

Safety and Efficacy of Jiaotai Wan in Patients with Depression: Study Protocol for a Randomized Controlled Trial

Chunquan Yu (✉ yuchuanquantj@126.com)

Tianjin University of Traditional Chinese Medicine <https://orcid.org/0000-0002-7814-1909>

Zhihuan Zhou

Tianjin University of Traditional Chinese Medicine

Shufei Fu

Tianjin University of Traditional Chinese Medicine

Yuhan Wang

Tianjin Hospital of ITCWM Nankai Hospital

Yi Tong

First Teaching Hospital of Tianjin University of Traditional Chinese Medicine

Yijia Liu

Tianjin University of Traditional Chinese Medicine

Huaien Bu

Tianjin University of Traditional Chinese Medicine

Yan Mei

Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital

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Abstract

Background: Depression is a common affective disorder characterised by marked and lasting melancholia, with corresponding thought and behaviour changes. Due to an accelerated pace of life and increased work pressure, the incidence of depression has risen sharply, causing great harm to family and social life. Jiaotai Wan (JTW) is a Chinese herbal formula that is commonly prescribed for depression and insomnia in clinical treatment, and exhibits antidepressant effects as shown in animal experimental research. However, there are no standard clinical trials to confirm its efficacy in treating depression and insomnia. Therefore, this study aims to assess the efficacy and safety of JTW in the treatment of depression.

Methods: A randomized, multicentre clinical trial with parallel groups was designed in this study. A total of 40 patients with depression were included and randomly divided to either the treatment or the control group with a ratio of 1:1. The patients received JTW plus fluoxetine or fluoxetine alone once per day for eight weeks. The primary outcome was analysed using the Hamilton Depression Rating Scalescore for patients in the treatment group compared with that in the control group. The secondary outcomes included Traditional Chinese medicine syndrome integral scale scores, Wisconsin Card Sorting Test, blood metabolomics, urine metabolomics, and brain structure and function by functional magnetic resonance imaging.

Discussion: The results of this trial will find changes in brain structure, brain function, and metabolism in patients with depression, and provide critical evidence for JTW in the treatment of depression.

Background

Depression is a common mood disorder with high incidence rates of recurrence, disability and suicide[1]. The World Psychiatric Association survey has shown that current incidences of depression are 4.2% globally and 6.9% in China, respectively. Depression has now become a serious worldwide public health and social issue to affect patients' physical and mental health and reduce the quality of life. Moreover, depression can even lead to aggressive behaviours, and cause harm to individuals and families[2–5].

Traditional Chinese medicine (TCM), with outstanding treatment effect on the depression-related symptoms, has been extensively applied in China to treat the depression [6–7]. Traditional antidepressant western medicine including tricyclic compounds, monoamine oxidase inhibitors and selective 5-hydroxytryptamine reuptake inhibitors, etc. can effectively relieve depressive symptoms. However, many deficiencies exist such as long medication cycle, serious toxic and side effects, poor medication compliance, repeated disease delay, etc., which can greatly affect the prognosis and clinical application of the disease [8]. TCM also has therapeutic effects on depression-related symptoms For example, Xiaoyaosan [9] is used to soothe liver, relieve depression and invigorate spleen; Kai-xin-san[10] is applied to invigorate qi, nourish heart and tranquilize mind; Chaihu Shugan San [11], etc. A meta-analysis result has shown that [12] Chaihu-longgu-muli decoction or combination of antidepressants is superior to

antidepressants alone in the treatment of depression, which can significantly reduce the incidence of adverse reactions during medication. JTW comprises two TCM herbs, *Coptis chinensis* Franch and *Cinnamomum cassia* Presl, which are mainly used to treat depression and insomnia. Several experimental animal studies have demonstrated the effect of JTW on depression mouse models, but no standard clinical evidences can support those claims [13–16]. Therefore, in this study, a clinical study was designed to evaluate the efficacy and safety of JTW on patients diagnosed with depression.

Methods/design

Study design

This is a multicentre, randomized and controlled trial to evaluate the efficacy and safety of JTW in patients with depression. A flowchart for the study is shown in Fig 1. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is shown in Supplemental file 1.

Qualified patients were randomly divided into the treatment and control groups with a ratio of 1:1, respectively. Recruited patients received JTW plus fluoxetine or fluoxetine alone once per day for eight weeks. After the 8-week treatment period, the patients were then followed up for four weeks. The outcome measures included the Hamilton Depression (HAMD) Rating Scale scores, TCM syndrome integral scale scores, Wisconsin Card Sorting Test (WCST), blood metabonomics, urine metabonomics and brain structure and function on functional magnetic resonance imaging (fMRI).

