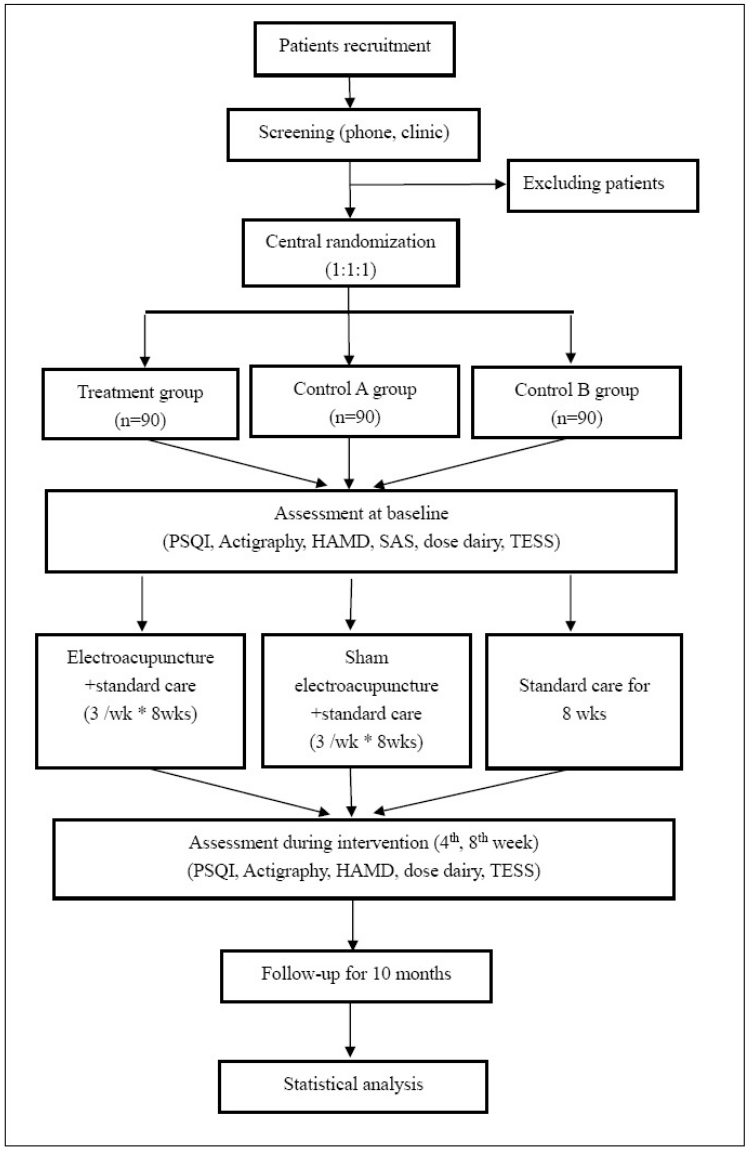
Table 2 Acupuncture method for each acupoint

Acupoint	Needling method
Baihui (GV20), Shenting(GV24)	The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anterior-posterior midline, and then insert the needle for about 1cm.
Yintang (GV29)	Pinch the local skin, and then puncture obliquely for about 1cm.
Anmian (EX-HN22)	The angle between the needle tip and the scalp is 30°. Puncture perpendicularly for about 1cm.
Shenmen (HT7), Sanyinjiao (SP6), Neiguan (PC6)	Puncture perpendicularly for about 1cm.

Figure legends

Figure 1: Flowchart of the study

Figure 2: Streitberger Placebo needle (asia-med GmbH&Co.KG)



Flowchart of the study

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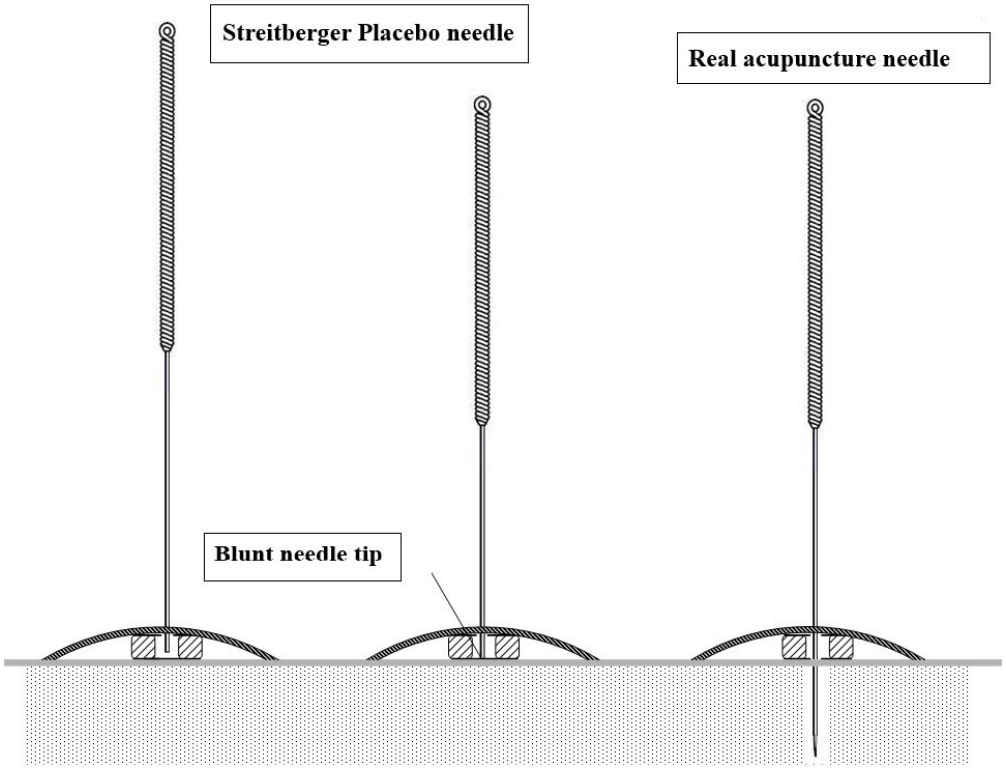

Streitberger Placebo needle (asia-med GmbH&Co.KG)

255x196mm (96 x 96 DPI)

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The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

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The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

Xuan Yin[1], Bo Dong[1], Tingting Liang[1], Ping Yin[1], Xia Li[2], Xiang Lin[2], Shuang Zhou[3], Xiaolu Qian[3], Lixing Lao[4,5], Shifen Xu[1]

1 Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, Shanghai University of TCM, Shanghai 200071, China

2 Shanghai Mental Health Center, Shanghai Jiaotong University of Medicine, Shanghai 200013, China

3 Changhai Hospital, Second Military Medical University, Shanghai 200433, China

4 School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong

5 Center for Integrative Medicine, School of Medicine, University of Maryland, Baltimore, MD 21201, USA

Correspondence should be addressed to ShifenXu; xu_teacher2006@126.com and Lixing Lao; lxlao1@hku.hk

Abstract

Introduction

Sleep disorders including insomnia occur frequently in depressive patients. Acupuncture is a widely recognized therapy to treat depression and sleep disorders in clinical practice. This multicenter randomized controlled trial is aimed to investigate the efficacy and safety of electroacupunture in the treatment of depression patients with insomnia.

Methods and analysis

We describe a protocol for a multicenter randomized controlled trial. A total of 270 eligible patients in three different healthcare centers in Shanghai will be randomly assigned to one of these three groups: Treatment group (electroacupuncture + standard care), Control A group (sham electroacupuncture + standard care) and Control B group (standard care). Treatment will be given three times per week for 8 consecutive weeks. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI). The secondary outcomes are sleep parameters recorded in the Actigraphy, Hamilton Rating Scale for Depression (HAMD) score and Self-rating Anxiety Scale (SAS) score. Daily dose of patients' antidepressant and sedative-hypnotic medication will be recorded in the dairy. All adverse effects will be assessed by the Treatment Emergent Symptom Scale (TESS). Outcomes will be evaluated at baseline, 4 weeks

post-treatment and 8 weeks post-treatment, as well as at 1 month, 3 months and 6 months follow-up.

Ethics and dissemination

The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2017SHL-KY-04). Written informed consent will be obtained from all participants. The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: NCT03122080

Key words: depression; insomnia; electroacupuncture; randomized controlled trial

Strengths and limitations of this study

- The study will use sleep indicators recorded in the wrist actigraphy as objective outcomes of the patients' sleep quality.
- Treatment effects on insomnia severity, depressive mood, as well as adverse events will be observed to comprehensively evaluate the efficacy and safety of acupuncture.
- Rigorous central randomization by Electronic Data Capture (EDC) system and allocation concealment methods will be applied in this study.
- The acupuncturists in this study can't blinded to the group assignment due to the nature of the acupuncture treatment procedure in which an acupuncturist is almost impossible to be blinded to the treatment assignments. Therefore, it can't be designed as a double-blinded trial which may minimize the bias.

- Individualized acupuncture treatment based on syndrome differentiation can be applied in this trial to provide more pragmatic evidence for treating sleep disturbances in depressive patients.

Introduction

Depression and its related sleep disorders are becoming serious public health problems affecting people worldwide. The global point prevalence of MDD is 4.7%[1], and the estimation of a 12-month cumulative incidence of depression in China is 5.23%[2], causing an urgent need to improve depressive patients' health. Sleeping disorders including insomnia, hypersomnia and pavor nocturnus occur frequently in patients with depression [3]. Insomnia may occur in 60-80% of patients with major depressive disorders [4]; it is one of the most frequent residual symptoms of depression [5], and may persist even after depressive mood symptoms have been relieved [6].

Insomnia is characterized by persistent dissatisfaction with sleep quantity or quality for at least 4 weeks, with specific complaints of difficulty falling asleep, frequent nighttime awakenings, and/or awakening earlier in the morning than desired [7].

Insomnia may be triggered by different factors including psychiatric disorders, organic diseases and the intake of drugs or alcohol [8]. In fact, depressive symptoms are the largest and most consistent risk factors for insomnia because it affects the normal sleep-wake cycle [9 10]. Previous studies supported that treating insomnia by Cognitive Behavioral Therapy for Insomnia (CBTI) in patients with depression is effective and also has a positive effect on mood [11 12]. With regard to the current medical conditions in China, the need for CBTI for patients with depression cannot be met. Although selective serotonin reuptake inhibitors (SSRIs) and barbiturates have considerably improved the efficacy and prognosis in the treatment of comorbid depression with insomnia, their side effects such as nausea, vomiting, tolerance, addiction, excessive

sedation and neurological toxicity cannot be ignored [13-15]. What makes the pharmacotherapy more difficult is that some antidepressant drugs may worsen insomnia or cause daytime sleepiness [16], and high hypnotic dosages for insomnia is closely associated with worsened depressive outcomes [17]. In these cases, a drug-free alternative intervention is urgently needed as an effective and safe therapeutic approach for treating insomnia and depression.

Our previous study about acupuncture for primary insomnia demonstrated that acupuncture is an effective treatment to improve patients' sleep efficacy, prolong total sleep time and relieve patients' depressive mood [18]. The preliminary result of our pilot study [19] about the effect of electroacupuncture (EA) for depression related insomnia showed that the Pittsburgh Sleep Quality Index (PSQI) score in depression patients with electroacupuncture treatment obviously decreased (from 16.47 ± 1.89 to 9.83 ± 3.11), and there was significant difference between EA and sham EA ($p<0.001$). Meta-analysis also suggested that acupuncture combined with SSRIs is an effective and well-tolerated therapy for depression and adverse effects of antidepressants [20]. However, other studies showed that acupuncture is not significantly effective in relieving residual insomnia associated with depression [21 22]. As a result, randomized clinical trials in high quality are needed to evaluate the clinical effects and long-term effectiveness of acupuncture in the treatment of depression related insomnia.

We planned this single-blinded, multi-center, randomized and controlled trial with a sufficient observation period in three healthcare centers in Shanghai, China. All interventions will be administrated by licensed acupuncturists and psychiatrists under the supervision of an independent Data and Safety Monitoring Board (DSMB). We hope to provide conclusive evidence to prove the hypothesis that acupuncture plus standard care would be superior than sham acupuncture plus standard care or standard care alone in treating depression related insomnia.

Methods and analysis

Design

This is a multi-center, patient-assessor-blinded, randomized and controlled trial, aimed at evaluating the efficacy and safety of electroacupuncture for insomnia in depression patients and comparing the effects between electroacupuncture plus standard care, sham acupuncture plus standard care and simple standard care.

The trial will be performed in three healthcare centers in Shanghai: the acupuncture department in Shanghai Municipal Hospital of Traditional Chinese Medicine, the acupuncture department in Changhai Hospital of Shanghai and the therapeutic department in Shanghai Mental Health Center. We will recruit 270 patients who meet the inclusion criteria and randomly assign them to one of 3 groups, receiving eletroacupuncture, sham acupuncture and/or standard medical care. After a week baseline, participants will enter an 8-month observation period in this trial. All treatments will be given 3 times a week (every other day) for 8 weeks. Participants will be assessed at the following time points: the baseline (1 week before treatment), the middle of the treatment (4 weeks after treatment starts), the end of the treatment (8 weeks after treatment starts) and follow-up (1 month, 3 months and 6 months after treatment finishes). All participants will complete the assessments by the PSQI, Actigraphy, HAMD, SAS and TESS (detailed trial process seen in Figure 1 and Table 1). We will follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [23] throughout the trial.

