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Acupuncture for Insomnia in Patients with Breast Cancer: A Single- Center, Single-Blind, Randomized, Controlled Trial Protocol

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ABSTRACT

Background and Purpose: Patients with breast cancer have a higher insomnia prevalence than those with other cancers. Acupuncture has fewer side effects than sleep medication and is a good option for patients with breast cancer experiencing insomnia. However, no established principle or guideline exists for patients with breast cancer who use multiple medicines. This study aims to describe a protocol for an 8-week acupuncture intervention to explore the efficacy and safety of acupuncture therapy using the "regulating spirit and soothing liver" method for treating insomnia patients with breast cancer.

Materials and methods: This study is a single-center, single-blind, randomized, controlled trial. We aim to recruit 70 females, aged 18-60 years, who will be randomly allocated to the intervention (acupuncture) or control (sham acupuncture) groups. The intervention will include an 8- week acupuncture therapy and a 3-month follow-up. The primary outcome is the Pittsburgh Sleep Scale (PSQI) total score measured every two weeks. Secondary outcomes include the Generalized Anxiety Disorder (GAD-7) and Patient Health Questionnaire (PHQ9) to assess emotional health and quality of life. We will record the names and dosages of drugs administered for severe insomnia and measure serum 5- hydroxytryptamine(5-HT) concentrations at baseline and 4 and 8 weeks. We will also assess adverse events in details and conduct intention-to-treat analyses using a global statistical test

Conclusion: The study will provide important results to help determine whether acupuncture can become a novel therapy for insomnia in patients with breast cancer.

INTRODUCTION

Insomnia affects patients with cancer more severely than the general population Howell et al. (2014), Savard et al. (2011), Palesh et al. (2010), Johnson et al. (2016), and patients with breast cancer exhibit a higher prevalence of insomnia than other types of cancer (42–69%) Savard et al. (2011). Patients with breast cancer experience insomnia for many reasons, including discomfort, pain, hot flashes, endocrine therapy, other hormonal changes associated with breast cancer treatment, and fear of recurrence Howell et al. (2014), Desai et al. (2013), Hatcher et al. (2020), Hall et al. (2019), Berrett-Abebe et al. (2015), Van Onselen et al. (2013). Consequently, insomnia not only contributes to a poor quality of life but also influences the therapeutic effect of treatment, increasing cancer mortality Innominato et al. (2015). Although an increasing number of studies have explored various approaches for treating insomnia in patients with breast cancer, such as cognitive behavioral therapy Zeichner et al. (2017), yoga Wang et al. (2020), and drugs, they still have a low rate of routine clinical recognition and intervention Zhou et al (2017), Kwak et al. (2020). Therefore, it is imperative to pay more attention to insomnia in patients with breast cancer and establish treatment standards.

The effect of acupuncture on insomnia in the general population has been widely studied for decades Cheuk et al. (2012), Kim et al. (2021), Pei et al. (2019), Montakab et al. (1999). and researchers have attempted to reveal the underlying mechanisms of its action Li et al. (2023), Wang et al. (2023), Wang et al. (2022), Yu et al. (2022). Meanwhile, the effect of acupuncture on cancer-related insomnia is also gradually becoming recognized Zhang et al. (2022). Furthermore, we hypothesize that acupuncture will be useful in the treatment of breast cancer-related insomnia, and we expect that related data and evidence

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will support this assertion. Many patients with breast cancer regularly use different kinds of anticancer drugs, such as endocrine drugs, targeted drugs, and chemotherapy. Therefore, taking sleep medicine may bring additional side effects because of interactions between drugs. Acupuncture is a physical therapy Yang et al. (2013). with acupuncture needle insertion at acupoints, which has fewer side effects and avoids interaction with anticancer drugs. Therefore, it is a good choice for patients with insomnia who also have breast cancer.