Participants

Inclusion criteria

To participate in the study, patients should meet the following criteria:

- (1) Conform to depression diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders' American psychiatric diagnosis standard', 4th Edition (DSM-IV);
- (2) Conform to the diagnostic criteria of TCM syndrome of disharmony between the heart and kidney;
- (3) HAMD 24-item score of ≥ 20 points and < 35 points;
- (4) Age, 18–65 years;
- (5) Total HAMA score of ≤ 21 points, depressed mood (item 6) score ≥ 2 points and anxious mood (item 1) score < 3 points;
- (6) Those who have not taken antidepressants or have taken them but have stopped taking them for two weeks;

(7) Sign the informed consent form.

Exclusion criteria

Patients with the following criteria will be excluded:

- (1) Secondary to other mental or physical illness and depression with severe psychotic symptoms;
- (2) Severe anxiety (HAMA total score >21 points);
- (3) Allergic constitution or previous research on drug allergy;
- (4) Suicidal thoughts;
- (5) Bipolar disorder, refractory depression;
- (6) Intracranial cerebrovascular disease, neurodegenerative diseases, intracranial tumour, high blood pressure, or diabetes, leading to brain vascular distribution or abnormal blood flow of systemic disorders;
- (7) Serious diseases of other systems or severe heart, liver and renal insufficiency;
- (8) Glaucoma and epilepsy;
- (9) Pregnancy or lactation or quasi-pregnancy;
- (10) Positive urine pregnancy test in women of childbearing age;
- (11) Contraindications on MR inspection and those who cannot complete MR scan or cannot adapt to the environment and noise of the MRI machine;
- (12) Participation in or planning to participate in other observational drug studies within 30 days;
- (13) Poor compliance or inability to be interviewed regularly.

Withdrawal and discontinuation

During the trial, if they had any adverse reactions, the participants could stop the trial at any time. No strategy was adopted to improve adherence to the study drug. During the trial, the drugs related to depression were banned, while those not related to depression could be used. Patients with severe illnesses could withdraw the trial and take the appropriate treatment.

Ethics and recruitment

All patients signed the informed consent forms prior to inclusion, which included the research protocols, the benefits and risks, confidentiality, costs, and voluntary principles. The study has been approved by the

Ethics Committee of Tianjin University of Traditional Chinese Medicine. If the protocol requires modification, ethical approval will be reapplied. Any revisions in the study protocol will be submitted to the Ethics Committee and the National Natural Science Foundation of China.

Through advertisements and referrals, a total of 40 qualified patients were recruited from two research centres: the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine and the Tianjin Academy of Traditional Chinese Medicine Affiliated Hospital.

Sample size

In reference to the relevant literature, the specific process to estimate the sample content of each group was as follows[17–19]. The sample size estimation formula for clinical trials is written as

$$n = \frac{2\sigma^2}{(\mu_1 - \mu_2)^2} \times f(\alpha, \beta)$$

where n is the number of cases required for each group, μ_1 and μ_2 are the expected averages of the treatment and control groups, respectively, and σ_2 is the standard deviation of the control group, $\alpha = 0.05$, $\beta = 0.1$, the output $f(\alpha, \beta)$ of the look-up table is 10.5. Taking the score of HAMD scale after treatment as the main evaluation index, through consulting previous literatures [20–22] and taking the average, $\mu_1 = 9.39$, $\mu_2 = 12.49$, and σ_2 of the control group is 2.97, the above research data were substituted into the above formula to calculate that n is 19.2, and the sample size of both the treatment and control groups was 20 cases with total 40 cases.

Randomization

Treatment allocation was done when participants met the inclusion criteria and signed the informed consent form. Patients were randomly divided into two groups, the treatment and control groups, with a 1:1 distribution ratio according to the random numbers generated by IBM SPSS Statistics software version 19.0. The recruiter obtained a sequence number from the distributor when a patient was eligible for the trial. The subjects' allocation was concealed inside the sealed, opaque and serialized envelopes to avoid the influence from the biases of the researchers, who took responsibility of recruitment and treatment assessment. To ensure strict confidentiality, the envelopes were not transparent, even under intense light. The envelopes would be opened, and the assigned intervention type would be recognized only after each subject finished all baseline evaluations.

Blinding methods

This study was a single-blind trial. The evaluators knew the group allocations and the treatment protocol for better operation, while the subjects and statisticians were unaware of the group allocations in order not to be disturbed by subjective factors. The treatment assignments were also kept secret for the principal investigator, statistician and outcome evaluator throughout the trial before locking the database.