Patients

The study will include 270 depression patients with insomnia. To ensure the precision of the results, we developed the following eligibility criteria.

Inclusion criteria

Participants meeting the following criteria will be included:

1. Male or female participants aged 18-70;
2. Participants who meet the diagnostic criteria of depression according to the

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[24];

3. Participants whose HAMD score is 20-35 (mild to moderate depression);

4. Participants who have taken the same antidepressants for more than 4 weeks or have not taken antidepressants;

5. Participants who complained about insomnia during first screening;

6. Participants whose PSQI score is more than 7;

7. Participants who have not received acupuncture treatment for at least one year;

8. Participants who voluntarily agree with the investigation and sign a written informed consent form for the clinical trial.

Exclusion criteria

Participants who report any of the following conditions will be excluded:

1. Participants with secondary depressive disorders caused by organic diseases, medicine, or psychotic disorders;

2. Participants who are in the depressive episode of bipolar disorder, or suffering from dysthymia, reactive depression and depressive syndrome caused by other diseases;

3. Participants who had severe diseases of the cardiovascular or hematopoietic systems, or had severe hepatic or renal insufficiency;

4. Participants with a history of alcohol abuse or drug dependence;

5. Participants who refuse to wear the actigraphy during the trial;

6. Pregnant or lactating women.

Recruitment

The participants will be recruited through hospital-based advertisements from outpatient clinics and from official websites of all three healthcare centers. If depression patients have interest in participating in the trial, they can take the phone screening first and then will be asked for face-to-face screening in any of the three healthcare centers where they need to fill in some forms with guidance from psychologists or doctors with professional training. Participants then will be asked to

wear a wrist actigraphy to monitor their sleep quality for 3 days. Once the participants meet the inclusion criteria, they will be asked to sign the written informed consent form before intervention begins.

Sample size calculation

The sample calculation is based on changes in the primary outcome of this trial, the Pittsburgh Sleep Quality Index (PSQI) score. In our previous trial, we also used PSQI score as the primary outcome to evaluate and compare the effects between acupuncture, superficial acupuncture at sham points and sham acupuncture on treating depression related insomnia [19]. According to the preliminary results, the PSQI score of the acupuncture group at the end of the 8 weeks' intervention was 9.83±3.11 and that of the sham acupuncture group was 13.93±3.22. We assumed 0.2 of the PSQI difference is the superior effect.

H0: A-B<= Δ but H1: A-B> Δ

We used the following formula to calculate the sample size in this trial:

$N = \left[\frac{(Z_\alpha + Z_\beta)\,\sigma}{\delta - \Delta}\right]^2 \times 2$, where δ is the difference between group, Δ is the assumed superior effect threshold and N is the estimated sample size of each group. σ is the $[\,(S_1^2 + S_2^2)\,/\,2\,]^{0.5}$

Since there will be a comparison between the Treatment group and the Control A group as well as a comparison between the Treatment group and the Control B group, a sample size of 15 in each group will have a power of 90% to detect the superior effect of 0.2 of PSQI at an α-value of 0.025 and a β-value of 0.1. Assuming a 20% dropout rate, a sample size of 19 for each group is needed. We have appropriately expanded the recruiting sample size to 30 for each group in each healthcare center to achieve a better power as well as to ensure enough participants taking part in the trial. As a result, the total number of participants needed to be randomized is 270.

Randomization and blinding

An online random allocation system will be designed by the central randomization system with a 1:1:1 ratio, using the Pocock and Simon minimization method [25]. Staff of Shanghai BioGuider Medicinal Technology Co. Ltd (No. 2277 Zuchongzhi Road, Pudong New District, Shanghai) established the Data Analysis System (DAS) for the Electronic Data Capture (EDC) 5.0 system and prepared the randomization database. They offered technical support for the central randomization service and are not connected with the study. The system is based on the IIS (Internet Information Server) 5.0 as the Web Server, the SQL Server 2000 as the Database server and the ASP (Active Server Page) as the scripting language [26]. Central randomization has strict limits of authority; only researchers and the specialists from the Data and Safety Monitoring Board (DSMB) in this trial have access to the system. If the participant meets the inclusion criteria and agrees to join in the trial, a researcher who is not involved in the intervention in each healthcare center will login in to the central randomization system with his own username and password, enter the participant's personal information, and then get the randomized number and the group assignment. The patients' personal information will be protected and keep confidential to the acupuncturists and the assessors before, during and after the trial.

We will conduct a patient-assessor-blinded trial where participants are not aware of their group assignments and acupuncturists will not be involved in the outcome assessment or data analysis. Participants will be informed that they have an equal chance of allocation to the three groups. Participants who are assigned to the electroacupuncture (EA) or sham electroacupuncture (SA) will be treated in a closed unit to avoid communication. Furthermore, they will be asked to wear eye masks before and during the trial. Since there are inserted needles around participants' wrist joints, they will not be able to move their hands easily and cannot take off the eye masks. With these methods, participants will not be aware of the difference between EA and SA. To test the success of blinding, all participants in three centers will be asked by their acupuncturists whether they received EA or SA treatment at the end of

treatment. Except the acupuncturists, other researchers including the statisticians, outcome assessors and data analysts are all blinded to the group assignments. All researchers will receive training on the specifications of this research method before the trial and strictly adhere to the task separation principle.

Intervention

Participants in Treatment group and Control A group will receive EA or SA treatment. Participants in these two groups will receive 24 sessions of different treatments, 3 times a week for 8 consecutive weeks. EA or SA treatment will be performed after skin cleansing, with patients wearing eye masks and lying supine. Each treatment will last for 30 minutes. The temperature of the treatment room cannot be lower than 25°C.

Considering the participants' psychological state, participants in all three groups can continue regular administration of antidepressants, sedatives, hypnotics or anxiolytics during the trial. They must record the dose, especially when they reduce the amount; and dose escalation will not be allowed unless the patient has consulted the psychiatrist. The patients will not be withdrawn the trial by changing the dose of the drug.

Treatment group

Participants in the Treatment group will receive electroacupuncture (EA) treatment. The acupuncture method of each acupoint is shown in Table 2. The regular acupuncture method will be applied at Baihui (GV20), Shenting (GV24), Yintang (GV29), bilateral Anmian (EX-HN22), Shenmen (HT7), Neiguan (PC6) and SanYinjiao (SP6). The acupuncture needles are produced by Asia-med GmbH&Co.KG (seen Figure 2), with the same appearance as those used in sham acupuncture treatment. After needle insertion, rotating manipulation or lifting-thrusting manipulation will be applied for "Deqi" sensation. The EA apparatus

(CMNS6-1, Wuxi Jiajian Medical Device CO., LTD, China) will be connected to the needles at Baihui (GV20) and Yintang (GV29) for 30 minutes and deliver a continuous wave to the patients. The frequency will be set to 30 Hz with a current intensity of 0.1 to 1 mA during the treatment, based on the tolerance of each patient.

Control A group

Participants in the Control A group will receive sham electroacupuncture treatment at the same acupoints as the Treatment group. Sham acupuncture will be applied with the placebo needles (Streitberger Placebo needle, asia-med GmbH&Co.KG, seen in Figure2) [27 28] that have been successfully used in our previous study [18 19]. When the tip of the blunt needles touches to the skin, the patient will get a pricking sensation but there is no real needle inserted into the skin. The EA apparatus will be set beside the patients and connected to the needles at Baihui (GV20) and Yintang (GV29). Acupuncturists will turn on the EA apparatus, but all the indicators will be set to "0". Participants will be informed when removing the needles after 30 minutes. Acupuncturists will use dry cotton balls to press the acupoints so that patients can feel the withdrawal of the 'needles'.

Control B group

Standard care (also known as treatment-as-usual or routine care) in RCTs is frequently employed as the control condition to establish if the intervention is a significant improvement over existing practice [29]. In this trial, we set Control B group as the standard care group to investigate the differences between EA treatment group and the blank control group so that the effects of EA for insomnia and depression will be observed more clearly. All 90 participants in three healthcare centers in Control B group will continue taking in their routine antidepressants and/or sedative-hypnotics as before from baseline to 8 weeks. After finishing all the required scales and actigraphy records, they will get 10 sessions of free acupuncture treatment for

insomnia.

Outcome Measurement

Primary outcome

The Pittsburgh Sleep Quality Index (PSQI) is a widely-used questionnaire with 19 items to assess sleep quality and disturbances over a one-month interval [30]. Four open-ended questions are followed by closed-ended questions that are rated on a 4-point Likert scale. The scores include the following indicators: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication, and daytime dysfunction. The accumulated scores of the seven indicators constitute the total score (ranging from 0–21). A higher score indicates worse sleep quality and more severe sleep disorders.

Secondary outcomes

1. The actigraphy (wActiSleep-BT. LLC, Pensacola, USA) worn on the patient's wrist can monitor the sleep quality, such as sleep onset, sleep latency, duration, awakenings during the night, etc. The software ActiLife6 (Version 6.8.1, ActiGraph, LLC) will be used to analyze every participant's sleep condition recorded in the actigraphy. The indicators used in our trial will be sleep efficiency (SE), sleep awakenings (SA) and total sleep time (TST).

2. The Hamilton Rating Scale for Depression (HAMD) is an observer-rating questionnaire with 17 items used to assess the symptoms of patients diagnosed as suffering from depressive states [31]. Each item is rated in 3- or 5-point scales. A higher total score indicates a higher depression level.

3. The Self-rating Anxiety Scale (SAS) is primarily used as a measure of somatic symptoms associated with anxiety [32]. In using the scale, the participant will be asked to rate each item from 0-3 points according to how it applies to him or her within the past week. The standard score is the sum of the integer part of 1.25 times the raw score of the 20 items. A standard score of more than 50 points means the subject has

anxious symptoms. A higher score indicates a more serious case of anxiety.

4. The dose dairy is a notebook where participants will be required to record their daily dose of antidepressants or sedative-hypnotics from baseline to 6 months follow-up, as well as the dosage time.

Adverse events

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring during the trial) related to the administration of antidepressant and sedative-hypnotics must be reported by patients and practitioners. These adverse events will be -recorded in the Treatment Emergent Symptom Scale (TESS) [33].

For the adverse events related to the acupuncture treatment, the most common ones include bleeding, faint, bruising ecchymoma, serious pain etc. These AE data will be assessed in terms of severity and causality, and the incidence will also be determined. The 3-point grading categories will be applied: grade 1, mild, grade 2, moderate, grade 3, severe or medically significant. The causality categories used will be certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable. The incidence of AEs was presented as the number of AEs per number of acupuncture sessions (%).

Statistical analysis

The statistical analyst will be blinded to the participants' personal information and their group assignment during the trial. The primary analysis will be a comparison of the changes of patients' PSQI score among three groups at 8 weeks after inclusion (comparison of the primary endpoint). The secondary analysis will be performed to assess the changes of the SE, TST and SA recorded in the actigraphy, as well as the HAMD scores and SAS scores from baseline to 8 weeks after inclusion. We will also count the number of patients who increase or decrease the drug dose, and then analyze the differences among three groups. All analyses will be performed on the

intention-to-treat (ITT) population of participants who have at least one treatment. Missing data will be handled using the multiple imputation method, on the assumption that values at each time point follow a specific distribution calculated by the computer software R V.3.5. We will also perform a complete-case analysis without imputation of missing data, to find out if the results are consistent. Data analyses will be performed with the use of the statistical software SPSS V.20.0. The *t*-test will be used to compare the measurement data between either two groups from the baseline to 6 months follow-up; the rank sum test will be used for ranked data while the χ^2 test will be used to analyze categorical data. The significance level that will be used for statistical analysis with 2-tailed testing will be 2.5%. Data values will mainly be presented as Mean±SD.

Patient and public involvement

This trial was designed to evaluate the effects and safety of acupuncture treatment for depression-related insomnia. In our clinical practice, depression patients always complain insomnia as the most disturbing problem affecting their quality of life. Acupuncture not only helps these patients improve their sleep quality, but also relieve their depression and pressure. The outcome measures used in this study were commonly used in clinical trials of sleep and mood disorders, and we applied the actigraphy as another outcome measure to provide more objective results. Depression patients with insomnia in the clinical department were consulted by the main researcher prior to the trial design. The treatment frequency and duration of this study were summarized from clinical experience and patients' feedback. We will recruit all participants from the outpatient clinics in three healthcare centers. Patients who were involved in the consultation about the trial design before will not be recruited as participants. A journal article manuscript will be written to present the results after the trial completed, and a brief summary of results with plain language will be sent to all participants. The burden of intervention will not be assessed by participants

themselves.

Ethics and dissemination

All acupuncturists are licensed doctors with 3-5 years of experience in acupuncture treatment; and they will join in the clinical training before the intervention to ensure the standard real and sham acupuncture operation in three centers. The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai, China (2017SHL-KY-04) and is registered with ClinicalTrials.gov (NCT03122080).

