

Efficacy and Safety of Jiuwei Zhenxin Granules Combined with Trazodone for Depression with Heart-Spleen Deficiency Syndrome: A Randomized Controlled Study

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Abstract: We evaluated the efficacy and patient-reported tolerability of adding Jiuwei Zhenxin Granules to trazodone in patients with depression and heart-spleen deficiency syndrome. Of 82 patients screened, 60 completed the study and were randomized to trazodone alone (n=30) or trazodone plus Jiuwei Zhenxin Granules (n=30) for 8 weeks. The primary outcome was the between-group difference in the 17-item Hamilton Depression Rating Scale (HAMD-17) score at week 8. Secondary outcomes included HAMA-14, the traditional Chinese medicine syndrome score (TCMDS), Pittsburgh Sleep Quality Index (PSQI), therapeutic grade, and patient-reported adverse events. At week 8, the HAMD-17 score was lower with combination therapy (6.93 ± 2.57 vs 11.90 ± 2.95 ; $t=6.948$; $P<0.001$). HAMA-14, TCMDS, and PSQI scores were also lower at weeks 4 and 8, and time-by-group interactions were significant for all scales (all $P<0.001$). Therapeutic-grade distribution favored combination therapy ($U=144.5$; $Z=-5.056$; $P<0.001$), with 43.3% of patients meeting the recovery criterion. No serious drug-related event was reported. Adding Jiuwei Zhenxin Granules to trazodone improved depressive and anxiety symptoms, TCM syndromes, and sleep quality, with good patient-reported tolerability.

1. Introduction

Persistent low mood and loss of interest or pleasure are the defining features of depression. Anxiety, disturbed sleep, and somatic symptoms are also common, and the disorder remains a major contributor to disability worldwide [1,2]. Although antidepressants remain central to treatment, their efficacy and acceptability vary [3]. Clinical decisions therefore need to account for symptom profile, previous response, tolerability, and patient preference.

Trazodone, a serotonin antagonist and reuptake inhibitor, has established antidepressant activity and may also benefit patients with insomnia [4]. Even so, monotherapy does not provide an adequate response for every patient. Adjunctive treatment may therefore be useful when residual symptoms persist.

In traditional Chinese medicine (TCM), excessive rumination, palpitations, fatigue, poor appetite, and disturbed sleep are characteristic of depression with heart-spleen deficiency syndrome. This presentation is attributed to deficiencies of heart blood and spleen qi [5]. Jiuwei Zhenxin Granules are intended to nourish the heart, strengthen the spleen, replenish qi, and calm the mind. Randomized studies and a meta-analysis have reported potential benefits in generalized anxiety disorder [6-8]. Whether these granules provide additional benefit when combined with trazodone for heart-spleen deficiency depression has not been well established.

Accordingly, we compared Jiuwei Zhenxin Granules plus trazodone with trazodone alone. The primary outcome was the between-group difference in the HAM-D-17 score at week 8.

2. Materials and methods

2.1 Study design and participants

We conducted a single-center, parallel-group randomized controlled study at Jilin Neuropsychiatric Hospital between July 2025 and August 2026. Among 82 outpatients screened for heart-spleen deficiency depression, 22 discontinued because of medication changes or treatment cessation. The remaining 60 patients completed the study and were allocated using a random-number table to the control group (n=30) or combination group (n=30). The Ethics Committee of Jilin Neuropsychiatric Hospital approved the study, and all participants provided written informed consent.

2.2 Diagnostic criteria

Depressive episodes were diagnosed according to the International Classification of Diseases, Tenth Revision. Heart-spleen deficiency syndrome was diagnosed according to the expert consensus on integrated Chinese and Western medicine for depression [5]. The primary symptoms were excessive rumination, insomnia or dream-disturbed sleep, and palpitations. Secondary symptoms included poor appetite, fatigue, dizziness, sweating, sighing, and a sallow complexion. Tongue and pulse findings comprised a pale tongue with a thin white coating and a thready pulse.

2.3 Inclusion criteria

Patients were aged 18-65 years of either sex; had a HAM-D score of at least 7; met the integrated diagnostic criteria for heart-spleen deficiency depression; had primary school education or above; and provided written informed consent.

2.4 Exclusion criteria

Exclusion criteria were comorbid bipolar disorder, schizophrenia, or other psychiatric disorders; a family history of psychosis; and a history of substance abuse. Additional exclusions were brain organic disease or head trauma, severe cardiac, hepatic, or renal insufficiency or other systemic diseases, pregnancy or lactation, and allergy to the study drugs. The withdrawal criteria were deviation from the prescribed medication regimen, withdrawal from the study, and failure to complete the scheduled scale assessments.

