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Original Article

Efficacy and Safety of Jianpi Jieyu Decoction for Patients with Mild-to-Moderate Depression of Xin (Heart)-Pi (Spleen) Deficiency Syndrome: A Multi-centre Randomized Controlled Study*

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ABSTRACT **Objective**: To evaluate the efficacy and safety of Jianpi Jieyu Decoction (JJD) for treating patients with mild-to-moderate depression of Xin (Heart)-Pi (Spleen) deficiency (XPD) syndrome. **Methods**: In this multi-center, randomized, controlled study, 140 patients with mild-to-moderate depression of XPD syndrome were included from Xiyuan Hospital of China Academy of Chinese Medical Sciences and Botou Hospital of Traditional Chinese Medicine from December 2017 to December 2019. They were randomly divided into JJD group and paroxetine group by using a random number table, with 70 cases in each group. The patients in the JJD group were given JJD one dose per day (twice daily at morning and evening, 100 mL each time), and the patients in the paroxetine group were given paroxetine (10 mg/d in week 1; 20 mg/d in weeks 2–6), both orally administration for a total of 6 weeks. The primary outcome was the change of 17-item Hamilton Depression Rating Scale (HAMD-17) score at week 6 from baseline. The secondary outcomes included the Hamilton Anxiety Scale (HAMA) score, Traditional Chinese Medicine Symptom Scale (TCMSS), and Clinical Global Impression (CGI) scores at the 2nd, 4th, and 6th weekends of treatment, HAMD-17 response (defined as a reduction in score of >50%) and HAMD-17 remission (defined as a score of ⩽7) at the end of the 6th week of treatment. Adverse events (AEs) were also recorded. **Results**: From baseline to week 6, the HAMD-17 scores decreased 10.2±4.0 and 9.1±4.9 points in the JJD and paroxetine groups, respectively (P=0.689). The HAMD-17 response occurred in 60% of patients in the JJD group and in 50% of those in the paroxetine group (P=0.292); HAMD-17 remission occurred in 45.7% and 30% of patients, respectively (P=0.128). The differences of CGI scores at the 6th week were not statistically significant (P>0.05). There were significant differences in HAMD-17 scores between the two groups at 2nd and 4th week (P=0.001 and P=0.014). The HAMA scores declined 8.1±3.0 and 6.9±4.3 points from baseline to week 6 in the JJD and paroxetine groups, respectively (P=0.905 between groups). At 4th week of treatment, there was a significant difference in HAMA between the two groups (P=0.037). TCMSS decreased 11.4±5.1, and 10.1±6.8 points in the JJD and paroxetine groups, respectively (P=0.080 between groups). At the 6th week, the incidence of AEs in the JJD group was significantly lower than that in the paroxetine group (7.14% *vs*. 22.86%, P<0.05). **Conclusion**: Compared with paroxetine, JJD was associated with a significantly lower incidence of AEs in patients with mild-to-moderate depression of XPD syndrome, with no difference in efficacy at 6 weeks. (Trial registration No. ChiCTR2000040922)

KEYWORD depression, Xin (Heart)-Pi (Spleen) deficiency syndrome, Chinese medicine, Jianpi Jieyu Decoction, depression, efficacy, safety

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Depression is a common mental disorder that mainly manifests as low mood, lack of interest, slow thinking, disordered sleep, and even self-injury and suicidal behaviours.[1-3] The condition is prolonged and occurs repeatedly, which can cause serious damage to the social function.[4-6] According to a survey, the lifetime prevalence rate of depression has reached 8.0% in females and 5.7% in males, seriously endangering the physical and mental health of human beings.[7] Selective serotonin reuptake inhibitors (SSRIs) are first-line treatments for depression; however, because most of the drugs take effect gradually within 2–4 weeks, and the early adverse reactions of the drugs are obvious, the patients' compliance with the drugs is poor.[8-10] Paroxetine, one of the SSRIs, is widely used clinically. However, many patients cannot tolerate the drug due to aggravation of anxiety in the early stage of use, and side effects such as dry mouth, dizziness, and constipation.[11,12]

