

# Jiao-tai-wan for insomnia symptoms caused by the disharmony of the heart and kidney: a study protocol for a randomized, double-blind, placebo-controlled trial

**Congcong Zeng**

Wenzhou Medical University First Affiliated Hospital

**Xi Liu**

Zhejiang Chinese Medical University Affiliated Wenzhou Hospital of Traditional Chinese Medicine

**Lufeng Hu**

Wenzhou Medical University First Affiliated Hospital

**Yuan Feng**

Wenzhou Medical University Second Affiliated Hospital

**Nengzhi Xia**

Wenzhou Medical University First Affiliated Hospital

**Haihuan Zeng**

Wenzhou Medical University First Affiliated Hospital

**Lin Luo**

China Academy of Chinese Medical Sciences

**Ren Ye**

Wenzhou Medical University First Affiliated Hospital

**zhengzhong Yuan** (✉ [wzyzz2008@126.com](mailto:wzyzz2008@126.com))

Wenzhou Medical University First Affiliated Hospital <https://orcid.org/0000-0002-7748-5312>

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## Study protocol

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# Abstract

**Background** Insomnia seriously affects people's normal lives and work. However, effective treatment strategies are scarce. The purpose of this study is to explore the efficacy and safety of Jiao-tai-wan (JTW) for ameliorating insomnia symptoms caused by disharmony of the heart and kidney. **Design** This is a randomized, double-blind, placebo-controlled pilot clinical trial. One hundred twenty-eight participants suffering from insomnia symptoms will randomly assigned to the JTW or placebo group in an equal ratio. The participants will be asked to take JTW or placebo granules twice a day for 1 week. All data will be gathered at baseline and at the end of the drug intervention after random allocation. The primary outcome measures will be the mean change in the Pittsburgh sleep quality index (PSQI) from baseline to the end of the drug intervention. Secondary outcome measures will include the altered sleep parameters in polysomnography, 1H-magnetic resonance spectroscopy (1H-MRS) evaluation, the Disharmony of Heart and Kidney Scoring System score and blood tests, including the levels of serum adenosine and melatonin. A laboratory test will be taken before and after treatment to assess the safety of JTW.

**Discussion** The outcomes of this study will confirm the efficacy of JTW for the treatment of insomnia symptoms and will also be used to monitor the safety of JTW.

## Background

Sleep is essential to human health, but unfortunately, nearly one-third to one-quarter of the population in developed countries suffers from insomnia at some level[1,2]. With the increasing incidence of insomnia, there are different degrees of depression, anxiety and other psychological diseases, which seriously affect the quality of a person's daily life[3]. Psychological and behavioral therapy, Western medicinal therapy and traditional medicinal therapy are the main treatments for insomnia[4]. Many clinical studies have supported the first two treatments; however, some risks of adverse reactions and tolerance have been reported. Also, dependence and addiction seriously impact clinical efficacy. For instance, the long-term use of zolpidem, which is relatively safe and frequently prescribed for the treatment of transient insomnia, will increase the risk of dementia[5]. Thus, interest in using traditional medicinal therapies is increasing, especially in traditional herbal medicine[6]. The superiority and soul of traditional East Asian medicine is the system called 'pattern identification', which is used to diagnose and treat diseases based on the symptoms and the signs observed in patients. According to this system, insomnia has many different patterns, but disharmony of the heart and kidney is the dominant pattern[7,8]. Moreover, Jiao-tai-wan(JTW) has been commonly used for the management of insomnia with a disharmony of heart and kidney pattern for centuries in China, Korea and Japan[9]. In a review article from Yeung W[10], JTW was listed as one of the 10 most frequently examined standardized traditional herbal formulas for insomnia. A clinical study conducted in China showed that administration of JTW for 60 consecutive days could improve the Pittsburgh sleep quality index (PSQI)[11]. Lu[12] reported a significant decrease in scores in the Disharmony of Heart and Kidney Scoring System. Another study[13] demonstrated the effects of JTW in detail by alleviating the symptoms of palpitation and dizziness caused by the disharmony of the heart and kidney. Although recent clinical studies have shown the efficacy of JTW in the treatment of insomnia,

a randomized, double-blind, placebo-controlled pilot clinical trial to confirm its efficacy has not yet been undertaken. We set up this study to better clarify the efficacy, safety, and feasibility of JTW for treating insomnia caused by disharmony of the heart and kidney and to provide data for evidence-based clinical practice.