To guarantee the quality of the study, this trial will be carried out under the supervision of an independent DSMB. The DSMB consists of three experts from different fields: Professor Bingshun Wang in medical statistics from the School of medicine at Shanghai Jiaotong University, Dr. Lin Sun in psychology from the Department of Geriatrics at Shanghai Mental Health Center, and Professor Xueyong Shen in acupuncture from the Acupuncture College at Shanghai University of Traditional Chinese Medicine. The DSMB works to identify problems in the project, examine collected data, and control bias. Researchers in each healthcare center will promptly input data on the website (https://ecdm2.drugchina.net/crct2/) so that members in the DSMB can supervise the process at any time. Once they find problems or serious adverse events during the intervention, they can raise objections directly and even stop the trial until the problem has been resolved. Meanwhile, a qualified clinical trial expert (Lixing Lao) will be invited to monitor this study.

The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Discussion

Acupuncture has been used to treat insomnia and some mental disorders since antiquity in China. According to the theory of traditional Chinese medicine,

acupuncture provides balance to the body by stimulating specific acupoints, helping the body to achieve a state of relative equilibrium (the harmony of *"yin-yang")*, thereby restoring the normal sleep-wake cycle. Recent systematic reviews indicate that acupuncture could be an alternative therapy to medication for treating insomnia but needs further studies using large samples and a rigorous study design to confirm its role [34 35].

Previous RCTs always focus on either the acupuncture treatment for insomnia or that for depression, ignoring the relationship between these two diseases. Insomnia has been identified as the most common sleep disorder comorbid to depressive disorders [36]; so a reasonable acupuncture treatment program should be developed to normalize sleep disturbance and to relieve depressive mood as well. At the time of this writing, there are no similar RCTs about acupuncture for insomnia in depression patients that included a large sample size and were conducted in multiple healthcare centers. Our trial intends to present a strictly designed trial to study the effects of EA on insomnia in depression patients and to overcome some existing limitations, including illogical design, imperfect blinding method and practical difficulties in previous acupuncture clinical researches. With a long follow-up period, we will be able to explore the persistent effects of acupuncture for insomnia and determine for how long the therapeutic effect will last.

For patients in the EA group, we decided to use EA at Baihui (GV20) and Yintang (GV29), with the frequency set to 30 Hz during the treatment. According to the TCM theory, GV20 is the convergent point of six yang meridians as well as the foot Jueyin meridian; it is located on the top of the head, governs yang qi of the body and is the key point of calming mind. GV29 promotes the circulation of qi and blood in the head and restores the function of brain. EA at GV20 and GV29 enhances the effect of soothing nerves. In addition, a functional connectivity MRI (fcMRI) study suggested that EA at GV20 and GV29 may have effect on mental disorders[37]. Using fcMRI to identify the key cerebral functional region affected by EA at GV20 and GV29 found that the center of the cerebral network changed from the caudate nucleus to the

parahippocampal gyrus and hypothalamus. The network centered on the parahippocampal gyrus and hypothalamus primarily functioned in somatic movement, sensation, vision, hearing and language. This finding may indicate a mechanism for treating depression using EA at GV20 and GV29.

A frequency-specific neurochemical response in the central nervous system may be related to differential response of the body to low- and high-frequency EA stimulation and different peripheral and central pathways[38]. Previous research found that low frequency EA could be useful in clinical settings to manage pain [39] while high-frequency stimulation has more potent effects on 5-HT activity[40]. Thirty Hz separates the continuous wave of the EA apparatus from disperse wave to dense wave and we chose 30Hz based on an acupuncture textbook [41].

Considering the complicated mental state of depression patients with insomnia, we will apply standard medication instead of unified antidepressants or sedative-hypnotics in this trial. Participants in all groups will continue taking in their individual routine dosage from baseline to 6 months follow-up. If their conditions obviously change during the study, they will be free to consult our psychologists from Shanghai Mental Health Center to adjust the dose. The use of standard care control groups has been the subject of much debate, with some pointing out that what constitutes standard care is unclear [42 43]. For better implementation of the standard care, researchers in our trial will try to carry out proper health education for all patients and supervise them in recording their daily medication dosage.

As a multi-center RCT conducted in a first-tier city, our study can provide more representative results about the role and value of acupuncture as a complementary and alternative therapy for insomnia and depressive moods than other single-center RCTs. Considering the high prevalence of insomnia and depression in rural areas in China [44 45], the correlated heavy economic burden and serious public health problems cannot be underestimated. In future studies, the focus might be on the acupuncture treatment for insomnia in nationwide healthcare centers.

Trial Status

This clinical trial is now recruiting participants.

Acknowledgments

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Abbreviations

EA: Electroacupuncture;

SA: Sham electroacupuncture;

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture;

PSQI: Pittsburgh Sleep Quality Index;

HAMD: Hamilton Rating Scale for Depression;

SAS: Self-Rating Anxiety Scale;

TESS: Treatment Emergent Symptom Scale;

ITT: Intention-To-Treat Set;

GV: Governor Vessel;

EX-HN: Extra acupoints on head;

SI: Small intestine meridian of hand taiyang;

SJ: Sanjiao meridian of hand shaoyang;

SP: Spleen meridian of foot taiyin;

HT: Heart meridian of hand shaoyin;

PC: Pericardium meridian of hand jueyin;

CRF: Case Report Form

Competing interests statement

The authors declare that they have no competing interests.

Authors' Contributions

SFX is the main researcher who provided conception, design of the study and contributed to the final approval of the manuscript. LXL is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XY contributed to the design of the protocol, writing and review of the manuscript. BD, TTL and Xiang Lin contributed to the manuscript draft. PY and XLQ contributed to the statistical design. Xia Li and SZ are the project managers for the design of the randomization. All authors read and approved the final manuscript.

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Table 1 Trial process chart

	Baseline	Treatment phase			Follow-up phase		
	Week -1	Week 0	Week 4	Week 8	Month 1	Month 3	Month 6

Patients						
Enrollment	×					
Signed informed consent		×				
	×					
Medical history	×					
Merger disease		×				
Randomization			×	×		
Intervention						
Primary outcomes	×		×	×	×	×	×
PSQI						
Secondary outcomes	×		×	×		
Actigraphy	×		×	×	×	×	×
HAMD	×		×	×		
SAS			×	×	×	×	×
TESS	×		×	×	×	×	×
Drug dose record			×	×	×	×	×
Patients' compliance						

PSQI: Pittsburgh Sleep Quality Index

SAS: Self-Rating Anxiety Scale;

HAMD: Hamilton Rating Scale for Depression

TESS: Treatment Emergent Symptom Scale

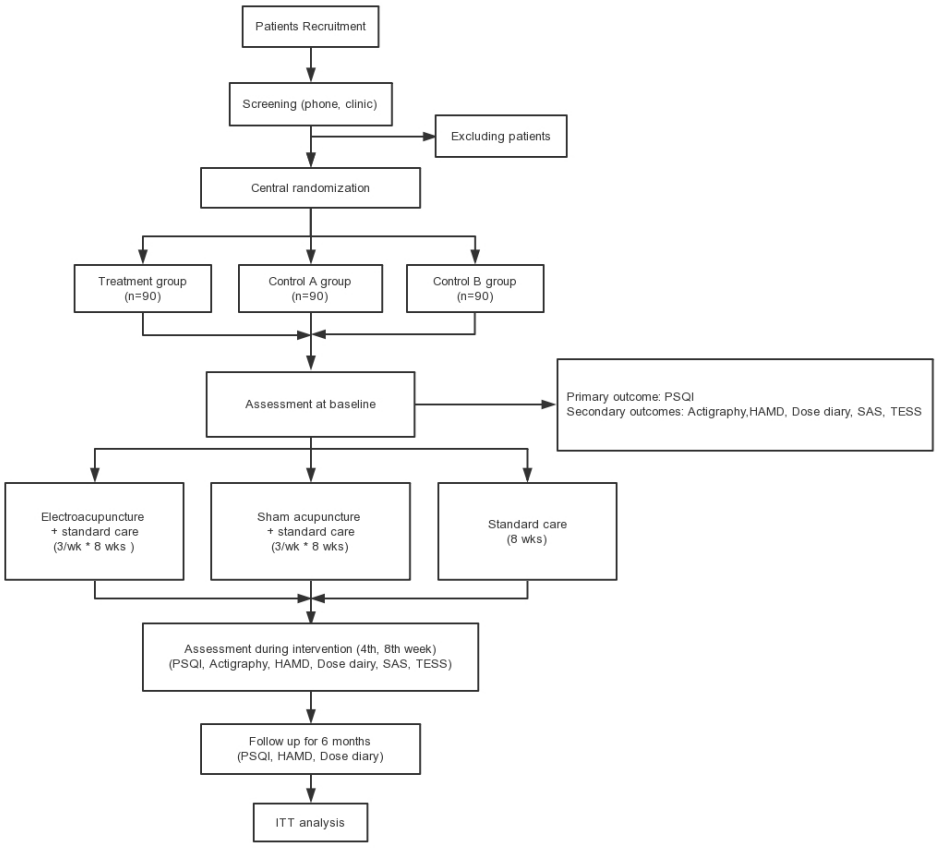
Table 2 Acupuncture method for each acupoint

Acupoint	Needling method
Baihui (GV20), Shenting(GV24)	The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anterior-posterior midline, and then insert the needle for about 1cm.
Yintang (GV29)	Pinch the local skin, and then puncture obliquely for about 1cm.
Anmian (EX-HN22)	The angle between the needle tip and the scalp is 30°. Puncture perpendicularly for about 1cm.
Shenmen (HT7), Sanyinjiao (SP6), Neiguan (PC6)	Puncture perpendicularly for about 1cm.

Figure legends

Figure 1: Flowchart of the study

Figure 2: Streitberger Placebo needle (asia-med GmbH&Co.KG)



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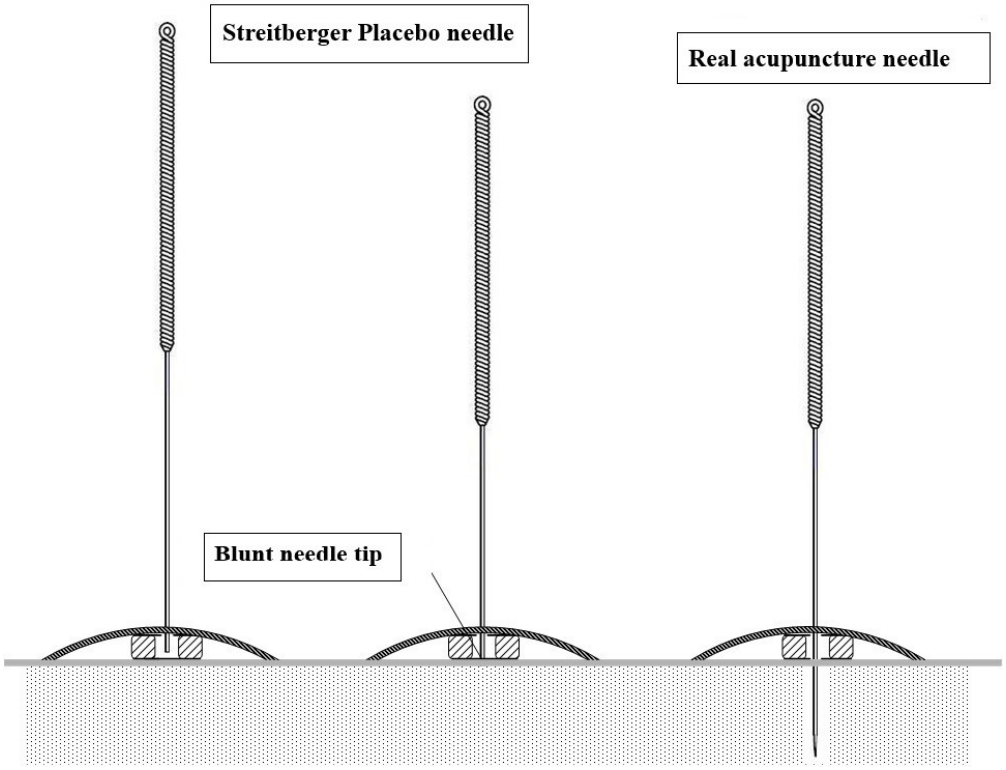

81x62mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, figure1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____17_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____14_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____14_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____YES_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____NO_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

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The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

Xuan Yin[1], Bo Dong[1], Tingting Liang[1], Ping Yin[1], Xia Li[2], Xiang Lin[2], Shuang Zhou[3], Xiaolu Qian[3], Lixing Lao[4,5], Shifen Xu[1]

1 Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, Shanghai University of TCM, Shanghai 200071, China

2 Shanghai Mental Health Center, Shanghai Jiaotong University of Medicine, Shanghai 200013, China

3 Changhai Hospital, Second Military Medical University, Shanghai 200433, China

4 School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong

5 Center for Integrative Medicine, School of Medicine, University of Maryland, Baltimore, MD 21201, USA

Correspondence should be addressed to ShifenXu; xu_teacher2006@126.com and Lixing Lao; lxlao1@hku.hk

Abstract

Introduction

Sleep disorders including insomnia occur frequently in depressive patients. Acupuncture is a widely recognized therapy to treat depression and sleep disorders in clinical practice. This multicenter randomized controlled trial is aimed to investigate the efficacy and safety of electroacupuncture in the treatment of depression patients with insomnia.