The treatment of Chinese herbal medicine for mental illness can be regarded as a multi-dimensional, multi-targeted intervention model.[13] Chinese medicine (CM) is effective in treating mild-to-moderate depression, with few adverse responses.[14-16] Our previous research found that the most common syndromes of depression are the Xin (Heart)-Pi (Spleen) deficiency (XPD) syndrome and Gan (Liver) qi stagnation syndrome.[17] Jianpi Jieyu Decoction (健脾解郁汤, JJD) was developed based on Guipi Decoction (归脾汤), an ancient CM prescription, combined with the addition and subtraction of previous core drug prescriptions. According to our exploration of the core drugs of CM for depression based on data mining technology,[18] *Bupleuri Radix* and *Albiziae Cortex* (soothing Gan and relieving depression), and fried *Gardeniae Fructus* (clearing Gan and draining fire) were added. It was found that the prescription can improve the symptoms of depression, fatigue, and other symptoms in patients with depression, and no obvious adverse reactions were found in clinical observation.[19] Our team previously conducted a preliminary small-sample retrospective study on patients with mild-to-moderate depression of XPD syndrome treated by JJD, and the results showed that the decoction could significantly reduce the Hamilton Depression Rating Scale-17 (HAMD-17) score of patients with mild-to-moderate depression. JJD showed benefits in improving depressed mood, anxiety-psychic, insomnia middle, and insomnia delayed. This study used a multi-centre randomized controlled method, with paroxetine as the control drug, to evaluate the efficacy and safety of JJD in treating patients with mild-to-moderate depression of XPD syndrome, aimed to provide a reference for the CM treatment of depression.

METHODS

Trial Overview

This multi-centre randomized controlled study was registered at the Chinese Clinical Trial Registry (No. ChiCTR2000040922). The trial was approved by the Medical Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (Approval No. 2016XLA107).

Diagnostic Criteria

The diagnostic criteria of depression referred to the "Diagnostic and statistical manual of mental disorders fifth edition" (DSM-5TM, American Psychiatric Association, 2015).[20] The standard of syndrome differentiation of XPD in CM referred to the "Diagnostic standard and treatment plan for TCM syndrome of depression" formulated by the China Association of Chinese Medicine.[21] Main symptoms included mental depression, lack of interest, fidget, slow thinking, fatigue, insomnia, forgetfulness, sexal hypoesthesia, and inappetence. Secondary symptoms included overthinking, palpitations, dreaminess, sallow complexion, hand and foot numbness, dizziness, shortness of breath, spontaneous sweating, abdominal distension, loose stool, irregular menstruation, pale and tender tongue with white coating, and weak pulse. Patients having mental depression and at the same time with more than 4 main symptoms and more than 5 secondary symptoms could be diagnosed.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) patients aged between 18 to 65 years old; (2) patients who met the above criteria of Western medicine diagnosis and syndrome differentiation of CM; (3) patients with the score ⩾18 and ⩽24 on the HAMD-17 item, as well as the score of depressed mood ⩾2.[22]

Exclusion criteria: (1) patients with suicidal tendencies, the score of suicidal items ⩾2 in HAMD-17; (2) patients with severe anxiety symptoms, the Hamilton Anxiety Scale (HAMA) score ⩾21; (3) patients with severe or unstable heart, liver, kidney, endocrine,

blood, and other internal diseases; (4) depressive episodes secondary to other mental or somatic diseases; (5) depressive episodes of bipolar disorder; (6) patients who have taken paroxetine or other antidepressants within 5 weeks; (7) those who are unsupervised or unable to take medicine as prescribed by the doctor; (8) those with the allergic constitution; (9) those who are pregnant or lactating.

Patients

Participants were assessed from December 2017 to December 2019. Eligible patients were recruited from the Department of Neurology of the Xiyuan Hospital, China Academy of Chinese Medical Sciences (Beijing, China) and Botou Hospital of Traditional Chinese Medicine (Hebei, China). Patients were recruited through the hospital website and screened by outpatient physicians. The patients discontinued any use of psychiatric medication before starting the trial, with complete discontinuation occurring at least 2 weeks before the start of trial medication; any use of psychotherapy was stopped at least 3 weeks before the start of trial medication.