## Methods

### Study design

This study is a randomized, double-blind, placebo-controlled pilot clinical trial. Eligible participants will be randomly assigned to either the JTW or placebo group in an equal proportion. The drug intervention will last for 1 week. Fig. 1 briefly shows the study flow chart, and Fig. 2 enumerates the treatment schedule and outcome measures. The study adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2013) checklist [14] (additional file 1).

### Participants

#### *Study population*

Patients suffering from insomnia symptoms caused by the disharmony of the heart and kidney will be recruited from the Traditional Chinese

Medicine Department and Sleep Centre of the First Affiliated Hospital of Wenzhou Medical University in Wenzhou, Zhejiang Province, China.

#### *Inclusion criteria*

1. Participants are 18-60 years of age, either male or female, and with a level of education above junior high school.
2. Insomnia is almost the only symptom, including difficulty sleeping, deep sleep, dreaminess, early-morning awakening, trouble going back to sleep, feeling tired after waking up, or daytime sleepiness (excluding secondary insomnia).
3. A Pittsburgh sleep quality index score of 7 or higher according to the Chinese Classification and Diagnostic Criteria of Mental Disorders-3 Version, CCMD-3[15].
4. A Disharmony of Heart and Kidney Scoring System score of 9 or higher.
5. Signed the informed consent before treatment.

#### *Exclusion criteria*

1. Insomnia caused by physical diseases or lifestyle changes or environmental disturbances.
2. Affective disorders, anxiety disorder, depression, schizophrenia and any other serious mental disorders.

3. Suffering from somatic diseases that affect the central nervous system
4. Serious heart, liver, kidney and hematopoietic system diseases, abnormal liver and kidney function.
5. Regular use of antipsychotic drugs in the last month.
6. Use of medicine to treatment sleeping disorders in the past week.
7. Allergic to a certain ingredient of the drug involved in this trial or suffering from allergies.
8. Alcohol abuse or (and) psychotropic drug addiction.
9. Pregnancy or lactation.

### **Randomization and allocation concealment**

A medical statistics professional will generate random sequences using the software R. The sequences will be concealed to all investigators and eligible participants. One hundred twenty-eight participants will be assigned to one of two groups by blocked randomization. Furthermore, allocation concealment will be maintained throughout the entire study.

### **Blinding**

This study will use a double-blind method. The placebos will be packaged identically as the study drugs in appearance, smell and colour. Then, the study coordinator will assign JTW or placebo according to the randomization codes and place them in special containers. The participants, outcome assessors, study coordinators, data managers, and statisticians will be blinded to the group allocation and numbered drug containers throughout the entire study. At the end of the study, the blinding codes will be revealed.

### **Intervention**

These eligible participants will ingest 2 g granules of JTW or placebo, twice a day at 4 PM and 9 PM for 1 week and present themselves at the termination of medication, followed by a scheduled examination.

Both JTW and placebo are manufactured by the Kangren Pharmaceutical Factory according to good manufacturing practice standards. JTW will be produced in the form of granules with a yellowish-brown color. The medication will be 2 g, containing 1.1 g JTW soft extract with 0.37 g of lactose hydrate and 0.88 g of corn starch as the excipient. The JTW soft extract will be made of a water extract of a mixture of two herbal medicines, as follows: Rhizome Coptidis (10 g) and Cortex Cinnamomi (1 g). The placebo will consist of corn starch, lactose hydrate, citric acid, and caramel color. The placebo and JTW will have the same appearance, smell and color.

### **Medication compliance monitoring**

To ensure compliance with the medication, participants will be asked to count the actual intake, and return the empty wrapping papers for the medication and any remaining medicine.

### **Prohibition and permission for concomitant treatment**

1. The use of any sedative hypnotics to help sleep will be prohibited during the study.
2. The use of any traditional medicine designed to treat insomnia, except for the intervention of this trial, will be prohibited during the study.
3. The use of functional foods or other medications intended to improve the symptoms of insomnia will be prohibited during the study.
4. Any psychotherapy for accelerating sleep quality will be prohibited during the study.
5. Medications used to treat other chronic diseases at the beginning of this trial will be allowed.
6. Routine physical training prior to the start of this clinical trial will be allowed.
7. Any change in medications or physical exercise during the study will be recorded in a clinical report form.