Published clinical randomized controlled trials of acupuncture for insomnia in patients with breast cancer are rare. This single-center, single-blind, randomized, controlled trial was designed to investigate the efficacy and safety of "regulating spirit and soothing liver therapy" for insomnia in patients with breast cancer

MATERIALS AND METHODS

Study design

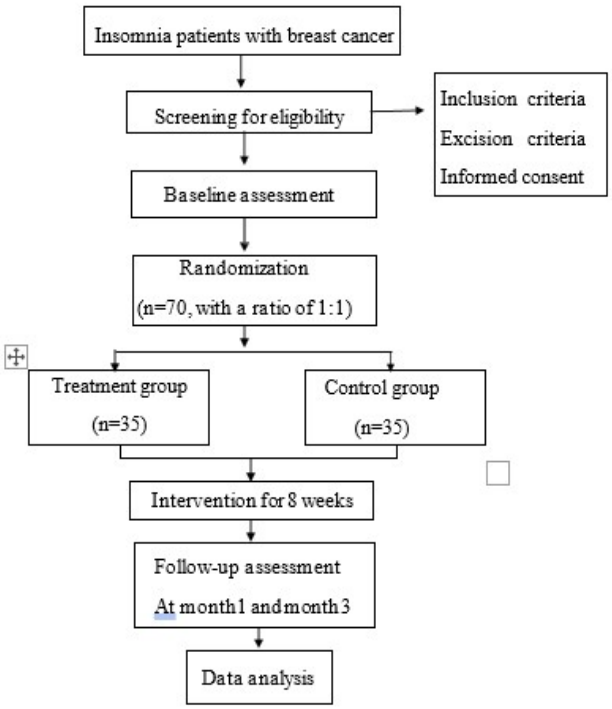
This is a single-center, single-blind, randomized, controlled trial in which 70 patients with breast cancer who are experiencing insomnia will be randomly assigned in a 1:1 ratio to the acupuncture treatment group or sham acupuncture control group. The treatment course lasts for 8 weeks, and the follow-up period is 3 months. The trial recruitment started on March 1, 2023, and will end by December 31, 2024. This study follows the CONSORT statement, STRICTA statement, and SPIRIT statement. The detailed schedule and process are presented in Table 1 and Figure 1, respectively.

Table 1: Schedule of enrolment, interventions, and assessments

		Treatment				Follow-up	
	Baseline	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Month 1**	**Month 3**
Enrolment							
Screening	√						
Signed informed consent	√						
Randomization	√						
Allocation concealment	√						
Intervention							
Acupuncture group	←	—	—	→			
Sham acupuncture group	←	—	—	→			
Assessments							
Primary outcome							
PSQI	√	√	√	√	√	√	√
Secondary outcomes							
GAD-7	√		√		√	√	√
PHQ-9	√		√		√	√	√
Serum and plasma 5-HT	√		√		√		
Other outcomes							
Temporary sleeping medication record	←	—	—	—	—	—	→
Adverse event	←	—	—	—	—	—	→

PSQI, Pittsburgh sleep Scale; GAD-7, Generalized Anxiety Disorder; PHQ-9, Patient Health Questionnaire.

Figure 1: The flow diagram of the trial



Patient resource

In this trial, most patients will be from the Oncology Department and Psychosomatic Medicine Department of our hospital. Patients with breast cancer who have insomnia will be recruited through posters, doctors' recommendations, and advertisements on WeChat. Researchers will screen eligible participants based on their insomnia history, symptoms, and Pittsburgh Sleep Quality Index (PSQI) results. The acupuncture intervention will be free after recruitment, and written informed consent will be obtained from each eligible patient before randomization.

Inclusion criteria

Participants who meet all the following requirements will be considered for inclusion:

1. Aged between 18 and 60 years. 2.Female. 3. Confirmed diagnosis of breast cancer and meeting the diagnostic criteria for insomnia in DSM-V Sateia et al. (2014), Cotton et al. (2023). 4. PSQI score ≥10. 5. Individuals who can answer and complete the questionnaire smoothly without experiencing language or mental disorders. 6. Volunteered to participate in this study and signed an informed consent form. 7. Having a correct understanding of acupuncture trials and good compliance with the intervention and evaluation phases of the study.

Exclusion criteria

The exclusion criteria include the following:

1. Severe diseases of the nervous, cardiovascular, urinary, digestive, and metabolic systems.
2. Lactating women, pregnant women, or women who are planning to be pregnant within 6 months. 3. Alcoholics and/or psychoactive drug users. 4. Fear of acupuncture or inability to receive acupuncture. 5. Individuals who have regularly taken medication or other interventions to sleep for over 3 months. 6. Surgery is scheduled within 1 month.