Randomization

In this study, group randomisation methods were used, and a random number table was generated using SAS 9.1.3 (SAS Institute Inc, USA). The participants were strictly included according to the sequence number. The random assignment of the participants in the two centres was carried out by an independent randomiser who did not participate in the clinical trial. The random coding table was generated by statistical units, which were sealed and properly preserved by the main researchers.

Intervention

The patients in the JJD group were given JJD orally, one dose a day, once in the morning and evening, respectively, 200 mL each time. JJD was composed of *Astragali Radix Praeparata Cum Melle*, *Codonopsis Radix*, fried *Atractylodes Macrocephala Rhizoma*, *Angelicae Sinensis Radix*, *Bupleuri Radix*, *Albiziae Cortex*, *Ziziphi Spinosae Semen*, *Poria with hostwood*, and *fried Gardeniae Fructus*. All herbal pieces were produced by Hebei Baicao Kangshen Pharmaceutical Co., Ltd., and prepared by the Decoction Room of Xiyuan Hospital China Academy of Chinese Medical Sciences and Botou Hospital of Traditional Chinese Medicine.

In the first week, the patients in the paroxetine group received 10 mg of paroxetine each morning after meals. From the 2nd week to the 6th week, the patients in the paroxetine group received 20 mg of paroxetine each morning after meals. Paroxetine was produced by Zhejiang Huahai Pharmaceutical Co., Ltd., China (batch No.008C16021, 20 mg × 20 s; batch No. 1354C18014, 20 mg × 14 s).

The course of treatment in both groups was 6 weeks. Patients with severe insomnia were allowed to take zopiclone 7.5 mg before bedtime for no more than 7 consecutive days and no more than 14 days totally during the 6 weeks treatment.

Outcomes

The primary clinical outcome was the change from baseline of the HAMD-17 score[22] at 6th week. Secondary outcomes included a response at 6th week according to the HAMD-17 (defined as a decrease in score by ⩾50% from baseline); remission at 6th week according to the HAMD-17 (defined as a score of ⩽7); the changes from baseline to week 6 in the scores on the HAMA,[23] and the Traditional Chinese Medicine Symptom Scale (TCMSS) score (Appendix 1);[21] CGI severity of illness (SI), global improvement (GI), and efficacy index (EI) score at the 6th week.[23] Changes in the scores of the 4 scales at the baseline and the end of the 2nd, 4th, and 6th weeks were observed in the two groups.

Safety Evaluation

Adverse events (AEs) were recorded at every visit or by every telephone call during day 1 to week 6. AEs to the drug were recorded using the Treatment Emergent Symptom Scale.[23] Additional details of the criteria used to report AEs are provided in the protocol. All AEs that occurred or worsened during dosing days were recorded.

Sample Size Calculation

According to the literature, the change of HAMD-17 score in patients with depression after 6 weeks of treatment was 8.0 in the paroxetine group and 10.5 in the JJD group, with an estimated standard deviation of 5.[24-26] PASS v2021 (PASS NCCS, USA) was used to estimate the sample size, the superiority design was adopted, and a one-sided test was used, α=0.025, β=0.20, and the ratio of the experimental group and the control group was 1:1. It was calculated that at

least 64 cases were needed in each group. During the process, the quality of the study was strictly controlled, and the lost follow-up rate was controlled within 10%. The total number of cases was 140, including 70 in the experimental group and 70 in the control group.

Statistical Analysis

SPSS 26.0 (SPSS IBM, USA) was used for statistical analysis. The measurement data were expressed by mean ± standard deviation ($\bar{x} \pm s$). *t*-test was used for those in accordance with normal distribution, and the rank-sum test was used for those who did not. A chi-square test was used to describe the frequency and percentage of counting data. The threshold of α =0.05 and $P \leqslant 0.05$ indicated a statistical difference. All the patients who had undergone randomization were included in an intention-to-treat analysis.