## **Outcome measurement**

### ***Pittsburgh sleep quality index (PSQI)***

The Pittsburgh Sleep Quality Index will be used at the baseline and the end of the drug intervention. The PSQI version used in this study is a 19-item self-reported retrospective questionnaire to assess the quality of sleep in the past 7 days, and it is designed to measure 7 domains called component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction [16,17]. Component scores range from 0 (no difficulty) to 3 points (severe difficulty), and when summed, produce a global score ranging from 0 to 21. A higher score denotes worse sleep. These syndromes are categorized as mild (0-1), moderate (2-7), or severe (8 or more) [18]. Then, the scores the participants obtained at baseline will be recorded as score 0, and the scores obtained at the end of drug intervention will be recorded as score 1. The recorder will calculate the reduction rate (RR) according to the following formula:  $RR = (\text{score 1} - \text{score 0}) / \text{score 0} * 100\%$ . Finally, we will assess the clinical curative effect based on the results of the RR. RR values greater than 75% will be regarded as a **clinical cure**, RR values between 50%-75% will be considered clinically effective, RR values between 25%-50% will be recognized as a clinical success and RR values less than 25% will be considered ineffective. Therefore, the mean change of the PSQI score from the baseline to the end of intervention and the RR will be the primary outcome measures of this study.

In addition, Xiancheng Liu et al. [17] presented their opinion that the Pittsburgh Sleep Quality Index is suitable for Chinese patients after they conducted reliability and validity tests.

### ***Polysomnography***

Polysomnography (PSG) will be taken twice both at the baseline and the end of drug intervention. On the first night, participants will adapt themselves to the laboratory environment. On the second night, participants will be placed on polysomnography monitoring to record the multiple physiological sleep parameters. The parameters [19,20] will include total sleep time, sleep efficiency, sleep latency, REM stage latency, wake after sleep onset and the time duration of the particular sleep stages (such as N1, N2, N3).

The mean changes of all the parameters from the baseline to the end of drug intervention will be used to measure the changes in sleep quality.

PSG is considered the gold standard for scoring sleep disorders. The scoring of sleep and arousals relies on visual inspection of continuous surface electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG) during PSG and then divides human sleep into 5 stages: wakefulness(W), rapid eye movement(REM), nonrapid eye movement (NREM), including N1, N2 and N3[21]. The American Academy of Sleep Medicine (AASM) defined the quantitative reference standard in PSG for adult insomnia as follows[22]: sleep latency  $\geq 30$ min; total sleep time  $< 390$  min; number of wake after sleep onset (WASO)  $\geq 2$  or time of WASO  $\geq 40$  min; time in N1/total sleep time  $> 60\%$ ; time in N2 / total sleep time  $> 60\%$  or time in N3/total sleep time  $< 10\%$ , or time in REM / total sleep time  $< 20\%$ . A higher or lower score corresponds to more severe symptoms.

### *<sup>1</sup>H-magnetic resonance spectroscopy(<sup>1</sup>H-MRS)*

<sup>1</sup>H-magnetic resonance spectroscopy (<sup>1</sup>H-MRS) will also be taken at the baseline and the end of drug intervention. <sup>1</sup>H-MRS, with its unique noninvasive advantages, is able to detect and quantify the important metabolites of living brain tissue, including N-acetylaspartate(NAA),

choline(Cho), creatine(Cr), gamma-aminobutyric acid (GABA) and myo-inositol (mi)[23]. In this study, single voxel hippocampus and thalamus metabolite ratios of GABA with Cr will be measured. The altered ratios of GABA with Cr between baseline and the end of drug intervention will be the second outcome measure.

Studies have revealed that the GABA/Cr ratio in the frontal lobe is significantly lower[24], and the average brain GABA levels are nearly 30% lower in patients with primary insomnia[25].

### ***Disharmony of Heart and Kidney Scoring System***

The Disharmony of Heart and Kidney Scoring System will be used

at the baseline and the end of drug intervention. It is a checklist covering 1 indispensable and 7 accompanying items. These items are the symptoms and signs of the disharmony of heart and kidney pattern according to the theory of the pattern identification system in traditional East Asia medicine. The score of the indispensable item uses a four-point scale (0, 3, 6 and 9) depending on the severity of the insomnia (0=none, 9=very severe); the 7 accompanying items including palpitations, dizziness, spermatorrhea or menstrual

irregularity, and night sweat and use 0-4-point scale based on their frequency. A total score of more than 9 out of 30 points is thought to demonstrate disharmony of the heart and kidney[26,27].