Randomization and allocation concealment

An independent researcher will generate a randomization sequence for each patient using SAS, V.9.4 (SAS Institute). Next, opaque sealed envelopes, with the participant's enrollment order printed outside and the randomly assigned group printed inside, will be used for allocation concealment. Researchers will enroll eligible participants after screening and then assign envelopes in enrolment order. The patients will open the envelope and be assigned to a random group. The entire process will be blinded. In contrast, blinding the acupuncturists is not possible owing to the nature of the acupuncture intervention. However, they will be trained to avoid communicating with the participants or outcome assessors regarding the treatment procedures. Furthermore, the outcome assessors and personnel involved in data collection and analysis will be blinded to the participants' group allocation throughout the trial. Patients are prohibited from communicating with each other; if enrolled patients need to seek medical care for various reasons during the treatment process and acupuncture is needed, blinding will be removed.

Intervention

All the acupoints follow the World Health Organization standards et al. (2008). "Regulating Spirit Acupuncture" includes DU20, EX-HN1, DU24, BG13, HT7, PC6, and SP6. Based on that selection, we also added LR3 (liver meridian), GB34 (gallbladder meridian), SP10 (spleen meridian), and ST36 (stomach meridian). Before acupuncture, we will paste customized foam pads Feng et al. (2022) with a diameter of 1 cm on all acupoints except GV20 and EX- HN1 because pasting foam pads firmly in those regions is difficult because of the presence of hair. The acupoints, needles, and manipulations that will be used in the treatment and control groups are shown in Table 2 and Figure 2.

Each acupoint will be retained for 30 min. All needles will be manually manipulated using rotation methods to produce a characteristic sensation known as De Qi (feeling of needle sensation that refers to the tenseness around the needle felt by the practitioner and numbness, distension, soreness, and heaviness around the point felt by the participant).

Acupuncture or sham acupuncture will be performed by licensed acupuncturists with at least 3 years of

treatment experience. All participants will receive acupuncture treatment for 8 weeks, with a frequency of three times per week. Each session (both acupuncture and sham acupuncture) will last for 30 min. Sterilized disposable needles (Huacheng Needles, Beijing, China) will be used for the acupuncture. Needles with 40 mm in length and 0.3 mm in diameter will be used for limb points, and needles with 25 mm in length and 0.3 mm in diameter will be used for points on the head, below the wrist, and ankle. Patients will be allowed to maintain the original treatment, which can be combined with targeted therapy, endocrine therapy, radiotherapy, chemotherapy, immunotherapy, and other Western anti-tumor treatments.

Patients can take temporary sleep medications when insomnia is severe; however, they must record the name, type, frequency, and dose of the medication.

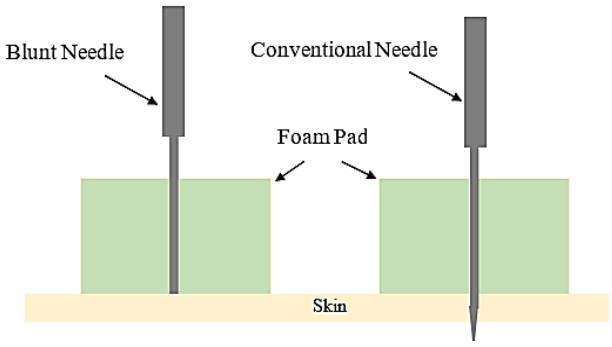
Sham acupuncture group

Before acupuncture, we will paste customized foam pads (Foshan Nanhai District Wangda Wang Adhesive Tape Trading Firm) with a diameter of 1 cm on all acupoints except GV20 and EX-HN1. Each acupoint is used in neutral supplementation and draining methods and will be retained for 30 min. The acupoints, needles, and manipulations that will be used in the treatment and control groups are shown in Table 2 and Figure 2.

Table 2: Acupoints, needles, and manipulations in the treatment and control groups.