2.5 Treatment

The control group received oral trazodone hydrochloride tablets at a starting dose of 50 mg once daily. The dose was adjusted according to clinical response and tolerability, with a maximum

outpatient dose of 400 mg/d in divided doses, for 8 weeks. The combination group received the same trazodone regimen plus Jiuwei Zhenxin Granules, one sachet (6 g) 3 times daily with warm water. The granules contain nine herbs: *Panax ginseng*, *Ziziphi Spinosae Semen*, *Schisandrae Chinensis Fructus*, *Poria*, *Polygalae Radix*, *Corydalis Rhizoma*, *Asparagi Radix*, *Rehmanniae Radix Praeparata*, and *Cinnamomi Cortex*.

2.6 Outcome measures

The primary outcome was the between-group difference in the HAM-D-17 score at week 8 [9]. Secondary outcomes were HAMA-14 [10], TCMDs, and PSQI [11] scores at baseline and weeks 1, 4, and 8, therapeutic grade, and patient-reported adverse events. Qualified raters who had completed standardized training administered the HAM-D-17 and HAMA-14. For the TCMDs, primary symptoms were scored from 0 to 6 and secondary symptoms from 0 to 2 or 0 to 3, with higher scores indicating greater syndrome severity. The PSQI total score ranges from 0 to 21, with higher scores indicating poorer sleep quality. Because the PSQI assesses the preceding month, the week-1 result was considered descriptive only.

2.7 Therapeutic response criteria

The HAM-D reduction rate was calculated as (baseline score - post-treatment score) / baseline score $\times$ 100%. Therapeutic grade was classified as recovery (cured) for a reduction rate of at least 75%, marked improvement for 50%-74%, improvement (effective) for 25%-49%, and no response for less than 25%.

2.8 Safety assessment

All participants were treated as outpatients. At each follow-up visit, investigators asked about adverse events and also recorded symptoms reported spontaneously by patients. The records included onset, severity, management, and outcome. Blood tests, liver or renal function tests, and electrocardiographic examinations were not mandated by the protocol.

2.9 Statistical analysis

Analyses were performed with SPSS version 22.0. Continuous variables with approximately normal distributions are reported as mean $\pm$ SD. Independent-samples t tests were used to compare groups at each time point. Repeated-measures analysis of variance assessed longitudinal changes and included time, group, and time-by-group interaction effects. The primary analysis compared HAM-D-17 scores at week 8. Because therapeutic grade was ordinal, it was analyzed with the Mann-Whitney U test. All tests were 2-sided, with $P < 0.05$ indicating statistical significance.

3. Results

3.1 Participants

Eighty-two patients were screened. Twenty-two discontinued after changing medication or stopping treatment. The remaining 60 patients completed the 8-week study and all scheduled assessments, with 30 patients in each group.

3.2 Primary outcome

At week 8, mean HAMD-17 scores were 6.93 ± 2.57 in the combination group and 11.90 ± 2.95 in the control group (mean difference, 4.97 points; $t=6.948$; $P<0.001$). A difference was also present at week 4 (13.60 ± 2.99 vs 16.47 ± 2.84 ; $t=3.809$; $P<0.001$). Significant effects were observed for time ($F=2276.721$; $P<0.001$), the time-by-group interaction ($F=85.955$; $P<0.001$), and group ($F=9.239$; $P=0.004$). (Table 1)

Table 1. HAMD scores at each time point (mean $\pm$ SD)

Time point	Control (n=30)	Combination (n=30)	t	P
Baseline	23.60 $\pm$ 2.09	23.87 $\pm$ 2.54	-0.443	0.659
Week 1	20.37 $\pm$ 2.43	20.10 $\pm$ 2.63	0.408	0.685
Week 4	16.47 $\pm$ 2.84	13.60 $\pm$ 2.99	3.809	<0.001
Week 8	11.90 $\pm$ 2.95	6.93 $\pm$ 2.57	6.948	<0.001

Note: Between-group comparisons used independent-sample t tests. Time main effect in repeated-measures ANOVA: $F=2276.721$, $P<0.001$; time-by-group interaction: $F=85.955$, $P<0.001$; group main effect: $F=9.239$, $P=0.004$.

3.3 Secondary outcomes

HAMA-14 scores were similar between groups at baseline and week 1. By week 4, the mean score was lower in the combination group (10.87 ± 3.05 vs 13.53 ± 2.69 ; $P=0.001$), and the difference remained at week 8 (7.70 ± 2.93 vs 10.53 ± 2.43 ; $P<0.001$). The time-by-group interaction was significant ($F=88.002$; $P<0.001$). (Table 2)

Table 2. HAMA scores at each time point (mean $\pm$ SD)

Time point	Control (n=30)	Combination (n=30)	t	P
Baseline	20.87 $\pm$ 2.35	22.07 $\pm$ 2.99	-1.728	0.089
Week 1	17.60 $\pm$ 2.33	18.20 $\pm$ 3.12	-0.844	0.402
Week 4	13.53 $\pm$ 2.69	10.87 $\pm$ 3.05	3.594	0.001
Week 8	10.53 $\pm$ 2.43	7.70 $\pm$ 2.93	4.079	<0.001