Covariance analysis was used to analyse the difference between the HAMD-17, HAMA, TCMSS scale scores, and baseline on the 6th weekend. The mean difference and 95% confidential interval (CI) of the two groups were calculated by the least squares' method. A logistic regression model was used to analyse the clinical effectiveness and cure rate of the HAMD-17 score, and the number of effective cases, percentage and rate difference between the two groups, and the 95% CI were described. The baseline values of the HAMD-17 score, group, sex, age, course of the disease, and body mass index (BMI) were used as covariates. A repeated measures analysis of variance in the general linear model was used to analyse the HAMD-17, HAMA, and TCMSS scores, considering grouping factors, time factors (treatment at 2, 4, and 6 weekends), and the interaction effects of both. Based on the model used to calculate the mean difference between the two groups of therapeutic effects and 95% CI, the covariates that needed to be adjusted included age, course of disease, and BMI.

RESULTS

Patients

A total of 200 patients underwent assessment. Sixty patients did not meet the inclusion criteria. Thus, 140 patients were enrolled and underwent randomisation, and 70 were assigned to the JJD and 70 to the paroxetine group. The participants' characteristics are summarised in Table 1, and there were no significant differences between the two groups at baseline with regard to the demographic characteristics, as well as HAMD-17, HAMA, and TCMSS scores (P>0.05).

Table 1. Comparison of Baseline Characteristics between Groups

Item	Jianpi Jieyu Decoction (70 cases)	Paroxetine (70 cases)	*P*-value
Age (Year, $\bar{x} \pm s$)	43.6 ± 13.9	45.9 ± 13.3	0.307
Disease course (Month, $\bar{x} \pm s$)	14.5 ± 19.1	16.6 ± 16.4	0.069
Male [Case (%)]	26 (37.1)	24 (34.3)	0.724
labor type [Case (%)]			0.805
mental labor	9 (12.9)	10 (14.3)	
manual labor	61 (87.1)	60 (85.7)	
Family history [Case (%)]	9 (12.9)	6 (8.6)	0.412
Comorbidity [Case (%)]	12 (17.1)	15 (21.4)	0.520
Number of insomniacs [Case (%)]	6 (8.6)	6 (8.6)	1.000
Body mass index ($\bar{x} \pm s$)	22.8 ± 2.6	23.6 ± 3.2	0.109
HAMD-17 score ($\bar{x} \pm s$)	19.2 ± 2.3	19.8 ± 2.3	0.090
HAMA score ($\bar{x} \pm s$)	15.7 ± 3.6	15.4 ± 3.8	0.482
TCMSS score ($\bar{x} \pm s$)	21.3 ± 4.6	21.0 ± 5.1	0.395

Notes: HAMD-17: 17-item Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; TCMSS: Traditional Chinese Medicine Symptom Scale; the same below. Comorbiditity include: hypertension, coronary heart disease, hyperlipidemia, severe insomnia, etc., and the drugs allowed to treat comorbidities include: antihypertensive drugs, lipid-lowering drugs, antiplatelet drugs, etc. Number of insomniacs refers to the number of patients required to take zopiclone during the trial, and zopiclone was taken 25 and 27 times in the JJD and paroxetine groups, respectively. Comorbidity and combination therapy do not violate the exclusion criteria.

At the end of this trial, in the paroxetine group, 9 patients did not complete the protocol requirements, 5 of them stopped taking paroxetine due to side effects, 2 stopped taking medication because they did not have time to participate in the follow-up, 1 stopped taking medicine for unknown reasons, and 1 withdrew due to cold and fever. In the JJD group, 2 patients did not complete all dosing procedures, both of which were due to unknown reasons (Figure 1). The missed follow-up rate in JJD and paroxetine groups was 2.9% (2/70) *vs*.12.8% (9/70), and a significant difference was shown between the two groups (P=0.028).