Interventions

Patients randomized to the treatment group were administered one bag of JTW granules (15 g *C.chinensis* Franch and 2g *Ci.cassia* Presl) dissolved in warm water plus fluoxetine 20 mg once daily for eight weeks. Patients in the control group received 20 mg fluoxetine once daily for eight weeks. JTW granules and fluoxetine were manufactured by Beijing Tcmages Pharmaceutical Co., Ltd and Eli Lilly Company, respectively.

Outcome Assessment

Primary outcome

HAMD scores: This study used 24-item HAMD scale, which is summarised as including seven categories of factors and can reflect the patient characteristics more concisely and clearly. The seven types of depression scale factors include the following: 1) anxiety/somatisation factor, 18 points; 2) weight: 2 points; 3) cognitive disturbance factor, 21 points; 4) day and night change factor, 2 points; 5) retardation, 14 points; 6) sleep dysfunction factor, 6 points and 7) withdrawal and self-accusation, 12 points. Factor scores can reflect the characteristics of patients with depression symptoms as well as the characteristics of the changes before and after the drug interventions. The total scores and factor scores were compared, respectively. And both the comparison of the total scores and factor scores showed the same results that the mean scores of 4 weeks, 8 weeks, and 4 weeks of discontinuation were different from those of 0 week.

Secondary outcome

1. TCM syndrome integral scale scores: TCM symptoms of all patients were evaluated by the TCM syndrome integral scale. The comparison of the total scores demonstrated that the mean scores of 4 weeks, 8 weeks, and 4 weeks of discontinuation were different from 0 weeks.
2. WCST: Patients were assessed for cognitive function using the computer version of WCST. WCST consists of 4 templates and 48 cards, which were used to assess the cognitive function of patients by the total number of WCST, number of correct responses, total number of errors, number of persistent errors, and number of random errors. The comparison of the WCST exhibited that the mean scores of 4 weeks, 8 weeks, and 4 weeks of discontinuation were different from 0 week.
3. Blood and urine metabonomics: To systematically analyse the metabolic status of patients with depression, the metabonomics characteristics of depression and metabolic changes after treatment were studied. Urine sample was collected on an empty stomach in the early morning, and centrifuged as soon as possible within two hours after sampling. The supernatant was taken at 4 °C with the centrifuge rate of 3000 rpm for 15 minutes; It was centrifuged again at 3500 rpm for 8 minutes; Finally, the supernatant was removed, and then aliquoted in 2 ml cryopreservation tube, sealed with a sealing film at the mouth of the tube, and kept at -80 °C for testing (generally 2-7 tubes with each tube of about 0.5 ml). 8 ml fasting venous blood was drawn and placed in a tube containing the

anticoagulant. The processing and storage methods were the same as above. Blood specimens were usually stored into 2–4 tubes with about 0.3 ml for each. The comparison of the blood and urine metabolomics revealed that the mean scores of 8 weeks were different from 0 weeks. The above samples were stored in the Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine. Upon the test was over, the samples were immediately destroyed and would not be used for later researches.

4. Brain structure and function on fMRI: MRI can reveal brain tissue abnormalities in patients with depression in the aspects of brain microstructure, brain function changes and brain metabolite changes, and fMRI combines the three aspects of function, anatomy and imaging[23–25]. Diffusion tensor imaging (DTI) technique was used to detect differences and changes in fractional anisotropy values in the whole brain. The changes in cerebral white matter integrity in patients with depression before and after treatment were compared in order to study the effect of JTW on brain metabolites and the changes in brain metabolites by magnetic resonance spectroscopy (MRS). The comparison of the brain structure and function on fMRI discovered that the mean scores of 8 weeks were different from 0 weeks.

Safety reporting

Adverse events (AEs) are defined as any unfavourable and unintended sign, symptom or disease arising in participants in either group during the trial period, regardless of their relation to the experimental treatment. Appropriate measures should be adopted to ensure participants' safety and follow up the outcome of any AEs. The relevant information for AEs was filled out in the safety evaluation form. The record included a detailed description of AEs, time of occurrence, time of suspension, duration (which can be recorded in days or hours), severity and frequency of the occurrence, manner of treatment, amount of treatment and course of treatment as well as the causal analysis of AEs and trial treatment. All clinical data for AEs were recorded in the case report forms (CRFs).