Acupoint	Meridian	Treatment Acupuncture				Sham Acupuncture			
		Acupoint choice	Foam pad	Needle	Manipulation	Acupoint choice	Foam pad	Needle	Manipulation
DU20	governor meridian	√	×	Conventional needle, L:25 mm, D: 0.3 mm	15°, 8 -15 mm	×	×	Blunt needle L:25 mm, D: 0.3 mm	None
EX-HN1	extra nerve points	√	×	Conventional needle, L:25 mm, D: 0.3 mm	15°, 8 -15 mm	×	×	Blunt needle L:25 mm, D: 0.3 mm	None
DU24	governor meridian	√	×	Conventional needle, L:25 mm, D: 0.3 mm	15°, 8 -15 mm	√	√	Blunt needle L:25 mm, D: 0.3 mm	None
BG13	gallbladder	√	×	Conventional	15°, 8 -15 mm	√	√	Blunt needle	None
	meridian			needle, L:25 mm, D: 0.3 mm				L:25 mm, D: 0.3 mm	
HT7	heart meridian	√	√	Conventional needle, L:25 mm, D: 0.3 mm	90°, 20 -30 mm	√	√	Blunt needle L:25 mm, D: 0.3 mm	90°
PC6	pericardial meridian	√	√	Conventional needle, L:25 mm, D: 0.3 mm	90°, 20 -30 mm	√	√	Blunt needle L:25 mm, D: 0.3 mm	90°
SP6	spleen meridian	√	√	Conventional needle, L:25 mm, D: 0.3 mm	90°, 25 -40 mm	√	√	Blunt needle L:40 mm, D: 0.3 mm	90°
LR3	liver meridian	√	√	Conventional needle.	90°, 25 -40 mm	√	√	Blunt needle L:25 mm, D: 0.3 mm	90°
				L:25 mm, D: 0.3 mm					
ST36	stomach meridian	√	√	Conventional needle, L:25 mm, D: 0.3 mm	90°, 25 -40 mm	√	√	Blunt needle L:40 mm, D: 0.3 mm	90°
SP10	spleen meridian	√	√	Conventional needle, L:25 mm, D: 0.3 mm	90°, 25 -40 mm	√	√	Blunt needle L:40 mm, D: 0.3 mm	90°
GB34	gallbladder meridian	√	√	Conventional needle, L:25 mm, D: 0.3 mm	90°, 25 -40 mm	√	√	Blunt needle L:40 mm, D: 0.3 mm	90°

Figure 2: The diagrammatic sketch of acupuncture in the treatment and control groups



Outcomes

Primary outcome measure

The primary outcome is the PSQI Buysse et al. (1989) score before and after the treatment course. The PSQI evaluates the sleep quality of patients using seven domains called component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. Component scores range from 0 (no difficulty) to 3 (severe difficulty) and produce a cumulative score ranging from 0 to 21. Scores > 10 indicate significant sleep disturbance. Data are obtained from patients filling out questionnaires at baseline (before treatment initiation); 2, 4, 6, and 8 weeks after the first acupuncture session; and 1 and 3 months after the last acupuncture session. This study will determine whether the intervention is effective based on the variation in PSQI scores before and after the intervention. Comparing the results of the intervention group and the sham acupuncture group will prove whether there is a significant difference ($p < 0.05$) in the results, indicating whether the intervention is effective.

Secondary outcome measures

Secondary outcome measures are assessed at baseline (before treatment initiation), 4 and 8 weeks after the first acupuncture session, and 1 and 3 months after the last acupuncture session, except for detection of serum 5-hydroxytryptamine (5-HT). 1. Anxiety levels will be measured using the Generalized Anxiety Disorder-7 (GAD-7) questionnaire Shevlin et al. (2022), Sawaya et al. (2016), which is a discrete variable. The GAD-7 has proven to be a practical self-measuring tool to monitor anxiety. The level of clinical anxiety will be indicated if the total points from the seven questions are equal to or greater than 10. This study will evaluate the degree of anxiety induced by the intervention by comparing the variation in GAD-7 before and after the intervention. 2. Depression level will be measured using the Patient Health Questionnaire-9 (PHQ9) Shevlin et al. (2022), Sawaya et al. (2016), which is a discrete variable. The PHQ9 questionnaire contains nine items based on the DSM-IV diagnostic criteria. It is a simple and effective scale for depressive disorders with good reliability and validity for the auxiliary diagnosis of depression and assessment of symptom severity. 3. Serum and plasma 5-HT concentrations will be measured using an enzyme-linked immunosorbent assay, which is a continuous variable. Blood will only be drawn at baseline and 4 and 8 weeks after the first acupuncture session to explore the potential mechanism of action. This outcome is an exploratory indicator by which we will preliminarily explore the mechanism of acupuncture for breast cancer-related insomnia. 5. Temporary sleep medication use is measured using the temporary sleep medication record form.