Primary Outcome

The mean change from baseline in the score of HAMD-17 at week 6 (the primary outcome) was –10.2 ± 4.0 in the JJD group and –9.1 ± 4.9 in the paroxetine group (difference, –1.0; 95% CI, –0.5 to 2.6; P=0.689, Table 2).

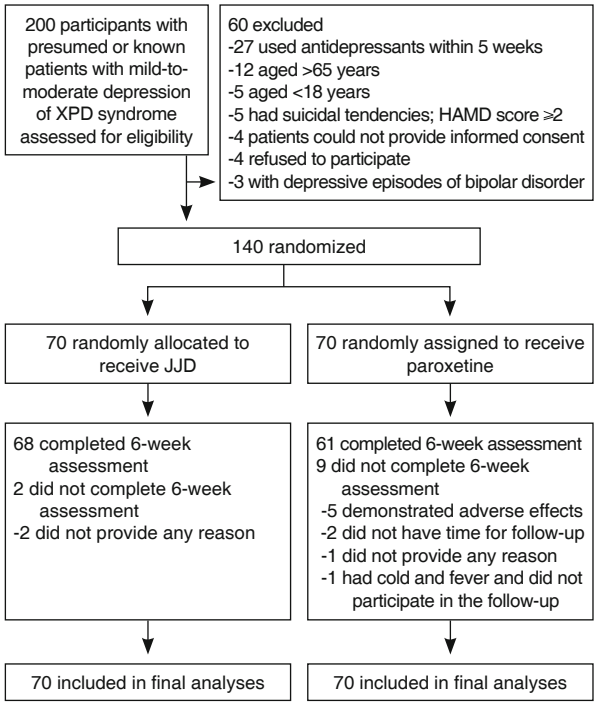

Figure 1. Flowchart of Enrolment of JJD Treatment for Patients with Depression

Notes: XPD: Xin (Heart)-Pi (Spleen) deficiency; JJD: Jianpi Jieyu Decoction; HAMD: Hamilton Depression Rating Scale

Secondary Outcomes

The results of the secondary outcome analyses are shown in Figure 2 and Table 2. The HAMD-17 response at 6 weeks occurred in 42 patients (60%) in the JJD group and 35 patients (50%) in the paroxetine group (difference, 10.0% points; 95% CI, –6.4 to 26.4; *P*=0.292), with no significant difference. HAMD-17 remission at week 6 occurred in 32 patients (45.7%) in the JJD group and 21 patients (30%) in the paroxetine group (difference, 15.7% points; 95% CI, –0.157 to 31.6; *P*=0.128). Other secondary measures of depression [changes from baseline to week 6 in the HAMA and TCMSS scores, and CGI (SI, GI, EI) scores at the 6th week] also indicated no significant differences between the two groups.

The repeated measures analysis of variance in the general linear model found that the time-point effect could significantly affect the changes in HAMD-17, HAMA, and TCMSS scores [$F(3,125)=3.04$, $P=0.031$; $F(3,125)=2.72$, $P=0.047$; $F(3,125)=4.99$, $P=0.003$]. Notably, there was a significant interaction

Table 2. Primary and Secondary Outcomes after 6-Week Treatment ($\bar{x} \pm s$)

Outcome	JJD (70 cases)	Paroxetine (70 cases)	*P*-value	Difference (95% CI)
Primary outcome				
Change in HAMD-17 score	–10.2 ± 4.0	–9.1 ± 4.9	0.689	–1.0 (–0.5, 2.6)
Secondary outcomes				
Change in HAMA score	–8.1 ± 3.0	–6.9 ± 4.3	0.905	–1.2 (–0.1, 2.5)
Change in TCMSS score	–11.4 ± 5.1	–10.1 ± 6.8	0.080	–1.0 (–1.0, 3.1)
HAMD-17 remission [Case (%)]	32 (45.7)	21 (30.0)	0.128	15.7% (–0.157, 31.6)
HAMD-17 response [Case (%)]	42 (60.0)	35 (50.0)	0.292	10.0% (–6.4, 26.4)
CGI-SI score	1.6 ± 0.6	1.5 ± 0.5	0.358	0.1 (–0.1, 0.3)
CGI-GI score	1.8 ± 0.8	1.7 ± 0.7	0.325	0.1 (–0.1, 0.4)
CGI-EI score	3.2 ± 0.8	3.3 ± 0.7	0.353	–0.1(–0.4, 0.1)