Data collection, management and quality control

The hard copies of CRFs were used to collect relevant data for each participant, and participants were assessed every four weeks during the study. Data on HAMD, WCST and TCM syndrome integral scale were collected at each visit (week 0 ± 3 days, week 4 ± 3 days, week 8 ± 3 days and week 12 ± 3 days). Blood metabolomics, urine metabolomics and fMRI were carried out only at the first and third visits (week 0 ± 3 days and week 8 ± 3 days, respectively). The SPIRIT flowchart of the trial is shown in Table 1.

After being reviewed by clinical inspectors, completed CRFs were sent to a specified statistics centre, and data input and processing were performed by two individual data administrators to ensure data accuracy. All documents gathered in this study were stored securely. Participants were referred to by a specific randomization number rather than by their names in all other documents in this study, except for the informed consent form.

A quality inspection system was developed in the treatment group, and a quality inspector was set up. The details of the quality inspector's implementation included examining the experimental protocols and procedures by the test operators and recording and reporting all research data and the truthful, accurate and complete CRFs, in order to assure that the original data were consistent.

Data analysis

Primary analysis of validity: To calculate the HAMD scores of the patients in the two groups during the treatment period and determine the mean and standard deviation of the values at baseline from those after treatment. The secondary analysis was described below. *Balance comparison:* To compare the demographics and other basic indicators to measure the comparability of the two groups. *Analysis of action mechanism:* To calculate the TCM syndrome integral scale scores, WCST, Blood and urine metabonomics, and analyse MRI image of the patients in the two groups. Statistical analysis or Pearson correlation coefficient was performed using analysis of variance (ANOVA).

Statistical analysis was conducted as an intention-to-treat analysis by using SPSS Statistics version 17.0 software. A two-sided P-value of <0.05 was considered to be statistical significant. Baseline differences among the groups were evaluated using 1-factor ANOVA for measurement data and the χ^2 test for enumeration data, respectively. In addition, χ^2 test was used for categorical variables. The changes in scores from baseline to endpoint of treatment were assessed using a paired *t* test for measurement data and a signed rank test for enumeration data, respectively. Comparisons between groups were performed using ANOVA and a rank test.

To limit the extent of missing data, when the assigned treatment was discontinued, efforts were made to obtain the participant's consent to collect the data on treatments and outcomes.

The researchers conducting the data analysis were not involved in experimental or clinical decision-making processes to avoid any bias caused by subjective factors from the researchers.

Discussion

Depression is one of the most common mental disorders and social issues worldwide. In the modern society, the incidence of depression has risen dramatically due to an accelerated pace of life and increased work pressure[26]. Treatment of depression by Western medicine has more side effects, more adverse reactions and shorter duration of action than that by TCM; therefore, Western medicine should not be used for a long term. In addition, many patients do not respond adequately to the treatment[27–28]. Prevention and treatment of depression by TCM can date back thousands of years ago. TCM is more stable and effective, with fewer side effects and better patient compliance than Western medicine; that is one of the reasons why China has become a hot spot for medical tourism in the recent years [29].

JTW is a commonly used formula for clinical treatment of insomnia and depression. The research team used mouse suspension experiments and mouse forced swimming experiments to study the

antidepressant effect of JTW in different proportions, the results showed that JTW had antidepressant effect, and the antidepressant effect was dose-dependent. The research group also conducted a mouse reserpine antagonism experiment, and found that JTW can exert antidepressant effects by regulating the levels of NE and 5-HT in hippocampal tissue and cortex [13–16]. Clinically, the addition and subtraction of JTW as the main prescription can obviously relieve the symptoms of palpitations, insomnia, anxiety, and irritability in patients with depression, but no standard clinical evidences can support those claims. Therefore, we conducted a multi-center clinical randomized controlled trial, using the HAMD scale and the TCM syndrome integral scale as the evaluation criteria for the efficacy, combined with the application of multimodal fMRI technology and combining metabolomics, to analyze the changes in brain structure and brain function, blood, urine metabolic fingerprints of patients with depression, and the intervention effects of JTW, to study the efficacy and mechanism of anti-depression of JTW, and provide scientific basis for clinical treatment of depression in JTW.

Our study has several limitations. First, since this study is undertaken in China, it is uncertain whether the effects of JTW would be similar in other ethnic groups. Second, because of the small sample size, the extrapolation of the results of this test is poor. Moreover, at present, the diagnosis of depression only depends on the subjective judgment of clinicians on the type and severity of symptoms, and lacks objective laboratory diagnostic methods, which also brought uncertainty for us to evaluate whether the clinical symptoms of depression were alleviated.