Other outcomes

Adverse events, including discomfort or bruising at the site of needle insertion, nausea, or feeling faint, will be measured using participant reporting throughout the 8-week acupuncture session. Researchers will identify any adverse events through patient self- reporting and monthly inquiries. All adverse events will be managed and recorded in time and categorized based on their relevance to the acupuncture treatment. If a severe adverse event occurs, researchers are instructed to report it to the principal investigator and the data and safety monitoring board within 24 h.

Sample size calculation

In a previous study Guo et al. (2017), the PSQI score after treatment was 9.5 ± 3.75 in the acupuncture group and 11.67 ± 3.58 days in the control group. Using the sample size calculation formula ($\alpha = 0.05$, $\beta = 0.2$) and allowing for a 10% withdrawal rate, we plan to include 70 participants, with 35 participants in each group.

$$n1=\frac{\left(1+\frac{1}{K}\right)\delta^2}{(\mu 2-\mu 1)^2} * \left(\mu_{\frac{\alpha}{2}} + \mu_{\beta}\right)^2$$

Statistical analysis

Statistical analyses will be performed based on the intention-to-treat principle with all randomly assigned patients included. Two-tailed p values of < 0.05 will be considered statistically significant for all analyses. Statisticians who are blinded to the allocation of patients will complete the analysis using SAS, V.9.4 (SAS Institute).

Data management

Trial data will be collected in a timely manner, uploaded, and input according to the indicator observation time node of the research plan to avoid supplementary records, record errors and omissions, arbitrary choices, and other operations affecting the quality of the clinical data, ensuring that there is no delay in collection, sorting, verification, or input. The database is established by Excel software.

Quality control

The proposed clinical trial passed scientific and ethical reviews. Before the trial, experts will be invited to conduct a scientific demonstration of the scheme, and the feasibility of the trial will be analyzed within the oncology department. Relevant professionals from the acupuncture, moxibustion department, and psychosomatic medicine departments will be invited to train the intervention operators in acupoint selection, acupuncture techniques, and sham acupuncture operations. The trial will be regularly monitored by researchers from our hospital. When collecting and counting patient data, the data will be checked by two or more people.

Data availability statement

All raw data will be preserved for at least 5 years after publication. The principal investigator will have access to the final trial dataset, and readers will be permitted to access the trial data by contacting the corresponding author. Patient information, including name, age, and telephone number, will remain anonymous.

Patient and public involvement

In this trial, we need patients to record their quality of sleep and the drugs that they take for serious insomnia. Apart from that, the design, conduction of the study, data collecting, and result reporting are all completed by the trial team. After the efficacy and safety verification, we will inform each patient of the group that they were involved in. If patients in the control group would like to receive acupuncture treatment, we will provide 4 weeks of treatment for free.

DISCUSSION

Patients with insomnia usually experience anxiety and depression, which are prevalent in patients with breast cancer. In this study, we aimed to improve sleep quality and emotional state. Therefore, in this trial, apart from assessing insomnia using the PSQI, we also set secondary outcomes such as the GAD-7 and PHQ9 to assess psychological health and quality of life. 5-HT is an essential neurotransmitter closely related to insomnia and depression. Because it is difficult to directly detect neurotransmitter concentrations, we will also set up a measurement of serum 5-HT in this study, which is a quantitative indicator of insomnia and may be used to explore the correlation between 5-HT and insomnia.

This single-center, single-blind, randomized, controlled trial aims to verify the efficacy and safety of acupuncture in patients with breast cancer who are experiencing insomnia. Patients with breast cancer seem more likely to experience insomnia, and insomnia may influence the curative effect of their breast cancer treatments. More importantly, the reduced quality of life due to insomnia is painful Kyle et al. (2010), Sarsour et al. (2011). Undoubtedly, more attention is needed regarding insomnia in patients with breast cancer; however, there is no established principle or guideline Zhou et al. (2017), Kwak et al. (2020) for patients with breast cancer who take multiple different medicines. Therefore, acupuncture may be useful as a less harmful intervention.