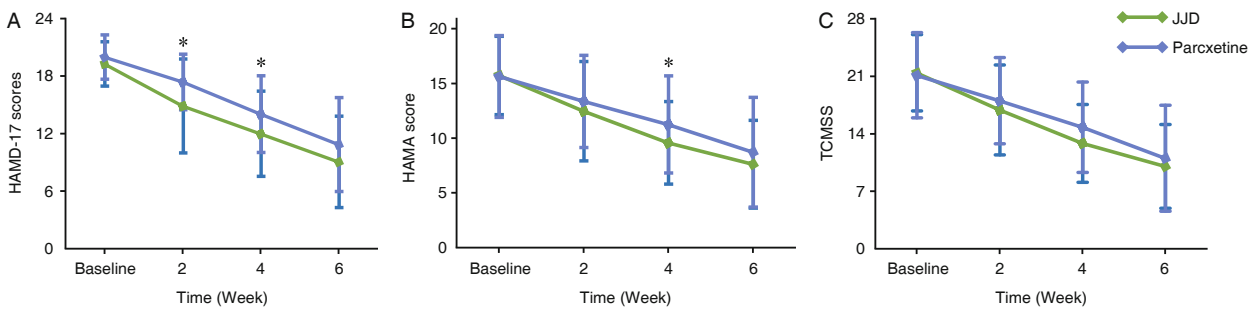

Figure 2. Comparison of HAMD-17, HAMA, and TCMSS Scores between Groups in Intention-to-Treat Analysis ($\bar{x} \pm s$)

Note: *P<0.05 *vs*. paroxetine group at the same time point

effect between time point and treatment mode [$F(3,125)=3.212$, $P=0.025$; $F(3,125)=3.763$, $P=0.013$; $F(3,125)=3.432$, $P=0.019$]. Furthermore, the HAMD-17, HAMA, and TCMSS scores of the patients in the JJD and paroxetine groups all showed significant changes from baseline to 2nd, 4th, and 6th week of treatment ($P<0.001$). There were no significant differences in HAMD-17, HAMA, and TCMSS scores between the JJD and paroxetine groups at 6th week treatment ($P=0.051$, $P=0.239$, $P=0.515$, respectively), but at 2th and 4th weeks, there was a significant difference in HAMD-17 scores between the two groups ($P=0.001$ and $P=0.014$); at 4th week of treatment, there was a significant difference in HAMA between the two groups ($P=0.037$).

Safety Evaluation

No abnormalities in blood routine, urine routine, stool routine, liver and kidney functions, and electrocardiogram were found in the two groups from baseline to the end of the 6th week. There were no serious AEs related to treatment in either group during the treatment period.

A total of 21 patients with AEs were found in the two groups during the treatment period. AEs were observed in 5 patients (7.1%) in the JJD group, including 5 cases of dry mouth, 1 case of constipation, and 1 case of abnormal urine and 16 patients (22.9%) in the paroxetine group, including 5 cases of dry mouth, 4 drowsiness, 1 dizziness, 3 headache, 2 sweating, 4 constipation, 2 anorexia, 2 tachycardia, 1 myotonia and tremor, 1 akathisia, 1 neck soreness, 1 abnormal urine, and 1 emotional depression. There was a significant difference in the incidence of AEs between the two groups ($P=0.009$).