Trial Status

The trial is currently recruiting patients. The protocol version number is V1.00. The protocol was approved by the Ethics Committee of Tianjin University of Traditional Chinese Medicine on September 18, 2016. The first patient was enrolled on March 8, 2017. Recruitment is expected to be completed in May, 2020.

Abbreviations

JTW: Jiaotai Wan; TCM: Traditional Chinese medicine; HAMD: Hamilton's Depression Scale; WCST: Wisconsin card sorting Test; fMRI: functional magnetic resonance imaging; MRS: Magnetic Resonance Spectroscopy; AEs: Adverse events; DTI: Diffusion tensor imaging; ANOVA: analysis of variance

Declarations

Ethics approval and consent to participate

This study received ethical approval from Ethics Committee of Tianjin University of Traditional Chinese Medicine (TJUTCM-EC20160004), covering all participating sites. Important changes to the protocol will be submitted to the TJUTCM for review. Informed consent will be obtained from all participants in the trial.

Consent for publication

The results will be offered for publication in peer-reviewed journals.

Competing interests

The authors declare that they have no competing interests.

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Availability of data and material

The results of this pilot study will be disseminated via peer-reviewed publications and the public platform (<http://www.bmj.com/content/352/bmj.i255>) within 6 months of completion of the trial. Anyone can access it. All the data will be available upon request.

Authors' contributions

ZHZ conceived and designed the trial and wrote the manuscript draft. CQY conceived the study and performed the critical revision of the manuscript. YJL drafted the manuscript. SFF was the general supervisor for this research. HEB was responsible for the statistical design and helped in the design of the study. YHW, YM and YT were in charge of the recruitment of patients, data collection and management. All authors read and approved the final manuscript.

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Supplementary File Legend

Additional file 1: The SPIRIT Checklist.

Table

Assessments	Baseline: Week 0	Week 4	Week 8	Week 12
Enrollment	X			
Written consent (signed and dated)	X			
Randomization	X			
General demography and relevant medical history	X			
Physical examination	X			
HAMD scale	X	X	X	X
TCM syndrome integral scale	X	X	X	X
WCST	X	X	X	X
blood metabolomics	X		X	
urine metabolomics	X		X	
fMRI	X		X	
Adverse event		X	X	X

Tab 1

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flowchart

Figures

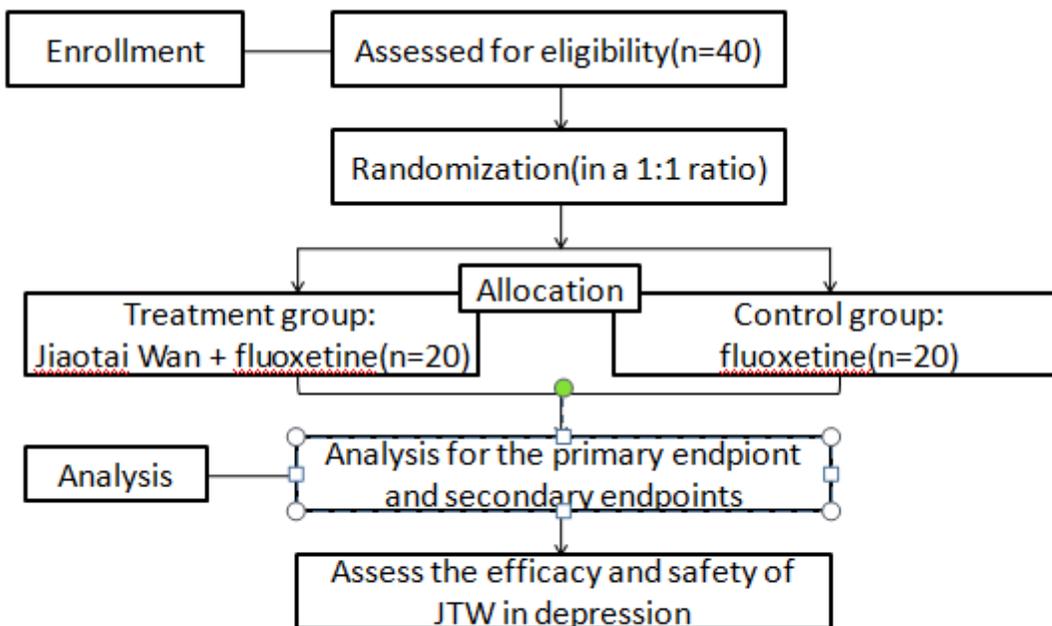


Fig 1
Flowchart of this study

Figure 1

Flowchart of this study.

Supplementary Files

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