Although there is no accurate evidence to explain the validity and reliability of this questionnaire, no other methods are currently available to identify the disharmony of heart and kidney pattern.

## ***Blood tests***

The levels of adenosine (AD) and melatonin (N-acetyl-5-methoxytryptamine) in blood samples will be recorded at the baseline and the end of the drug intervention, will then be analyzed by the clinical lab.

Sleep homeostasis in adults is affected by the sleep-regulatory substances AD and melatonin[28,29]. AD is a product of brain metabolism, and is closely related to sleep parameters. A previous study[30] showed that AD levels were elevated as a consequence of sustained wakefulness. Melatonin is an endogenous hormone produced by the pineal gland and is released exclusively at night. Melatonin has been shown to synchronize the circadian rhythms, and improve the onset, duration and quality of sleep. Takaesu Y and his colleagues thought that reduced melatonin secretion may be involved in the mechanism of insomnia[31].

In this study, high-performance liquid chromatography (HPLC) will be developed to determine the levels of adenosine, and an enzyme-linked immunosorbent assay will be used to detect the concentration of melatonin.

## **Safety outcomes**

At the end of this trial, participants will participate in a routine

physical examination, including breath rate, heart rate, temperature, blood pressure, weight, routine urine test, routine blood test, liver, kidney function tests, and an electrocardiogram.

## **Adverse event reporting and treating**

During the treatment period, the researchers will record any adverse events (AEs) that will be defined as unpredictable, undesirable symptoms, signs or diseases related to the treatment during daily telephone calls. Then, the researchers will comprehensively evaluate the correlation between these adverse events and the experimental drugs according to the recorded details about AEs, including the manifestation, occurrence time, duration, cause and treatment measures. Simultaneously, if any AE occurs, the investigator will take proper measures such as dose adjustment, drug withdrawal and symptomatic treatment to ensure the safety of participants, and all details will be written down carefully. Furthermore, continuous follow-up will be insisted upon until the condition of the participants returns to normal.

## **Sample size**

The ratio of cases between the JTW group and the placebo group is set to 1:1, and this study is designed to achieve a statistical power of 85% (one-sided type-1 error of  $\alpha = 5\%$   $\beta = 10\%$ ). Based on previous clinical practice[32,33], we assume a treatment success rate of 40% in the placebo group and 70% in the JTW group over 7 days using the following formula:

where  $\Phi$  is the cumulative distribution function of the standard normal distribution. Considering a 20% drop-out rate, a sample size of  $N \approx 53 \times 1.2 \approx 64$  is needed for each group. Thus a total of 128 patients are needed in this study.

## Data management

The experimental data will be carefully saved in Microsoft Access, which is a database management system (DBMS) from Microsoft. To guarantee the data quality, data will be input and checked twice by two researchers along with regular monitoring.

## Statistical analysis

R is used for statistical analysis in this study by an independent statistician. The mean and standard deviation shall be applied to the continuous variables, and percentages to the categorical variables. For comparison of two independent samples, the  $t$  test and analysis of variance will be applied for continuous variables and the chi-square test will be applied for categorical variables. In addition, the rank sum test has the best efficiency among

nonparametric tests, and is frequently used. Then  $p < 0.05$  is considered statistically significant.

## Discussion

JTW, first appearing in an old classical text of ancient Chinese medicine[34], is a well-known tranquilizing formula to treat insomnia due to disharmony of the heart and kidney[35]. As mentioned, modern scientific studies have shown that JTW may be helpful for people suffering from insomnia[10-13], but to the best of our knowledge, this is the first RCT that will determine the efficacy and safety of JTW in the therapy of insomnia symptoms, which is why we intend to perform this study.

However, this study has some limits. First, the study period is short, without long time follow-up times. Second, the pattern of insomnia in this study is relatively simple, with only the pattern of disharmony of the heart and kidney included. Lastly, a single-center sample study is less convincing than a multi-center sample study. Despite these limits, this study is reasonably well designed. The results of this study are expected to guide physicians or traditional medical doctors at clinics more clearly in prescribing JTW, and to widely spread the use of traditional medicine in other countries.