Methods and analysis

We describe a protocol for a multicenter randomized controlled trial. A total of 270 eligible patients in three different healthcare centers in Shanghai will be randomly assigned to one of these three groups: Treatment group (electroacupuncture + standard care), Control A group (sham electroacupuncture + standard care) and Control B group (standard care). Treatment will be given three times per week for 8 consecutive weeks. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI). The secondary outcomes are sleep parameters recorded in the Actigraphy, Hamilton Rating Scale for Depression (HAMD) score and Self-rating Anxiety Scale (SAS) score. Daily dose of patients' antidepressant and sedative-hypnotic medication will be recorded in the dairy. All adverse effects will be assessed by the Treatment Emergent Symptom Scale (TESS). Outcomes will be evaluated at baseline, 4 weeks post-treatment and 8 weeks post-

treatment, as well as at 1 month, 3 months and 6 months follow-up.

Ethics and dissemination

The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2017SHL-KY-04). Written informed consent will be obtained from all participants. The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: NCT03122080

Key words: depression; insomnia; electroacupuncture; randomized controlled trial

Strengths and limitations of this study

- The study will use sleep indicators recorded in the wrist actigraphy as objective outcomes of the patients' sleep quality.
- Treatment effects on insomnia severity, depressive mood, as well as adverse events will be observed to comprehensively evaluate the efficacy and safety of acupuncture.
- Rigorous central randomization by Electronic Data Capture (EDC) system and allocation concealment methods will be applied in this study.
- The acupuncturists in this study can't blinded to the group assignment due to the nature of the acupuncture treatment procedure in which an acupuncturist is almost impossible to be blinded to the treatment assignments. Therefore, it can't be designed as a double-blinded trial which may minimize the bias.
- Individualized acupuncture treatment based on syndrome differentiation can be

applied in this trial to provide more pragmatic evidence for treating sleep disturbances in depressive patients.

Introduction

Depression and its related sleep disorders are becoming serious public health problems affecting people worldwide. The global point prevalence of MDD is 4.7% [1], and the estimation of a 12-month cumulative incidence of depression in China is 5.23% [2], causing an urgent need to improve depressive patients' health. Sleeping disorders including insomnia, hypersomnia and pavor nocturnus occur frequently in patients with depression [3]. Insomnia may occur in 60-80% of patients with major depressive disorders [4]; it is one of the most frequent residual symptoms of depression [5], and may persist even after depressive mood symptoms have been relieved [6].

Insomnia is characterized by persistent dissatisfaction with sleep quantity or quality for at least 4 weeks, with specific complaints of difficulty falling asleep, frequent nighttime awakenings, and/or awakening earlier in the morning than desired [7]. Insomnia may be triggered by different factors including psychiatric disorders, organic diseases and the intake of drugs or alcohol [8]. In fact, depressive symptoms are the largest and most consistent risk factors for insomnia because it affects the normal sleep-wake cycle [9 10]. Previous meta-analysis indicated moderate to large effect size (ES) improvement in depression as measured with the Hamilton Depression Rating Scale (ES = -1.29, 95%CI [-2.11, -0.47]), supporting that treating insomnia by Cognitive Behavioral Therapy for Insomnia (CBTI) in patients with depression is effective and also have a positive effect on mood [11 12]. With regard to the current medical conditions in China, the need for CBTI for patients with depression cannot be met. Although selective serotonin reuptake inhibitors

(SSRIs) and barbiturates have considerably improved the efficacy and prognosis in the treatment of comorbid depression with insomnia, their side effects such as nausea, vomiting, tolerance, addiction, excessive sedation and neurological toxicity cannot be ignored [13-15]. What makes the pharmacotherapy more difficult is that some antidepressant drugs may worsen insomnia or cause daytime sleepiness [16], and high hypnotic dosages for insomnia is closely associated with worsened depressive outcomes [17]. In these cases, a drug-free alternative intervention is urgently needed as an effective and safe therapeutic approach for treating insomnia and depression.

Our previous study about acupuncture for primary insomnia demonstrated that acupuncture is an effective treatment to improve patients' sleep efficacy, prolong total sleep time and relieve patients' depressive mood [18]. The preliminary result of our pilot study [19] about the effect of electroacupuncture (EA) for depression related insomnia showed that the Pittsburgh Sleep Quality Index (PSQI) score in depression patients with electroacupuncture treatment obviously decreased (from 16.47 ± 1.89 to 9.83 ± 3.11), and there was significant difference between EA and sham EA ($p<0.01$). Meta-analysis also suggested that acupuncture combined with SSRIs is an effective and well-tolerated therapy for depression and adverse effects of antidepressants [20]. However, other studies showed that acupuncture is not significantly effective in relieving residual insomnia associated with depression [21 22]. As a result, randomized clinical trials in high quality are needed to evaluate the clinical effects and long-term effectiveness of acupuncture in the treatment of depression related insomnia.

We planned this patient-blinded, multicenter, randomized and controlled trial with a sufficient observation period in three healthcare centers in Shanghai, China. We aim to observe the effects of EA treatment on sleep status, and eliminate the possible placebo effect by setting reasonable sham methods. All interventions will be administrated by licensed acupuncturists and psychiatrists under the supervision of an independent Data and

Safety Monitoring Board (DSMB). The results will help to demonstrate if EA is an effective and safe therapy for improving sleep quality in patients with depression.

Methods and analysis

Hypothesis

We hope to provide conclusive evidence to test the hypothesis that acupuncture plus standard care is superior than sham acupuncture plus standard care or standard care alone in treating depression related insomnia.

Design

This is a multi-center, patient-assessor-blinded, randomized and controlled trial, aimed at evaluating the efficacy and safety of electroacupuncture for insomnia in depression patients and comparing the effects between electroacupuncture plus standard care, sham acupuncture plus standard care and simple standard care.

The trial will be performed in three healthcare centers in Shanghai: the acupuncture department in Shanghai Municipal Hospital of Traditional Chinese Medicine, the acupuncture department in Changhai Hospital of Shanghai and the therapeutic department in Shanghai Mental Health Center. We will recruit 270 patients who meet the inclusion criteria and randomly assign them to one of 3 groups, receiving electroacupuncture, sham acupuncture and/or standard medical care. After a week baseline, participants will enter an 8-month observation period in this trial. All treatments will be given 3 times a week (every other day) for 8 weeks. Participants will be assessed at the following time points: the baseline (1 week before treatment), the middle of the treatment (4 weeks after treatment starts), the end of the treatment (8 weeks after treatment starts) and follow-up (1 month, 3 months and 6 months after treatment finishes). All participants will complete the assessments by the PSQI, Actigraphy, HAMD, SAS and TESS (detailed trial process seen

in Figure 1 and Table 1). We will follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [23] throughout the trial.

Patients

The study will include 270 depression patients with insomnia. To ensure the precision of the results, we developed the following eligibility criteria.

Inclusion criteria

Participants meeting the following criteria will be included:

1. Male or female participants aged 18-70;
2. Participants who meet the diagnostic criteria of depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [24];
3. Participants whose HAMD score is 20-35 (mild to moderate depression);
4. Participants who have taken the same antidepressants for more than 4 weeks or have not taken antidepressants;
5. Participants who complained about insomnia during first screening;
6. Participants whose PSQI score is more than 7;
7. Participants who have not received acupuncture treatment for at least one year;
8. Participants who voluntarily agree with the investigation and sign a written informed consent form for the clinical trial.

Exclusion criteria

Participants who report any of the following conditions will be excluded:

1. Participants with secondary depressive disorders caused by organic diseases, medicine, or psychotic disorders;
2. Participants who are in the depressive episode of bipolar disorder, or suffering from dysthymia, reactive depression and depressive syndrome caused by other diseases;
3. Participants who had severe diseases of the cardiovascular or hematopoietic systems, or

had severe hepatic or renal insufficiency;

4. Participants with a history of alcohol abuse or drug dependence;

5. Participants who refuse to wear the actigraphy during the trial;

6. Pregnant or lactating women.

Recruitment

The participants will be recruited through hospital-based advertisements from outpatient clinics and from official websites of all three healthcare centers. If depression patients have interest in participating in the trial, they can take the phone screening first and then will be asked for face-to-face screening in any of the three healthcare centers where they need to fill in some forms with guidance from psychologists or doctors with professional training. Participants then will be asked to wear a wrist actigraphy to monitor their sleep quality for 3 days. Once the participants meet the inclusion criteria, they will be asked to sign the written informed consent form before intervention begins.

Sample size calculation

The sample calculation is based on changes in the primary outcome of this trial, the Pittsburgh Sleep Quality Index (PSQI) score. In our previous trial, we also used PSQI score as the primary outcome to evaluate and compare the effects between acupuncture, superficial acupuncture at sham points and sham acupuncture on treating depression related insomnia [19]. According to the preliminary results, the PSQI score of the acupuncture group at the end of the 8 weeks' intervention was 9.83 ± 3.11 and that of the sham acupuncture group was 13.93 ± 3.22. We assumed 1.5 of the PSQI difference is the superior effect.

H0: $A-B <= \Delta$ but H1: $A-B > \Delta$

We used the following formula to calculate the sample size in this trial:

$N = \left[\frac{(Z_\alpha + Z_\beta)\ \sigma}{\delta - \Delta}\right]^2 \times 2$, where δ is the difference between group, Δ is the assumed superior effect threshold and N is the estimated sample size of each group. σ is the $[\ (S_1^2+S_2^2)\ /\ 2\ ]^{0.5}$

According to the previous study[25], the minimal clinically important difference (MCID) of PSQI is about 1.14-1.75. Since there will be a comparison between the Treatment group and the Control A group as well as a comparison between the Treatment group and the Control B group, a sample size of 27 in each group will have a power of 90% to detect the superior effect of 1.5 of PSQI at an α-value of 0.025 and a β-value of 0.1. Assuming a 10% dropout rate, a sample size of 30 for each group is needed. For a better power and quality control among centers, we decided the recruiting sample size to 30 for each group in each healthcare center. As a result, the total number of participants needed to be randomized is 270.

Randomization and blinding

An online random allocation system will be designed by the central randomization system with a 1:1:1 ratio, using the Pocock and Simon minimization method [26]. Staff of Shanghai BioGuider Medicinal Technology Co. Ltd (No. 2277 Zuchongzhi Road, Pudong New District, Shanghai) established the Data Analysis System (DAS) for the Electronic Data Capture (EDC) 5.0 system and prepared the randomization database. They offered technical support for the central randomization service and are not connected with the study. The system is based on the IIS (Internet Information Server) 5.0 as the Web Server, the SQL Server 2000 as the Database server and the ASP (Active Server Page) as the scripting language [27]. Central randomization has strict limits of authority; only researchers and the specialists from the Data and Safety Monitoring Board (DSMB) in this trial have access to the system. If the participant meets the inclusion criteria and agrees to join in the trial, a researcher who is not involved in the intervention in each healthcare center will login in to

the central randomization system with his own username and password, enter the participant's personal information, and then get the randomized number and the group assignment. The patients' personal information will be protected and keep confidential to the acupuncturists and the assessors before, during and after the trial.

We will conduct a patient-assessor-blinded trial where participants are not aware of their group assignments and acupuncturists will not be involved in the outcome assessment or data analysis. Participants will be informed that they have an equal chance of allocation to the three groups. Participants who are assigned to the electroacupuncture (EA) or sham electroacupuncture (SA) will be treated in a closed unit to avoid communication. Furthermore, they will be asked to wear eye masks before and during the trial. Since there are inserted needles around participants' wrist joints, they will not be able to move their hands easily and cannot take off the eye masks. With these methods, participants will not be aware of the difference between EA and SA. To test the success of blinding, all participants in three centers will be asked by their acupuncturists whether they received EA or SA treatment at the end of treatment. Except the acupuncturists, other researchers including the statisticians, outcome assessors and data analysts are all blinded to the group assignments. All researchers will receive training on the specifications of this research method before the trial and strictly adhere to the task separation principle.

Intervention

Participants in Treatment group and Control A group will receive EA or SA treatment. They will receive 24 sessions of treatment, 3 times a week for 8 consecutive weeks. EA or SA treatment will be performed after skin cleansing, with patients wearing eye masks and lying supine. Each treatment will last for 30 minutes. The temperature of the treatment room cannot be lower than 25°C.

Considering the participants' psychological state, participants in all three groups can

continue regular administration of antidepressants, sedatives, hypnotics or anxiolytics during the trial. They must record the dose, especially when they reduce the amount; and dose escalation will not be allowed unless the patient has consulted the psychiatrist. The patients will not be withdrawn the trial by changing the dose of the drug.