Note: Between-group comparisons used independent-sample t tests. Time main effect: $F=2410.664$, $P<0.001$; time-by-group interaction: $F=88.002$, $P<0.001$; group main effect: $F=1.833$, $P=0.181$. TCMDs scores were lower in the combination group at weeks 4 and 8 (both $P<0.001$). A significant time-by-group interaction was also observed ($F=93.380$; $P<0.001$). (Table 3)

Table 3. TCMDs scores at each time point (mean $\pm$ SD)

Time point	Control (n=30)	Combination (n=30)	t	P
Baseline	28.30 $\pm$ 2.88	28.43 $\pm$ 3.04	-0.175	0.862
Week 1	24.00 $\pm$ 2.61	23.70 $\pm$ 3.15	0.401	0.690
Week 4	18.67 $\pm$ 3.11	15.27 $\pm$ 3.22	4.162	<0.001
Week 8	14.10 $\pm$ 2.85	9.57 $\pm$ 3.21	5.786	<0.001

Note: Between-group comparisons used independent-sample t tests. Time main effect: $F=3789.426$, $P<0.001$; time-by-group interaction: $F=93.380$, $P<0.001$; group main effect: $F=7.276$, $P=0.009$.

PSQI scores were lower in the combination group at weeks 4 and 8 (both $P<0.001$), and the time-by-group interaction was significant ($F=61.682$; $P<0.001$). Because the PSQI has a 1-month recall period, the week-1 result was treated as descriptive.(Table 4)

Table 4. PSQI scores at each time point (mean $\pm$ SD)

Time point	Control (n=30)	Combination (n=30)	t	P
Baseline	15.17 $\pm$ 1.95	14.50 $\pm$ 1.76	1.392	0.169
Week 1	13.17 $\pm$ 2.05	12.60 $\pm$ 1.79	1.139	0.259
Week 4	10.33 $\pm$ 2.26	7.43 $\pm$ 1.98	5.284	<0.001
Week 8	7.87 $\pm$ 2.33	4.27 $\pm$ 1.93	6.519	<0.001

Note: Between-group comparisons used independent-sample t tests. Time main effect: $F=1600.857$, $P<0.001$; time-by-group interaction: $F=61.682$, $P<0.001$; group main effect: $F=15.465$, $P<0.001$. The PSQI covers the preceding month and does not match the week-1 time point; week-1 data are presented for description only. The repeated-measures model included all four time points (baseline, weeks 1, 4, and 8).

3.4 Therapeutic grade

Thirteen patients in the combination group were classified as recovered, and 17 were markedly improved. In the control group, 17 patients were markedly improved and 13 were improved. The distribution of therapeutic grades favored combination therapy (Mann-Whitney $U=144.5$; $Z=-5.056$; $P<0.001$). Overall, 43.3% of patients receiving combination therapy met the prespecified recovery criterion.

3.5 Safety

Three patients in the control group and 2 in the combination group reported mild dry mouth and constipation during follow-up. The symptoms resolved without specific treatment. No serious drug-related event was reported. These observations describe patient-reported tolerability; laboratory and electrocardiographic safety were not assessed.

4. Discussion

Adding Jiuwei Zhenxin Granules to trazodone was associated with a greater reduction in depressive symptoms than trazodone alone. The difference was apparent at week 4 and larger at week 8. Similar time-by-group patterns for HAMD-17, HAMA-14, TCMDS, and PSQI indicate that the benefit was not confined to depressive symptoms but extended to anxiety, TCM syndromes, and sleep quality.

The anxiety findings developed more gradually. No between-group difference was apparent during the first week, whereas differences emerged at week 4 and remained at week 8. This pattern, together with the time-by-group interaction, is consistent with an add-on benefit after several weeks of treatment.

Few adverse events were reported during outpatient follow-up. Mild dry mouth and constipation resolved without intervention, and no serious drug-related event was reported. These observations support acceptable short-term clinical tolerability, although they do not constitute a comprehensive laboratory safety assessment.

Several limitations should be considered. The study was conducted at one center and included 60 completers, which may restrict the generalizability of the findings. Follow-up lasted 8 weeks,

precluding assessment of sustained benefit, recurrence, or delayed adverse events. The study also relied on clinical scales and did not include biomarkers that might clarify underlying mechanisms. Confirmation in larger multicenter studies with longer follow-up is needed.

5. Conclusion

In patients with heart-spleen deficiency depression, adding Jiuwei Zhenxin Granules to trazodone produced greater improvement than trazodone alone. Differences emerged by week 4 and persisted through week 8 across depressive symptoms, anxiety, TCM syndromes, and sleep quality. Patient-reported tolerability was acceptable, and no serious drug-related event was reported. The results support Jiuwei Zhenxin Granules as an adjunct to trazodone within an integrated Chinese and Western medicine approach.

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