## Trial Status

Protocol vision date and number: January 28, 2016; vision 1.

Patient recruitment began in September 2018 and it will be completed by December 2020.

## Abbreviations

JTW: Jiao-tai-wan; RCT: Randomized controlled trial;

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; CCMD-3: Chinese Classification and Diagnostic Criteria of Mental Disorder-3 Version; AASM: American Academy of Sleep Medicine; PSQI: Pittsburgh sleep quality index; PSG: Polysomnography;

<sup>1</sup>H-MRS:<sup>1</sup>H-magnetic resonance spectroscopy;

EEG: electroencephalography; EMG: electromyography;

EOG: electrooculography; W: wakefulness; REM: rapid eye movement; NREM: nonrapid eye movement; WASO: wake after sleep onset;

NAA:N-acetylaspartate; Cho: choline; Cr: creatinine; GABA: gamma-aminobutyric acid; ml: Myo-inositol; RR: Reducing rate; AD: adenosine; HPLC: high performance liquid chromatography; AE:Adverse event.

## **Declarations**

### **Ethics approval and consent to participate**

The study has been approved by the Ethical Research Committees of the First Affiliated Hospital of Wenzhou Medical University (2016045). Written informed consent will be obtained from all participants by the investigator.

### **Consent for publication**

Not Applicable.

### **Availability of data and materials**

The datasets used or analyzed during the current study will be available from the corresponding author upon reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

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### **Authors' contributions**

YZZ and YR were responsible for the conception and design of the study, and for a critical revision and final approval of the manuscript. ZCC and LX were responsible for the concept and design of the study

and writing and final approval of the manuscript. HLF was responsible for blood tests and critical revision and final approval of the manuscript. FY was responsible for data collection. XNZ was responsible for the magnetic resonance spectroscopy. ZHH was responsible for the polysomnography and sleep data collection. LL was responsible for data management and analysis. All authors read and approved the final manuscript.

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Not applicable

## Authors' information

<sup>a</sup> Department of Traditional Chinese Medicine, The First Affiliated Hospital of Wenzhou Medical University, Nanbaixiang, Ouhai District, 325035, Wenzhou, Zhejiang, China. <sup>b</sup> Department of Nephrology, Wenzhou Hospital of Traditional Chinese Medicine, Liuhongqiao Road, Ouhai District, 325035, Wenzhou, Zhejiang, China. <sup>c</sup> Department of Pharm, The First Affiliated Hospital of Wenzhou Medical University. <sup>d</sup> The 2<sup>nd</sup> Clinical College of Wenzhou Medical University, Chashan Higher Education Park, 325035, Wenzhou,

Zhejiang, China. <sup>e</sup> X-ray Department, The First Affiliated Hospital of Wenzhou Medical University. <sup>f</sup> Sleep monitoring center, The First Affiliated Hospital of Wenzhou Medical University. <sup>g</sup> Research Institute of China Academy of Chinese Medical Sciences, No.16 Nanxiao Street, Dongzhimen, Dongcheng District, 100700, Beijing, China.