Treatment group

Participants in the Treatment group will receive electroacupuncture (EA) treatment. The acupuncture method of each acupoint is shown in Table 2. The regular acupuncture method will be applied at Baihui (GV20), Shenting (GV24), Yintang (GV29), bilateral Anmian (EX-HN22), Shenmen (HT7), Neiguan (PC6) and SanYinjiao (SP6). The acupuncture needles are produced by Asia-med GmbH&Co.KG (seen Figure 2), with the same appearance as those used in sham acupuncture treatment. After needle insertion, rotating manipulation or lifting-thrusting manipulation will be applied for "Deqi" sensation. Two electrodes of the electro-stimulator (CMNS6-1, Wuxi Jiajian Medical Device CO., LTD, China) will be connected to the needles at Baihui (GV20) and Yintang (GV29) for 30 minutes, delivering a continuous wave. The frequency will be set to 30 Hz with a current intensity of 0.1 to 1 mA during the treatment, based on the tolerance of each patient.

Control A group

Participants in the Control A group will receive sham electroacupuncture treatment at the same acupoints as the Treatment group. Sham acupuncture will be applied with the placebo needles (Streitberger Placebo needle, asia-med GmbH&Co.KG, seen in Figure2) [28 29] that have been successfully used in our previous study [19 30]. When the tip of the blunt needles touches to the skin, the patient will get a pricking sensation but there is no real needle inserted into the skin. The electro-stimulator will be set beside the patients and two electrodes will be connected to the needles at Baihui (GV20) and Yintang (GV29).

Acupuncturists will turn on the electro-stimulator, but all indicators will be set to "0". Participants will be informed when removing the needles after 30 minutes. Acupuncturists will use dry cotton balls to press the acupoints so that patients can feel the withdrawal of the 'needles'.

We are aware that some of the published trials show that non-needle insertion Streitberger sham device may also have non-specific effect which may lead to "negative" results. However, based on our own experience, this is the most appropriate control for a randomized patient-blinded controlled trial. Our previous study on acupuncture for primary insomnia show that acupuncture was superior to the non-insertion sham control [18]. Therefore, we are confident that the non-specific effect of Streitberger sham device will be minimized.

Control B group

Standard care (also known as treatment-as-usual or routine care) in RCTs is frequently employed as the control condition to establish if the intervention is a significant improvement over existing practice [31]. In this trial, we set Control B group as the standard care group to investigate the differences between EA treatment group and the blank control group so that the effects of EA for insomnia and depression will be observed more clearly. All 90 participants in three healthcare centers in Control B group will continue taking in their routine antidepressants and/or sedative-hypnotics as before from baseline to 8 weeks. After finishing all the required scales and actigraphy records, they will get 10 sessions of free acupuncture treatment for insomnia.

Outcome Measurement

Primary outcome

The Pittsburgh Sleep Quality Index (PSQI) is a widely-used questionnaire with 19 items to

assess sleep quality and disturbances over a one-month interval [32]. Four open-ended questions are followed by closed-ended questions that are rated on a 4-point Likert scale. The scores include the following indicators: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication, and daytime dysfunction. The accumulated scores of the seven indicators constitute the total score (ranging from 0–21). A higher score indicates worse sleep quality and more severe sleep disorders.

Secondary outcomes

1. The actigraphy (wActiSleep-BT. LLC, Pensacola, USA) worn on the patient's wrist can monitor the sleep quality, such as sleep onset, sleep latency, duration, awakenings during the night, etc. The software ActiLife6 (Version 6.8.1, ActiGraph, LLC) will be used to analyze every participant's sleep condition recorded in the actigraphy. The indicators used in our trial will be sleep efficiency (SE), sleep awakenings (SA) and total sleep time (TST).

2. The Hamilton Rating Scale for Depression (HAMD) is an observer-rating questionnaire with 17 items used to assess the symptoms of patients diagnosed as suffering from depressive states [33]. Each item is rated in 3- or 5-point scales. A higher total score indicates a higher depression level.

3. The Self-rating Anxiety Scale (SAS) is primarily used as a measure of somatic symptoms associated with anxiety [34]. In using the scale, the participant will be asked to rate each item from 0-3 points according to how it applies to him or her within the past week. The standard score is the sum of the integer part of 1.25 times the raw score of the 20 items. A standard score of more than 50 points means the subject has anxious symptoms. A higher score indicates a more serious case of anxiety.

4. The dose dairy is a notebook where participants will be required to record their daily dose of antidepressants or sedative-hypnotics from baseline to 6 months follow-up, as well as the dosage time.

Adverse events

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring during the trial) related to the administration of antidepressant and sedative-hypnotics must be reported by patients and practitioners. These adverse events will be -recorded in the Treatment Emergent Symptom Scale (TESS) [35].

For the adverse events related to the acupuncture treatment, the most common ones include bleeding, faint, bruising ecchymoma, serious pain etc. These AE data will be assessed in terms of severity and causality, and the incidence will also be determined. The 3-point grading categories will be applied: grade 1, mild, grade 2, moderate, grade 3, severe or medically significant. The causality categories used will be certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable. The incidence of AEs was presented as the number of AEs per number of acupuncture sessions (%).

Statistical analysis

The statistical analyst will be blinded to the participants' personal information and their group assignment during the trial. The primary analysis will be a comparison of the changes of patients' PSQI score among three groups at 8 weeks after inclusion (comparison of the primary endpoint). The secondary analysis will be performed to assess the changes of the SE, TST and SA recorded in the actigraphy, as well as the HAMD scores and SAS scores from baseline to 8 weeks after inclusion. We will also count the number of patients who increase or decrease the drug dose, and then analyze the differences among three groups. All analyses will be performed on the intention-to-treat (ITT) population of participants who have at least one treatment. Missing data will be handled using the multiple imputation method, on the assumption that values at each time point follow a specific distribution calculated by the computer software R V.3.5. We will also perform a complete-case analysis without imputation of missing data, to find out if the results are consistent. Data

analyses will be performed with the use of the statistical software SPSS V.20.0. The *t*-test will be used to compare the measurement data between either two groups from the baseline to 6 months follow-up; the rank sum test will be used for ranked data while the χ^2 test will be used to analyze categorical data. The significance level that will be used for statistical analysis with 2-tailed testing will be 2.5%. Data values will mainly be presented as Mean±SD.

Patient and public involvement

This trial was designed to evaluate the effects and safety of acupuncture treatment for depression-related insomnia. In our clinical practice, depression patients always complain insomnia as the most disturbing problem affecting their quality of life. Acupuncture not only helps these patients improve their sleep quality, but also relieve their depression and pressure. The outcome measures used in this study were commonly used in clinical trials of sleep and mood disorders, and we applied the actigraphy as another outcome measure to provide more objective results. Depression patients with insomnia in the clinical department were consulted by the main researcher prior to the trial design. The treatment frequency and duration of this study were summarized from clinical experience and patients' feedback. We will recruit all participants from the outpatient clinics in three healthcare centers. Patients who were involved in the consultation about the trial design before will not be recruited as participants. A journal article manuscript will be written to present the results after the trial completed, and a brief summary of results with plain language will be sent to all participants. The burden of intervention will not be assessed by participants themselves.

Ethics and dissemination

All acupuncturists are licensed doctors with 3-5 years of experience in acupuncture treatment; and they will join in the clinical training before the intervention to ensure the standard real and sham acupuncture operation in three centers. The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai, China (2017SHL-KY-04) and is registered with ClinicalTrials.gov (NCT03122080).

To guarantee the quality of the study, this trial will be carried out under the supervision of an independent DSMB. The DSMB consists of three experts from different fields: Professor Bingshun Wang in medical statistics from the School of medicine at Shanghai Jiaotong University, Dr. Lin Sun in psychology from the Department of Geriatrics at Shanghai Mental Health Center, and Professor Xueyong Shen in acupuncture from the Acupuncture College at Shanghai University of Traditional Chinese Medicine. The DSMB works to identify problems in the project, examine collected data, and control bias. Researchers in each healthcare center will promptly input data on the website (https://ecdm2.drugchina.net/crct2/) so that members in the DSMB can supervise the process at any time. Once they find problems or serious adverse events during the intervention, they can raise objections directly and even stop the trial until the problem has been resolved. Meanwhile, a qualified clinical trial expert (Lixing Lao) will be invited to monitor this study.

The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Discussion

Acupuncture has been used to treat insomnia and some mental disorders since antiquity in China. According to the theory of traditional Chinese medicine, acupuncture provides balance to the body by stimulating specific acupoints, helping the body to achieve a state

of relative equilibrium (the harmony of *"yin-yang")*, thereby restoring the normal sleep-wake cycle. Recent systematic reviews indicate that acupuncture could be an alternative therapy to medication for treating insomnia but needs further studies using large samples and a rigorous study design to confirm its role [36 37].

Previous RCTs always focus on either the acupuncture treatment for insomnia or that for depression, ignoring the relationship between these two diseases. Insomnia has been identified as the most common sleep disorder comorbid to depressive disorders [38]; so a reasonable acupuncture treatment program should be developed to normalize sleep disturbance and to relieve depressive mood as well. At the time of this writing, there are no similar RCTs about acupuncture for insomnia in depression patients that included a large sample size and were conducted in multiple healthcare centers. Our trial intends to present a strictly designed trial to study the effects of EA on insomnia in depression patients and to overcome some existing limitations, including illogical design, imperfect blinding method and practical difficulties in previous acupuncture clinical researches. With a long follow-up period, we will be able to explore the persistent effects of acupuncture for insomnia and determine for how long the therapeutic effect will last.

For patients in the EA group, we decided to use EA at Baihui (GV20) and Yintang (GV29), with the frequency set to 30 Hz during the treatment. According to the TCM theory, GV20 is the convergent point of six yang meridians as well as the foot Jueyin meridian; it is located on the top of the head, governs yang qi of the body and is the key point of calming mind. GV29 promotes the circulation of qi and blood in the head and restores the function of brain. EA at GV20 and GV29 enhances the effect of soothing nerves. In addition, a functional connectivity MRI (fcMRI) study suggested that EA at GV20 and GV29 may have effect on mental disorders[39]. Using fcMRI to identify the key cerebral functional region affected by EA at GV20 and GV29 found that the center of the cerebral network changed from the caudate nucleus to the parahippocampal gyrus and hypothalamus. The network centered on the parahippocampal gyrus and hypothalamus

primarily functioned in somatic movement, sensation, vision, hearing and language. This finding may indicate a mechanism for treating depression using EA at GV20 and GV29.

A frequency-specific neurochemical response in the central nervous system may be related to differential response of the body to low- and high-frequency EA stimulation and different peripheral and central pathways[40]. Previous research found that low frequency EA could be useful in clinical settings to manage pain [41] while high-frequency stimulation has more potent effects on 5-HT activity[42]. Thirty Hz separates the continuous wave of the electro-stimulator from disperse wave to dense wave and we chose 30Hz based on an acupuncture textbook [43].

Considering the complicated mental state of depression patients with insomnia, we will apply standard medication instead of unified antidepressants or sedative-hypnotics in this trial. Participants in all groups will continue taking in their individual routine dosage from baseline to 6 months follow-up. If their conditions obviously change during the study, they will be free to consult our psychologists from Shanghai Mental Health Center to adjust the dose. The use of standard care control groups has been the subject of much debate, with some pointing out that what constitutes standard care is unclear [44] [45]. For better implementation of the standard care, researchers in our trial will try to carry out proper health education for all patients and supervise them in recording their daily medication dosage.

As a multi-center RCT conducted in a first-tier city, our study can provide more representative results about the role and value of acupuncture as a complementary and alternative therapy for insomnia and depressive moods than other single-center RCTs. Considering the high prevalence of insomnia and depression in rural areas in China [46] [47], the correlated heavy economic burden and serious public health problems cannot be underestimated. In future studies, the focus might be on the acupuncture treatment for insomnia in nationwide healthcare centers.

Trial Status

This clinical trial is now recruiting participants.

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Abbreviations

EA: Electroacupuncture;

SA: Sham electroacupuncture;

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture;

PSQI: Pittsburgh Sleep Quality Index;

HAMD: Hamilton Rating Scale for Depression;

SAS: Self-Rating Anxiety Scale;

TESS: Treatment Emergent Symptom Scale;

ITT: Intention-To-Treat Set;

GV: Governor Vessel;

EX-HN: Extra acupoints on head;

SI: Small intestine meridian of hand taiyang;

SJ: Sanjiao meridian of hand shaoyang;

SP: Spleen meridian of foot taiyin;

HT: Heart meridian of hand shaoyin;

PC: Pericardium meridian of hand jueyin;

CRF: Case Report Form

Competing interests statement

The authors declare that they have no competing interests.

Authors' Contributions

SFX is the main researcher who provided conception, design of the study and contributed to the final approval of the manuscript. LXL is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XY contributed to the design of the protocol, writing and review of the manuscript. BD, TTL and Xiang Lin contributed to the manuscript draft. PY and XLQ contributed to the statistical design. Xia Li and SZ are the project managers for the design of the randomization. All authors read and approved the final manuscript.