DISCUSSION

The classic hypothesis for the pathogenesis of depression is the monoamine neurotransmitter theory, which states that the pathogenesis of depression is related to the insufficient content of serotonin (5-HT) in the hypothalamus and prefrontal cortex. Currently recognized effective drugs for the treatment of depression are SSRIs, such as fluoxetine, paroxetine, and sertraline, which block the reuptake of 5-HT in the synaptic cleft, thereby increasing the brain's 5-HT content, which can achieve the purpose of treating depression.[10,27] However, the use of SSRIs is not risk-free and can aggravate somatic anxiety symptoms in the early stages of treatment.[12,28] Therefore, in this study, the currently recognised effective SSRI drug paroxetine was selected as the positive control drug, and a controlled, multi-centre, randomised trial design was used to evaluate JJD in treating patients with mild-to-moderate depression of XPD syndrome. It aims to provide a safe and effective treatment plan for patients with mild-to-moderate depression and to provide evidence-based medical treatment.

In this randomised controlled trial, after 6-week treatment the reduction in the total score of HAMD-17 in the JJD group was slightly higher than that of the paroxetine group, the same trend was also observed in the secondary endpoints, including HAMA and TCMSS scores. In terms of the HAMD-17 remission rate and response rate, the JJD group was 15% and 10% points higher than the paroxetine group, respectively. However, the above differences between groups did not reach statistical significance. It is worth noting that through the analysis of repeated measurement variance in the general linear model, we found that there was a statistically significant difference in the change of HAMD-17 scores between the JJD and the paroxetine groups after 2 and 4 weeks of treatment, and at 4th week of treatment, there was a significant difference in HAMA between the two groups, indicating that the JJD group may have a faster onset effect than paroxetine in the early stage in patients with mild-to-moderate depression of XPD syndrome, and can improve anxiety symptoms related to depression. With the prolongation of the treatment time, there was no statistical difference in the HAMD-17 scores between JJD and paroxetine after 6-week treatment, without significant difference in efficacy between groups, indicating that the therapeutic effects of JJD and paroxetine were similar.

There were 22.9% and 7.1% of the participants in the paroxetine and JJD groups who reported at least one AE, respectively. The paroxetine group had a significantly higher number of AEs possibly related to the treatment drugs than the JJD group. Although no serious AEs occurred, for depressed patients with anxiety, even mild adverse reactions may affect their medication compliance. This is consistent with the conclusion that 5 of the 9 subjects dropped out of the paroxetine group and terminated the trial due to AEs.

Although no placebo group was set in this trial, as a positive control drug, paroxetine is a

classic selective 5-HT reuptake inhibitor (SSRI), with abundant evidence-based medical treatment and wide clinical application. Therefore, JJD is effective in treating patients with mild-to-moderate depression of XPD syndrome and is slightly better than paroxetine because, for this patient group, the small difference in efficacy is meaningful. JJD has the characteristics of fast onset, low adverse reactions, good compliance, and early efficacy is better than paroxetine, which makes it suitable for the treatment of patients with mild to moderate depression and XPD syndrome.

In our trial, we enrolled participants in two groups according to the syndrome criteria of XPD syndrome and excluded patients with existing mental disorders who were considered unsuitable for JJD treatment. Such exclusion criteria may have biased the trial sample towards those who could receive JJD without adverse effects, resulting in fewer AEs being reported than paroxetine. Another limitation of this trial is the brief duration of paroxetine treatment received by participants because this drug has a delayed therapeutic effect on depression. If the course of paroxetine was extended, it would be possible to observe and compare long-term efficacy in patients receiving both therapies. Although we recruited patients through a multi-centre method, most of the volunteers recruited expressed a preference for the JJD group over paroxetine. Therefore, it cannot be confident that resistance to paroxetine assignments or the expectation of favoring JJD did not influence the results. This resulted in a selected trial population and limited the generalisability of the results. The patients in the trial were not from diverse ethnic or socioeconomic backgrounds. Therefore, a strategy needs to be adopted to improve the recruitment of more diverse study populations in studies of the JJD for depression. In addition, the average symptom severity scores at baseline were in the range of moderate depression. Thus, extrapolations are limited to patients with severe or treatment-resistant depression.