As part of traditional Chinese medicine, acupuncture is becoming increasingly recognized in different areas of the world Joo et al. (2017), Muller et al. (2023), Liao et al. (2023). Acupuncture can not only improve sleep quality Cheuk et al. (2012), Kim et al. (2021) but also help with breast cancer-related symptoms Zhang et al. (2022), making it reasonable to explore its efficacy for insomnia among patients with breast cancer. To compare the efficacy of acupuncture with a control group Feng et al. (2022), we will use a foam pad for the sham acupuncture group. Specifically, the acupuncture group uses conventional needles, while the control group uses blunt-headed needles that do not penetrate the skin but achieve good blinding in terms of appearance and physical sensation. The "Spirit-Regulating acupoints combination" was proposed by Mr. Zhou De'an, a famous acupuncturist who enjoys a high reputation nationwide in China Mao et al. (2023), Yang et al. (2019), Liu et al. (2015), Sha et al. (2013), Xia et al (2010), and many people with insomnia have benefited from it. In traditional Chinese medicine theory, deficiency syndrome is the fundamental cause of cancer occurrence, and the spleen and stomach are the foundation of life after birth. Therefore, it is undoubtedly necessary to take acupoints on the spleen and stomach meridians to tonify Qi and nourish the blood. The liver is a key viscus in women's physiology, and liver depression is another important potential cause of breast cancer in women, which is generally accepted by traditional Chinese medicine oncologists. As the liver and gallbladder meridians are patrolled around the breast, it is essential and beneficial to take acupoints on the liver and gallbladder meridians to relieve liver depression and regulate the liver and gallbladder meridians. Therefore, based on the "Spirit-Regulating acupoints combination," we added several acupoints from the spleen, stomach, liver, and gallbladder meridians and named this process "regulating spirit and soothing liver therapy" to treat breast cancer-related insomnia.

The designer of this study has also noticed that patients with breast cancer are not only prone to insomnia but also usually experience anxiety and depression. Insomnia is often intertwined with anxiety and depression. Therefore, in addition to evaluating sleep quality using PSQI, we will assess the severity of anxiety and depression using the PHQ9 and GAD7 to determine whether acupuncture can improve their psychological health. If acupuncture can simultaneously improve emotions at the same time as alleviating insomnia, it should be the preferred treatment choice for these patients. The mechanisms underlying acupuncture

treatment for insomnia mainly focus on regulating the levels of various neurotransmitters and hormones, which affect sympathetic nerve excitation, the hypothalamic–pituitary–adrenal axis activation, and other functions Irwin et al. (2015), Hoxtermann et al. (2021). Since 5-HT is an important neurotransmitter for insomnia as well as anxiety and depression, we also measure serum 5-HT in this study, which is a quantitative indicator of insomnia. Therefore, it can be used to explore the correlation between 5-HT and insomnia through clinical trials.

This study has several limitations. First, it is impossible to blind acupuncturists to the operational characteristics of acupuncture manipulation; thus, we will provide detailed training for acupuncturists on standardized communication with patients to minimize deviation. Second, a foam pad will be used as a control to improve the reliability of the results. However, because GV20 and EX-HN1 are covered by hair, the foam pad cannot be pasted on these points. Therefore, although we directly use needles in the treatment group, we choose a blank control instead of sham acupuncture in the control group at these points, which may increase the risk of breaking blinding. Third, the primary outcome of the PSQI is assessed based on patients' self-reports, as there is a lack of objective evaluation methods for insomnia. As one of the most common methods for measuring insomnia, the PSQI has good validity and reproducibility and is recommended by current guidelines Pilz et al. (2018). Fourth, this study is a small-sample study in a single center. Consequently, the result may provide a reference point but still needs further verification.

DECLARATIONS

Ethics approval and informed consent

The Institutional Ethics Committee of the Beijing Hospital of Traditional Chinese Medicine, Capital Medical University (2022BL02-059-02) approved this trial. Enrolled patients will provide written informed consent for participation.

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Disclosure

The authors report no conflicts of interest in this work.

Authors' contributions

Tingting Ma, Xiaomin Wang and Linpeng Wang designed the trial and will oversee the overall conduct of the study. Wei Lu, Mingwei Yu, Qing Zhang, Yongmei Xu suggested the study design and interventions. Tingting Ma and Ganlin Zhang drafted the manuscript language. Yi Zhang advised on the statistical methods. Bingcong Zhao collected the diagnostic criteria and evaluation scale and will enroll eligible patients. All of the authors have viewed and approved the manuscript.

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