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Table 1 Trial process chart

	Baseline	Treatment phase			Follow-up phase		
	Week -1	Week 0	Week 4	Week 8	Month 1	Month 3	Month 6
Patients							

Enrollment	×						
Signed informed consent		×					
Medical history	×						
Merger disease	×						
Randomization		×					
Intervention			×	×			
Primary outcomes							
PSQI	×		×	×	×	×	×
Secondary outcomes							
Actigraphy	×		×	×			
HAMD	×		×	×	×	×	×
SAS	×		×	×			
TESS			×	×	×	×	×
Drug dose record	×		×	×	×	×	×
Patients' compliance			×	×	×	×	×

PSQI: Pittsburgh Sleep Quality Index;

SAS: Self-Rating Anxiety Scale;

HAMD: Hamilton Rating Scale for Depression;

TESS: Treatment Emergent Symptom Scale

Table 2 Acupuncture method for each acupoint

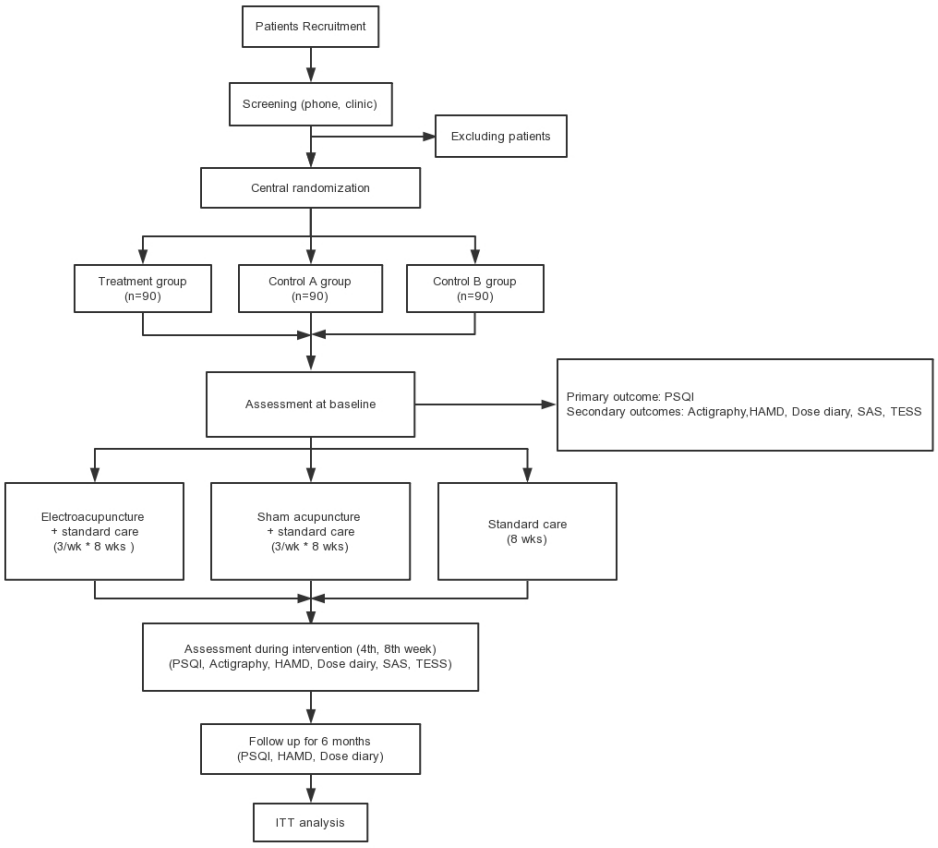
Acupoint	Needling method

Baihui (GV20), Shenting (GV24)	The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anterior-posterior midline, and then insert the needle for about 1cm.
Yintang (GV29)	Pinch the local skin, and then puncture obliquely for about 1cm.
Anmian (EX-HN22)	The angle between the needle tip and the scalp is 30°. Puncture perpendicularly for about 1cm.
Shenmen (HT7), Sanyinjiao (SP6), Neiguan (PC6)	Puncture perpendicularly for about 1cm.

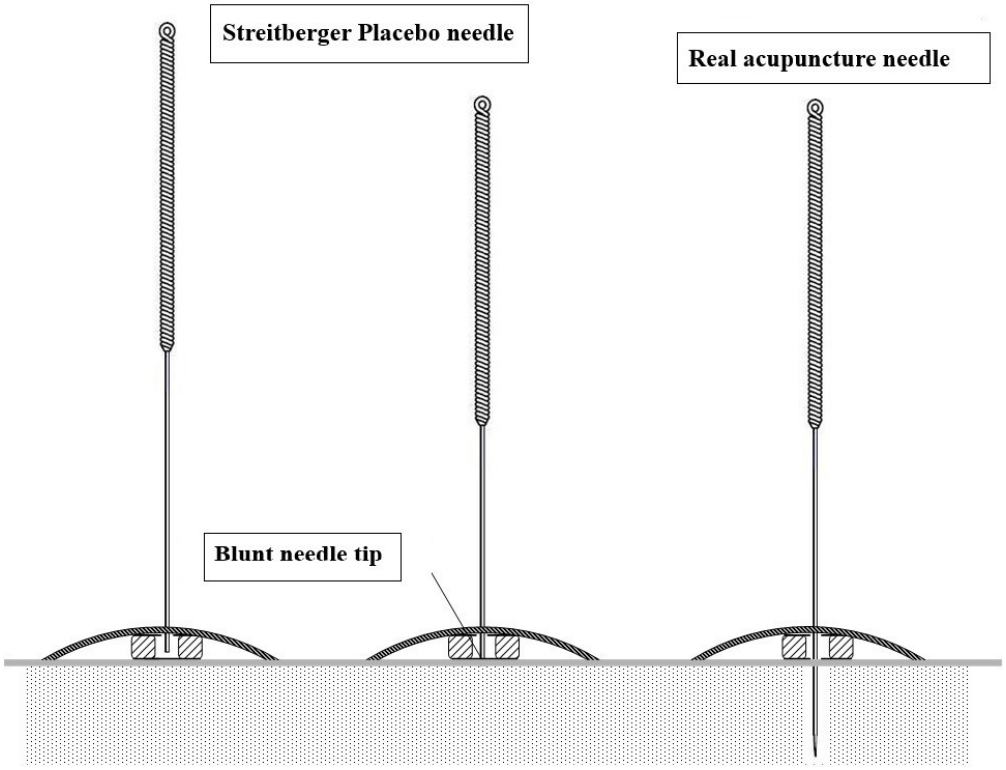
Figure legends

Figure 1: Flowchart of the study

Figure 2: Streitberger Placebo needle (asia-med GmbH&Co.KG)



91x83mm (300 x 300 DPI)



81x62mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, figure1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____9_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____17_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____14_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____14_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____YES_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____NO_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

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The efficacy and safety of electroacupuncture on treating depression related insomnia: a study protocol for a multicenter randomized controlled trial

Xuan Yin[1], Bo Dong[1], Tingting Liang[1], Ping Yin[1], Xia Li[2], Xiang Lin[2], Shuang Zhou[3], Xiaolu Qian[3], Lixing Lao[4,5], Shifen Xu[1]

1 Shanghai Municipal Hospital of Traditional Chinese Medicine Shanghai, Shanghai University of TCM, Shanghai 200071, China

2 Shanghai Mental Health Center, Shanghai Jiaotong University of Medicine, Shanghai 200013, China

3 Changhai Hospital, Second Military Medical University, Shanghai 200433, China

4 School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam, Hong Kong

5 Center for Integrative Medicine, School of Medicine, University of Maryland, Baltimore, MD 21201, USA

Correspondence should be addressed to ShifenXu; xu_teacher2006@126.com and Lixing Lao; lxlao1@hku.hk

Abstract

Introduction

Sleep disorders including insomnia occur frequently in depressive patients. Acupuncture is a widely recognized therapy to treat depression and sleep disorders in clinical practice. This multicenter randomized controlled trial is aimed to investigate the efficacy and safety of electroacupuncture in the treatment of depression patients with insomnia.

Methods and analysis

We describe a protocol for a multicenter randomized controlled trial. A total of 270 eligible patients in three different healthcare centers in Shanghai will be randomly assigned to one of these three groups: Treatment group (electroacupuncture + standard care), Control A group (sham electroacupuncture + standard care) and Control B group (standard care). Treatment will be given three times per week for 8 consecutive weeks. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI). The secondary outcomes are sleep parameters recorded in the Actigraphy, Hamilton Rating Scale for Depression (HAMD) score and Self-rating Anxiety Scale (SAS) score. Daily dose of patients' antidepressant and sedative-hypnotic medication will be recorded in the dairy. All adverse effects will be assessed by the Treatment Emergent Symptom Scale (TESS). Outcomes will be evaluated at baseline, 4 weeks post-

treatment and 8 weeks post-treatment, as well as at 1 month, 3 months and 6 months follow-up.

Ethics and dissemination

The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2017SHL-KY-04). Written informed consent will be obtained from all participants. The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Trial registration number: NCT03122080

Key words: depression; insomnia; electroacupuncture; randomized controlled trial

Strengths and limitations of this study

- This is a strictly designed, single-blinded, randomized controlled trial with long intervention and follow-up period.
- Sleep indicators in the actigraphy will be used as objective outcomes of patients' sleep quality.
- We will do comprehensive evaluation about the efficacy of acupuncture treatment.
- Rigorous central randomization and allocation concealment methods will be applied.
- This can't be designed as a double-blinded trial because acupuncturists can't be blinded to the group assignment.

Introduction

Depression and its related sleep disorders are becoming serious public health problems worldwide. The global point prevalence of MDD is 4.7% [1], and the estimation of a 12-month cumulative incidence of depression in China is 5.23% [2], causing an urgent need to improve depressive patients' health. . Insomnia may occur in 60-80% of patients with major depressive disorders [3]; it is one of the most frequent residual symptoms of depression [4], and may persist even after depressive mood symptoms have been relieved [5].

Insomnia is characterized by persistent dissatisfaction with sleep quantity or quality for at least 4 weeks, with specific complaints of difficulty falling asleep, frequent nighttime awakenings, and/or awakening earlier in the morning than desired [6].

It may be triggered by different factors including psychiatric disorders, organic diseases and the intake of drugs or alcohol [7]. In fact, depressive symptoms are the largest and most consistent risk factors for insomnia because it affects the normal sleep-wake cycle [8 9]. Previous meta-analysis indicated moderate to large effect size (ES) improvement in depression as measured with the Hamilton Depression Rating Scale (ES = -1.29, 95%CI [-2.11, -0.47]), supporting that treating insomnia by Cognitive Behavioral Therapy for Insomnia (CBTI) in patients with depression is effective and also have a positive effect on mood [10 11]. With regard to the current medical conditions in China, the need for CBTI for patients with depression cannot be met. Although selective serotonin reuptake inhibitors (SSRIs) and barbiturates have considerably improved the efficacy and prognosis in the treatment of comorbid depression with insomnia, their side effects such

as nausea, vomiting, tolerance, addiction, excessive sedation and neurological toxicity cannot be ignored [12-14]. What makes the pharmacotherapy more difficult is that some antidepressant drugs may worsen insomnia or cause daytime sleepiness [15], and high hypnotic dosages for insomnia is closely associated with worsened depressive outcomes [16]. In these cases, a drug-free alternative intervention is urgently needed as an effective and safe therapeutic approach for treating insomnia and depression.

Our previous study demonstrated that acupuncture is an effective treatment to improve patients' sleep efficacy, prolong total sleep time and relieve patients' depressive mood[17]. The preliminary result of our pilot study [18] about the effect of electroacupuncture (EA) for depression related insomnia showed that the Pittsburgh Sleep Quality Index (PSQI) score in depression patients with electroacupuncture treatment obviously decreased (from 16.47 ± 1.89 to 9.83 ± 3.11), and there was significant difference between EA and sham EA ($p<0.01$). Meta-analysis also suggested that acupuncture combined with SSRIs is an effective and well-tolerated therapy for depression and adverse effects of antidepressants [19]. However, other studies showed that acupuncture is not significantly effective in relieving residual insomnia associated with depression [20 21]. As a result, randomized clinical trials in high quality are needed to evaluate the clinical effects and long-term effectiveness of acupuncture in the treatment of depression related insomnia.

We planned this patient-blinded, multi-center, randomized and controlled trial with a sufficient observation period in three healthcare centers in Shanghai, China. We aim to observe the effects of EA treatment on sleep status, and eliminate the possible placebo effect by setting reasonable sham methods. All interventions will be administrated by licensed acupuncturists and psychiatrists under the supervision of an independent Data and Safety Monitoring Board (DSMB). The results will help to demonstrate if EA is an effective and safe therapy for improving sleep quality in patients with depression.

Methods and analysis

Hypothesis

We hope to provide conclusive evidence to test the hypothesis that acupuncture plus standard care is superior than sham acupuncture plus standard care or standard care alone in treating depression related insomnia.

Design

This is a multi-center, patient-assessor-blinded, randomized and controlled trial, aimed at evaluating the efficacy and safety of electroacupuncture for insomnia in depression patients and comparing the effects between electroacupuncture plus standard care, sham acupuncture plus standard care and simple standard care.