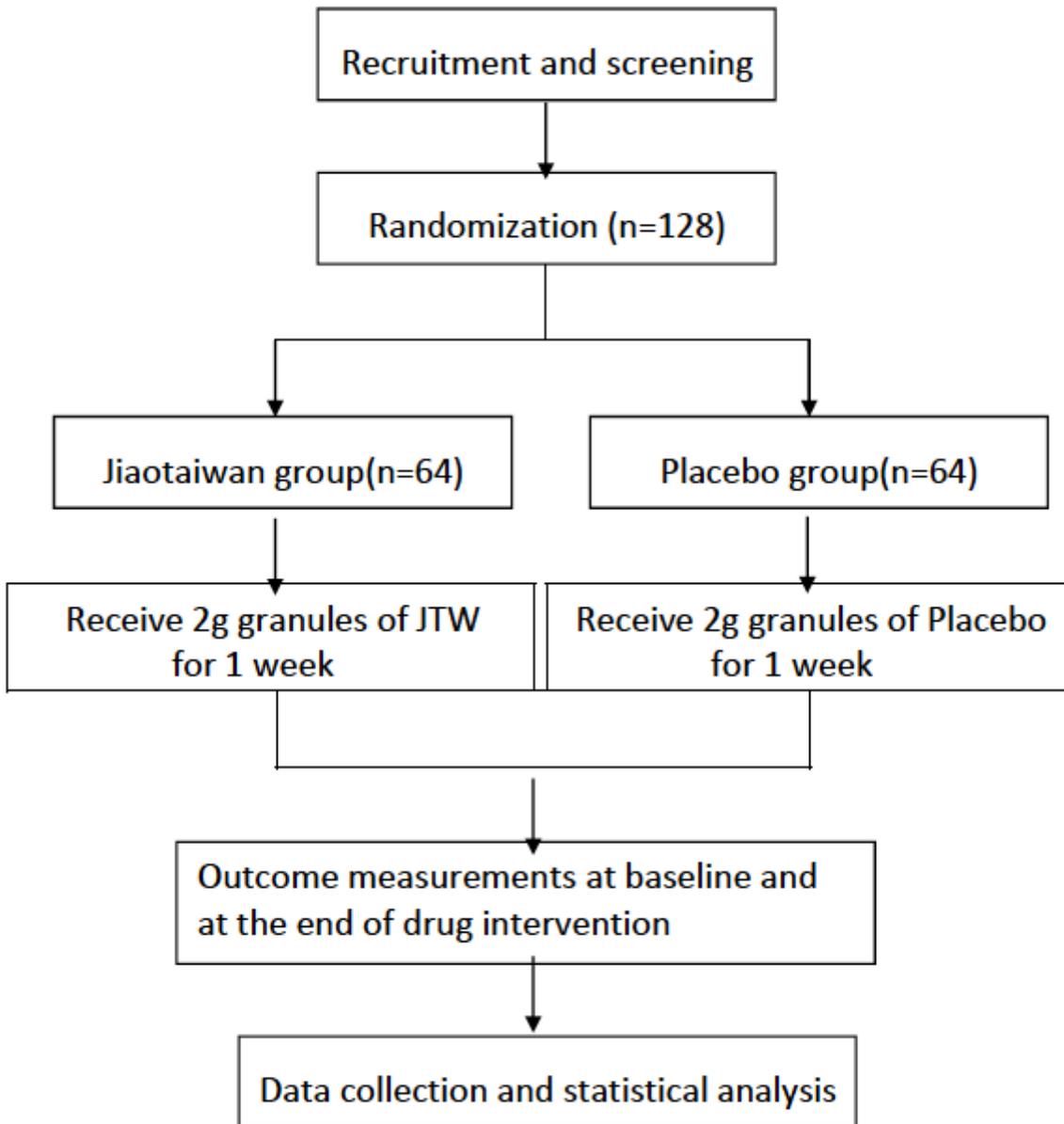
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## Figures



**Figure 1**

Flow chart of the study design.

	Baseline		7-day Intervention							Assess	
Time point	DAY -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 1	Day 2
<b>Enrollment</b>											
Eligibility screen	×										
Informed consent	×										
Allocation		×									
<b>Intervention</b>											
Treatment group			×	×	×	×	×	×	×		
Placebo group			×	×	×	×	×	×	×		
<b>Assessments</b>											
Socio-demographics	×										
Medical history	×										
Physical examination <sup>a</sup>	×										×
Concomitant treatment			×	×	×	×	×	×	×		
PSQI <sup>b</sup>	×									×	
Polysomnography	×	×								×	×
<sup>1</sup> H-MRS <sup>c</sup>	×									×	
DHKSS <sup>d</sup>	×									×	
Blood tests <sup>e</sup>		×									×
Medication adherence			×	×	×	×	×	×	×		
Adverse events			×	×	×	×	×	×	×	×	×
Blinding test											×

Abbreviations. PSQI: Pittsburgh Sleep Quality Index; <sup>1</sup>H-MRS: 1H-magnetic resonance spectroscopy; DHKSS: Disharmony of Heart and Kidney Scoring System.

Physical examination<sup>a</sup>: breath rate, heart rate, temperature, blood pressure, weight, routine urine, routine blood test, liver, kidney function tests, and electrocardiogram.

Blood tests: The levels of adenosine (AD) and melatonin (N-acetyl-5-methoxytryptamine).

## Figure 2

SPRIT schedule for enrollment, treatment and assessments.

## Supplementary Files

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