The research team has engaged in some clinical researches on CM on depression and accumulated rich experience.[17-19] In the early stages, it was concluded that the pathogenesis of depression is the mostly emotional disturbance, stagnation of qi and even the onset of visceral qi, blood, yin and yang disharmony. Although the disease location involves the five internal organs, it ultimately affects Xin and the vital viscus of the body.[29] In CM theory, Xin governs spirit, and Pi governs thinking, excessive thinking will damage both Xin and Pi, leading to depression, restlessness, insomnia and other symptoms.[30] Therefore, the main pathological site of depression located at Xin, Gan, and Pi, and depression treatment should be advocated from Xin and Pi, with the method of tonifying Xin and Pi.[19]

Based on the data mining technology of 101 CM syndromes of depression, we found that the most frequently distributed syndromes were the XPD syndrome and Gan-qi stagnation syndrome. We further carried out complex network-based research to find the core drugs of CM for the treatment of depression.[17,18] According to literature, Guipi Decoction has the effect of improving depression, and the guidelines also recommend Guipi Decoction for the treatment of depression patients with XPD syndrome.[31,32] Meanwhile, during clinical observation and syndrome research, we found that most of the depression patients with XPD were accompanied by symptoms of Gan-qi stagnation and Gan stagnation transforming into fire. Therefore, the treatment method emphasizes nourishing Xin and Pi, as well as soothing Gan and clearing Gan fire. In preliminary clinical practice we found that JJD could effectively improve the symptoms of depression, such as grievances and crying, overthinking, mental fatigue, insomnia and forgetfulness.[19]

It has been shown that CM invigorating Pi and relieving depression can significantly increase serum 5-HT in patients with depression and exert an antidepressant effect.[33] *In vitro* experiments, *Astragali Radix* can play an antidepressant effect by promoting the proliferation of neurons.[34] Angelica extract exerts an antidepressant effect through the brain-derived neurotrophic factor (BDNF) signaling pathway, which can promote expression of the BDNF protein and the phosphorylation of its downstream targets (ERK 1/2, CREB) were upregulated in the hippocampus.[35] Studies have found that *Bupleuri Radix* can reduce severity of depression. It may exert antidepressant effects through the hypothalamic-pituitary-adrenal (HPA) axis.[36,37] *Gardeniae Fructus* is a compound that works against depression, which is rich in crocin.[38] Crocin produces an antidepressant effect by upregulating pituitary adenylate cyclase-activating polypeptide and its downstream extracellular regulated protein kinases and cyclic

adenosine monophosphate response element-binding protein signaling pathways.[39] These pharmacological studies point to the currently recognized molecular mechanisms of depression (increased levels of inflammation, hyperactivity of the HPA axis).[40] In the primary trial protocol, we intent to detect the serum level of BDNF in some of the participants, however, BDNF was not reported in the final report due to control under COVID-19 and accidental failure of the storage equipment. However, we believed that data missing of this indicator would not have impact on our main findings.

In conclusion, the incidence of AEs of JJD in treating patients with mild-to-moderate depression of XPD syndrome is significantly lower than that of paroxetine, with no difference in efficacy at 6 weeks. JJD can improve patients' anxiety symptoms associated with depression, and the compliance was significantly better than paroxetine. Trials with larger sample size and longer observation time are needed to compare the JJD with established treatments for depression in the future.

Conflicts of Interest

This was an investigator-initiated trial sponsored by Xiyuan Hospital, China Academy of Chinese Medical Sciences. The authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. There was no industry involvement in the collection or analysis of the data, and no agreements were in place between the authors and any commercial entity.

Author Contributions

Hong X was involved in the conception and design of the study and is the corresponding author; Hong X and Chen JX designed the experiment. Chen X completed the data analysis with the assistance of Hong X, Zhao Y and Meng S, and completed the paper with the assistance of Hong X, Chen JX, Han XY and Cao J. Chen JX, Liang S, Qi JX, Chen D, LI MX, Jiao YX, Wang TT conducted the experiment and collected the data. Clinical supervision of the trial was provided by Jiao XZ, Liu HM and Guo CL.

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Data Availability

The data used to support the study are available from the corresponding author upon request.

Electronic Supplementary Material: Supplementary material (Appendix 1) is available in the online version of this article at https://doi.org/10.1007/s11655-022-3685-6.

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