The trial will be performed in three healthcare centers in Shanghai: the acupuncture department in Shanghai Municipal Hospital of Traditional Chinese Medicine, the acupuncture department in Changhai Hospital of Shanghai and the therapeutic department in Shanghai Mental Health Center. We will recruit 270 patients who meet the inclusion criteria and randomly assign them to one of 3 groups, receiving electroacupuncture, sham acupuncture and/or standard medical care. After a week baseline, participants will enter an 8-month observation period in this trial. All treatments will be given 3 times a week (every other day) for 8 weeks. Participants will be assessed at the following time points: the baseline (1 week before treatment), the middle of the treatment (4 weeks after treatment starts), the end of the treatment (8 weeks after treatment starts) and follow-up (1 month, 3 months and 6 months after treatment finishes). All participants will complete the assessments by the PSQI, Actigraphy, HAMD, SAS and TESS (detailed trial process seen in Figure 1 and Table 1). We will follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [22] throughout the trial.

Patients

The study will include 270 depression patients with insomnia. To ensure the precision of the results, we developed the following eligibility criteria.

Inclusion criteria

Participants meeting the following criteria will be included:

1. Male or female participants aged 18-70;
2. Participants who meet the diagnostic criteria of depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)[23];
3. Participants whose HAMD score is 20-35 (mild to moderate depression);
4. Participants who have taken the same antidepressants for more than 4 weeks or have not taken antidepressants;
5. Participants who complained about insomnia during first screening;
6. Participants whose PSQI score is more than 7;
7. Participants who have not received acupuncture treatment for at least one year;
8. Participants who voluntarily agree with the investigation and sign a written informed consent form for the clinical trial.

Exclusion criteria

Participants who report any of the following conditions will be excluded:

1. Participants with secondary depressive disorders caused by organic diseases, medicine, or psychotic disorders;
2. Participants who are in the depressive episode of bipolar disorder, or suffering from dysthymia, reactive depression and depressive syndrome caused by other diseases;
3. Participants who had severe diseases of the cardiovascular or hematopoietic systems, or had severe hepatic or renal insufficiency;
4. Participants with a history of alcohol abuse or drug dependence;
5. Participants who refuse to wear the actigraphy during the trial;
6. Pregnant or lactating women.

Recruitment

The participants will be recruited through hospital-based advertisements from outpatient clinics and from official websites of all three healthcare centers. If depression patients have interest in participating in the trial, they can take the phone screening first and then will be asked for face-to-face screening in any of the three healthcare centers where they need to fill in some forms with guidance from psychologists or doctors with professional training. Participants then will be asked to wear a wrist actigraphy to monitor their sleep quality for 3 days. Once the participants meet the inclusion criteria, they will be asked to sign the written informed consent form before intervention begins. Before intervention, we will incorporate the expectation questionnaire which is modified from Vincent's four questions [24] to value patients' anticipation of acupuncture treatment. Patients will be asked to rate their expectations of the treatment from very pessimistic to very optimistic, in on a 5-point Likert scale.

Sample size calculation

The sample calculation is based on changes in the primary outcome of this trial, the Pittsburgh Sleep Quality Index (PSQI) score. In our previous trial, we also used PSQI score as the primary outcome to evaluate and compare the effects between acupuncture, superficial acupuncture at sham points and sham acupuncture on treating depression related insomnia [18]. According to the preliminary results, the PSQI score of the acupuncture group at the end of the 8 weeks' intervention was 9.83 ± 3.11 and that of the sham acupuncture group was 13.93 ± 3.22. We assumed 0.2 of the PSQI difference is the superior effect.

H0: A-B<= Δ but H1: A-B> Δ

We used the following formula to calculate the sample size in this trial:

$N = \left[\frac{(Z_\alpha + Z_\beta)\ \sigma}{\delta - \Delta}\right]^2 \times 2$, where δ is the difference between group, Δ is the assumed superior effect threshold and N is the estimated sample size of each group. σ is the $[\ (S_1^2+S_2^2)\ /\ 2\ ]^{0.5}$

According to the previous study[25], the minimal clinically important difference

(MCID) of PSQI is about 1.14-1.75. Since there will be a comparison between the Treatment group and the Control A group as well as a comparison between the Treatment group and the Control B group, a sample size of 27 in each group will have a power of 90% to detect the superior effect of 1.5 of PSQI at an α-value of 0.025 and a β-value of 0.1. Assuming a 10% dropout rate, a sample size of 30 for each group is needed. For a better power and quality control among centers, we decided the recruiting sample size to 30 for each group in each healthcare center. As a result, the total number of participants needed to be randomized is 270.

Randomization and blinding

An online random allocation system will be designed by the central randomization system with a 1:1:1 ratio, using the Pocock and Simon minimization method [26]. Staff of Shanghai BioGuider Medicinal Technology Co. Ltd (No. 2277 Zuchongzhi Road, Pudong New District, Shanghai) established the Data Analysis System (DAS) for the Electronic Data Capture (EDC) 5.0 system and prepared the randomization database. They offered technical support for the central randomization service and are not connected with the study. The system is based on the IIS (Internet Information Server) 5.0 as the Web Server, the SQL Server 2000 as the Database server and the ASP (Active Server Page) as the scripting language [27]. Central randomization has strict limits of authority; only researchers and the specialists from the Data and Safety Monitoring Board (DSMB) in this trial have access to the system. If the participant meets the inclusion criteria and agrees to join in the trial, a researcher who is not involved in the intervention in each healthcare center will login in to the central randomization system with his own username and password, enter the participant's personal information, and then get the randomized number and the group assignment. The patients' personal information will be protected and keep confidential to the acupuncturists and the assessors before, during and after the trial.

We will conduct a patient-assessor-blinded trial where participants are not aware of their group assignments and acupuncturists will not be involved in the outcome assessment or data analysis. Participants will be informed that they have an equal

chance of allocation to the three groups. Participants who are assigned to the electroacupuncture (EA) or sham electroacupuncture (SA) will be treated in a closed unit to avoid communication. Furthermore, they will be asked to wear eye masks before and during the trial. Since there are inserted needles around participants' wrist joints, they will not be able to move their hands easily and cannot take off the eye masks. With these methods, participants will not be aware of the difference between EA and SA. To test the success of blinding, all participants in three centers will be asked by their acupuncturists whether they received EA or SA treatment at the end of treatment. Except the acupuncturists, other researchers including the statisticians, outcome assessors and data analysts are all blinded to the group assignments. All researchers will receive training on the specifications of this research method before the trial and strictly adhere to the task separation principle.

Intervention

Participants in Treatment group and Control A group will receive EA or SA treatment. Participants in these two groups will receive 24 sessions of different treatments, 3 times a week for 8 weeks. EA or SA treatment will be performed after skin cleansing, with patients wearing eye masks and lying supine. Each treatment will last for 30 minutes. The temperature of the treatment room cannot be lower than 25°C.

Considering the participants' psychological state, participants in all three groups can continue regular administration of antidepressants, sedatives, hypnotics or anxiolytics during the trial. They must record the dose, especially when they reduce the amount; and dose escalation will not be allowed unless the patient has consulted the psychiatrist. The patients will not be withdrawn the trial by changing the dose of the drug.

Treatment group

Participants in the Treatment group will receive electroacupuncture (EA) treatment. The acupuncture method of each acupoint is shown in Table 2. The regular acupuncture

method will be applied at Baihui (GV20), Shenting (GV24), Yintang (GV29), bilateral Anmian (EX-HN22), Shenmen (HT7), Neiguan (PC6) and SanYinjiao (SP6). The acupuncture needles are produced by Asia-med GmbH&Co.KG (seen Figure 2), with the same appearance as those used in sham acupuncture treatment. After needle insertion, rotating manipulation or lifting-thrusting manipulation will be applied for "Deqi" sensation. Two electrodes of the electro-stimulator (CMNS6-1, Wuxi Jiajian Medical Device CO., LTD, China) will be connected to the needles at Baihui (GV20) and Yintang (GV29) for 30 minutes, delivering a continuous wave. The frequency will be set to 30 Hz with a current intensity of 0.1 to 1 mA during the treatment, based on the tolerance of each patient.

Control A group

Participants in the Control A group will receive sham electroacupuncture treatment at the same acupoints as the Treatment group. Sham acupuncture will be applied with the placebo needles (Streitberger Placebo needle, asia-med GmbH&Co.KG, seen in Figure2) [28 29] that have been successfully used in our previous study [18 30]. When the tip of the blunt needles touches to the skin, the patient will get a pricking sensation but there is no real needle inserted into the skin. The electro-stimulator will be set beside the patients and two electrodes will be connected to the needles at Baihui (GV20) and Yintang (GV29). Acupuncturists will turn on the electro-stimulator, but all indicators will be set to "0". Participants will be informed when removing the needles after 30 minutes. Acupuncturists will use dry cotton balls to press the acupoints so that patients can feel the withdrawal of the 'needles'.

We are aware that some of the published trials show that non-needle insertion Streitberger sham device may also have non-specific effect which may lead to "negative" results. However, this is the most appropriate control for a randomized patient-blinded controlled trial at present. Our previous study on acupuncture for primary insomnia show that acupuncture was superior to the non-insertion sham control[17]. Therefore, we are confident that the non-specific effect of Streitberger sham device will be minimized.

Control B group

Standard care (also known as treatment-as-usual or routine care) in RCTs is frequently employed as the control condition to establish if the intervention is a significant improvement over existing practice [31]. In this trial, we set Control B group as the standard care group to investigate the differences between EA treatment group and the blank control group so that the effects of EA for insomnia and depression will be observed more clearly. All 90 participants in three healthcare centers in Control B group will continue taking in their routine antidepressants and/or sedative-hypnotics as before from baseline to 8 weeks. After finishing all the required scales and actigraphy records, they will get 10 sessions of free acupuncture treatment for insomnia.

Outcome Measurement

Primary outcome

The Pittsburgh Sleep Quality Index (PSQI) is a widely-used questionnaire with 19 items to assess sleep quality and disturbances over a one-month interval [32]. Four open-ended questions are followed by closed-ended questions that are rated on a 4-point Likert scale. The scores include the following indicators: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication, and daytime dysfunction. The accumulated scores of the seven indicators constitute the total score (ranging from 0–21). A higher score indicates worse sleep quality and more severe sleep disorders.

Secondary outcomes

1. The actigraphy (wActiSleep-BT. LLC, Pensacola, USA) worn on the patient's wrist can monitor the sleep quality, such as sleep onset, sleep latency, duration, awakenings during the night, etc. The software ActiLife6 (Version 6.8.1, ActiGraph, LLC) will be used to analyze every participant's sleep condition recorded in the actigraphy. The

indicators used in our trial will be sleep efficiency (SE), sleep awakenings (SA) and total sleep time (TST).

2. The Hamilton Rating Scale for Depression (HAMD) is an observer-rating questionnaire with 17 items used to assess the symptoms of patients diagnosed as suffering from depressive states [33]. Each item is rated in 3- or 5-point scales. A higher total score indicates a higher depression level.

3. The Self-rating Anxiety Scale (SAS) is primarily used as a measure of somatic symptoms associated with anxiety [34]. In using the scale, the participant will be asked to rate each item from 0-3 points according to how it applies to him or her within the past week. The standard score is the sum of the integer part of 1.25 times the raw score of the 20 items. A standard score of more than 50 points means the subject has anxious symptoms. A higher score indicates a more serious case of anxiety.

4. The dose dairy is a notebook where participants will be required to record their daily dose of antidepressants or sedative-hypnotics from baseline to 6 months follow-up, as well as the dosage time.

Adverse events

Any adverse events (described as unfavorable or unintended signs, symptoms or diseases occurring during the trial) related to the administration of antidepressant and sedative-hypnotics must be reported by patients and practitioners. These adverse events will be -recorded in the Treatment Emergent Symptom Scale (TESS) [35].

For the adverse events related to the acupuncture treatment, the most common ones include bleeding, faint, bruising ecchymoma, serious pain etc. These AE data will be assessed in terms of severity and causality, and the incidence will also be determined. The 3-point grading categories will be applied: grade 1, mild, grade 2, moderate, grade 3, severe or medically significant. The causality categories used will be certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable. The incidence of AEs was presented as the number of AEs per number of acupuncture sessions (%).

Statistical analysis

The statistical analyst will be blinded to the participants' personal information and their group assignment during the trial. The primary analysis will be a comparison of the changes of patients' PSQI score among three groups at 8 weeks after inclusion (comparison of the primary endpoint). The secondary analysis will be performed to assess the changes of the SE, TST and SA recorded in the actigraphy, as well as the HAMD scores and SAS scores from baseline to 8 weeks after inclusion. We will also count the number of patients who increase or decrease the drug dose, and then analyze the differences among three groups. All analyses will be performed on the intention-to-treat (ITT) population of participants who have at least one treatment. Missing data will be handled using the multiple imputation method, on the assumption that values at each time point follow a specific distribution calculated by the computer software R V.3.5. We will also perform a complete-case analysis without imputation of missing data, to find out if the results are consistent. Data analyses will be performed with the use of the statistical software SPSS V.20.0. The *t*-test will be used to compare the measurement data between either two groups from the baseline to 6 months follow-up; the rank sum test will be used for ranked data while the χ^2 test will be used to analyze categorical data. The significance level that will be used for statistical analysis with 2-tailed testing will be 2.5%. Data values will mainly be presented as Mean±SD.

Patient and public involvement

Depression patients with insomnia in the clinical department were consulted by the main researcher prior to the trial design. The treatment frequency and duration of this study were summarized from clinical experience and patients' feedback. We will recruit all participants from the outpatient clinics in three healthcare centers. Patients who were involved in the consultation about the trial design before will not be recruited as

participants. A journal article manuscript will be written to present the results after the trial completed, and a brief summary of results with plain language will be sent to all participants. The burden of intervention will not be assessed by participants themselves.

Ethics and dissemination

All acupuncturists are licensed doctors with 3-5 years of experience in acupuncture treatment; and they will join in the clinical training before the intervention to ensure the standard real and sham acupuncture operation in three centers. The trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai, China (2017SHL-KY-04) and is registered with ClinicalTrials.gov (NCT03122080).

To guarantee the quality of the study, this trial will be carried out under the supervision of an independent DSMB. The DSMB consists of three experts from different fields: Professor Bingshun Wang in medical statistics from the School of medicine at Shanghai Jiaotong University, Dr. Lin Sun in psychology from the Department of Geriatrics at Shanghai Mental Health Center, and Professor Xueyong Shen in acupuncture from the Acupuncture College at Shanghai University of Traditional Chinese Medicine. The DSMB works to identify problems in the project, examine collected data, and control bias. Researchers in each healthcare center will promptly input data on the website (https://ecdm2.drugchina.net/crct2/) so that members in the DSMB can supervise the process at any time. Once they find problems or serious adverse events during the intervention, they can raise objections directly and even stop the trial until the problem has been resolved. Meanwhile, a qualified clinical trial expert (Lixing Lao) will be invited to monitor this study.

The results of this study will be published in peer-reviewed journals or presented at academic conferences.

Discussion

Acupuncture has been used to treat insomnia and some mental disorders since antiquity in China. According to the theory of traditional Chinese medicine, acupuncture provides balance to the body by stimulating specific acupoints, helping the body to achieve a state of relative equilibrium (the harmony of *"yin-yang")*, thereby restoring the normal sleep-wake cycle.

Previous RCTs always focus on either the acupuncture treatment for insomnia or that for depression, ignoring the relationship between these two diseases. Insomnia has been identified as the most common sleep disorder comorbid to depressive disorders [36]; so a reasonable acupuncture treatment program should be developed to normalize sleep disturbance and to relieve depressive mood as well. At the time of this writing, there are no similar RCTs about acupuncture for insomnia in depression patients that included a large sample size and were conducted in multiple healthcare centers. Our trial intends to present a strictly designed trial to study the effects of EA on insomnia in depression patients and to overcome some existing limitations, including illogical design, imperfect blinding method and practical difficulties in previous acupuncture clinical researches. With a long follow-up period, we will be able to explore the persistent effects of acupuncture for insomnia and determine for how long the therapeutic effect will last.

For patients in the EA group, we decided to use EA at Baihui (GV20) and Yintang (GV29), with the frequency set to 30 Hz during the treatment. According to the TCM theory, GV20 is the convergent point of six yang meridians as well as the foot Jueyin meridian; it is located on the top of the head, governs yang qi of the body and is the key point of calming mind. GV29 promotes the circulation of qi and blood in the head and restores the function of brain. EA at GV20 and GV29 enhances the effect of soothing nerves. In addition, a functional connectivity MRI (fcMRI) study suggested that EA at GV20 and GV29 may have effect on mental disorders[37]. Using fcMRI to identify the key cerebral functional region affected by EA at GV20 and GV29 found that the center of the cerebral network changed from the caudate nucleus to the parahippocampal gyrus and hypothalamus. The network centered on the parahippocampal gyrus and

hypothalamus primarily functioned in somatic movement, sensation, vision, hearing and language. This finding may indicate a mechanism for treating depression using EA at GV20 and GV29.

A frequency-specific neurochemical response in the central nervous system may be related to differential response of the body to low- and high-frequency EA stimulation and different peripheral and central pathways[38]. Previous research found that low frequency EA could be useful in clinical settings to manage pain [39] while high-frequency stimulation has more potent effects on 5-HT activity[40]. Thirty Hz separates the continuous wave of the electro-stimulator from disperse wave to dense wave and we chose 30Hz based on an acupuncture textbook [41].

Considering the complicated mental state of depression patients with insomnia, we will apply standard medication instead of unified antidepressants or sedative-hypnotics in this trial. Participants in all groups will continue taking in their individual routine dosage from baseline to 6 months follow-up. If their conditions obviously change during the study, they will be free to consult our psychologists from Shanghai Mental Health Center to adjust the dose. The use of standard care control groups has been the subject of much debate, with some pointing out that what constitutes standard care is unclear [42 43]. For better implementation of the standard care, researchers in our trial will try to carry out proper health education for all patients and supervise them in recording their daily medication dosage.

As a multi-center RCT conducted in a first-tier city, our study can provide more representative results about the role and value of acupuncture as a complementary and alternative therapy for insomnia and depressive moods than other single-center RCTs. Considering the high prevalence of insomnia and depression in rural areas in China [44 45], the correlated heavy economic burden and serious public health problems cannot be underestimated. In future studies, the focus might be on the acupuncture treatment for insomnia in nationwide healthcare centers.

Trial Status

This clinical trial is now recruiting participants.

Acknowledgments

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Abbreviations

EA: Electroacupuncture;

SA: Sham electroacupuncture;

STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture;

PSQI: Pittsburgh Sleep Quality Index;

HAMD: Hamilton Rating Scale for Depression;

SAS: Self-Rating Anxiety Scale;

TESS: Treatment Emergent Symptom Scale;

ITT: Intention-To-Treat Set;

GV: Governor Vessel;

EX-HN: Extra acupoints on head;

SI: Small intestine meridian of hand taiyang;

SJ: Sanjiao meridian of hand shaoyang;

SP: Spleen meridian of foot taiyin;

HT: Heart meridian of hand shaoyin;

PC: Pericardium meridian of hand jueyin;

CRF: Case Report Form

Competing interests statement

The authors declare that they have no competing interests.

Authors' Contributions

SFX is the main researcher who provided conception, design of the study and contributed to the final approval of the manuscript. LXL is the co-researcher who contributed to the design of the study and critical revision of the manuscript. XY contributed to the design of the protocol, writing and review of the manuscript. BD, TTL and Xiang Lin contributed to the manuscript draft. PY and XLQ contributed to the statistical design. Xia Li and SZ are the project managers for the design of the randomization. All authors read and approved the final manuscript.

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Table 1 Trial process chart

	Baseline	Treatment phase			Follow-up phase		
	Week -1	Week 0	Week 4	Week 8	Month 1	Month 3	Month 6
Patients							
Enrollment	×						
Signed informed consent		×					
Medical history	×						
Merger disease	×						
Randomization		×					
Intervention			×	×			
Primary outcomes							
PSQI	×		×	×	×	×	×
Secondary outcomes							

Actigraphy	×		×	×		
HAMD	×		×	×	×	×	×
SAS	×		×	×		
TESS			×	×	×	×	×
Drug dose record	×		×	×	×	×	×
Patients' compliance			×	×	×	×	×

PSQI: Pittsburgh Sleep Quality Index;

SAS: Self-Rating Anxiety Scale;

HAMD: Hamilton Rating Scale for Depression;

TESS: Treatment Emergent Symptom Scale

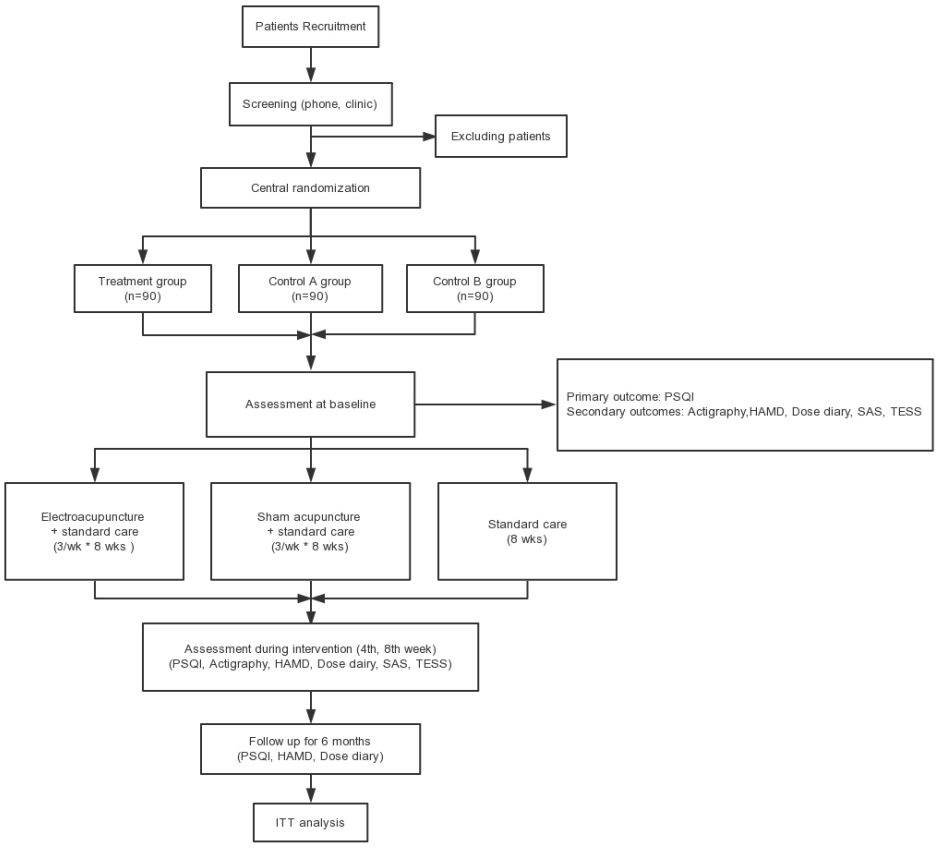
Table 2 Acupuncture method for each acupoint

Acupoint	Needling method
Baihui (GV20), Shenting (GV24)	The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anterior-posterior midline, and then insert the needle for about 1cm.
Yintang (GV29)	Pinch the local skin, and then puncture obliquely for about 1cm.
Anmian (EX-HN22)	The angle between the needle tip and the scalp is 30°. Puncture perpendicularly for about 1cm.
Shenmen (HT7), Sanyinjiao (SP6), Neiguan (PC6)	Puncture perpendicularly for about 1cm.

Figure legends

Figure 1: Flowchart of the study

Figure 2: Streitberger Placebo needle (asia-med GmbH&Co.KG)



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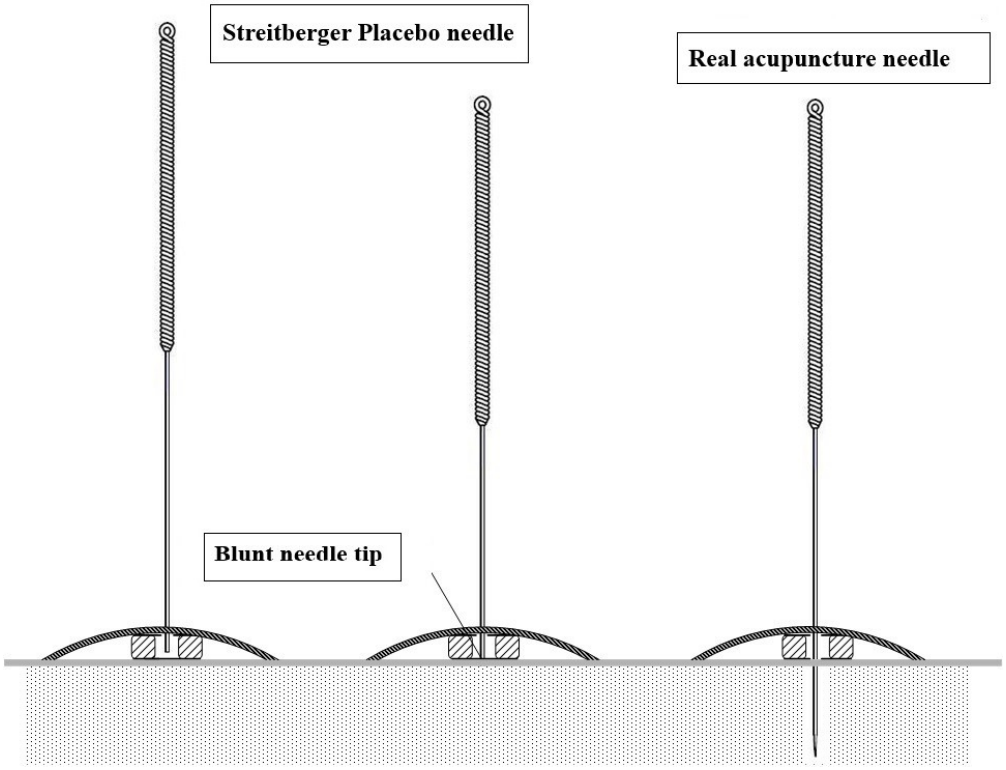

81x62mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, figure1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9,13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	YES
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NO

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.