Research Article
The Effect of Zao Ren An Shen Capsule on Insomnia among Patients with Anxiety: A Randomized Controlled Trial

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Background. Zao Ren An Shen capsule (ZRASC) is one of the most widely used Chinese herbal medicine (CHM) in treating insomnia, but its effect on insomnia patients with anxiety remains unclear. We aimed to examine the effect of ZRASC combined with alprazolam in anxiety patients compared with those only with alprazolam prescription.

Methods. We conducted a single-blind, parallel-group, randomized trial involving persons from 2 hospitals in China. Participants were randomly assigned in a 1:1 ratio to the intervention group, in which the participants were provided with ZRASC and alprazolam, or to the control group, in which the participants were provided with alprazolam. The primary outcomes were insomnia symptoms measured by the insomnia severity index (ISI). The secondary outcomes were anxiety symptoms measured with the Hamilton anxiety rating scale (HAMA). All participants were followed up at 2-week and 4-week after the treatment. The effect was estimated using the mixed-effect models.

Results. A total of 334 patients were enrolled in the trial. 167 of them (mean(SD) age, 44.4 (12.8) years; 43.1% female) were assigned to the usual treatment group, while 167 (mean(SD) age, 46.0 (13.4) years; 43.7% female) were assigned to the ZRASC group. From baseline to the 4-weekfollow-up, the mean differences in ISI and HAMA scores between the ZRASC group and the usual care group were −2.542 and −2.563, respectively (both \( p < 0.001 \)). Patients in the ZRASC group were more likely to have remission of insomnia and anxiety than those in the control group at the 4-weekfollow-up, with incidence rate ratios of 265% and 213%, respectively (both \( p < 0.001 \)). Proportions of remission were 74.93% (\( p < 0.001 \)) for insomnia and 85.80% (\( p < 0.001 \)) for anxiety at 4-weekfollow-up. Conclusions. This randomized study showed that adjunctive treatment with ZRASC was able to reduce insomnia and anxiety symptoms at the 4-weekfollow-up. Trial Registration. This study was registered in the Chinese Clinical Trial Registry (ChiCTR1800019913).

1. Introduction

Insomnia is a distressing condition in the general population, with a prevalence rate of up to 30% depending on various diagnostic criteria [1, 2]. There is a high comorbidity of insomnia with other psychiatric illnesses, such as depression and anxiety. It is also one of the criteria for diagnosing anxiety disorder due to its overlapped neurobiological and psychosocial factors. Previous research has shown that 40–60% of insomnia patients have comorbid anxiety disorders [3–6], suggesting a close link between these two illnesses. The presence of insomnia in psychiatric patients might negatively impact the trajectory of mood symptoms and worsen the symptoms, while treatment of insomnia could alleviate the anxiety symptoms. In addition, the comorbidity of insomnia and anxiety could further intensify the negative influence associated with illnesses such as drug abuse and alcohol addiction [7].

Conventional approaches to treat insomnia are pharmacotherapies or psychological interventions or a combination of both. Cognitive-behavioral therapy for insomnia (CBT-I) has been considered the first-line treatment for adults with insomnia [8]. Due to its lower accessibility and the limited number of trained therapists, the application of
CBT-I is underutilized [9–11]. While for the pharmacotherapy approach, the commonly prescribed medication, benzodiazepine receptor agonists (BZRAs) is considered an effective treatment for insomnia; however, it has a potential risk of tolerance and addiction after long-term use [12]. Short-term side effects such as drowsiness and dizziness are commonly reported [11, 13, 14]. Moreover, help-seeking behavior is relatively low among insomnia patients [1, 15–17].

Among patients who seek treatment for managing their sleep problems, complementary and alternative medicines (CAMs) have been considered the most preferred therapeutic approach [17]. For example, previous research has reported that a growing number of people are using herbal medications, not only for medical illnesses but also in the psychiatric population [18–21]. A study from the United States National Health Interview Survey has revealed that about 5% of adults have used CAM to treat their insomnia problems in the past 1 year [22], with Chinese herbal medicine (CHM) as one of the most commonly used CAMs [23].

Among the various types of CHM, the Zao Ren An Shen capsule (ZRASC) is one of the most widely used CHMs in treating insomnia [24–26]. ZRASC is shown to have the function of hypnotic and sedative effects through the GABAergic and serotonergic systems. Previous studies have suggested the effectiveness of ZRASC in treating insomnia [27, 28]. However, due to methodological limitations and the limited number of randomized controlled trials, there remain concerns and doubts about the safety and efficacy of using herbal medicine to treat insomnia in the psychiatric population [18, 19, 29].

The majority of the studies using ZRASC as a treatment are focused on insomnia alone. Given the close association between insomnia and psychiatric disorders such as anxiety, it is worth examining the effect of this herbal medicine on both insomnia and anxiety. Thus, this study is aimed at examining the effect of ZRASC combined with alprazolam on insomnia patients with anxiety compared with those only treated with alprazolam. It is hypothesized that anxiety patients who received additional herbal medicine would demonstrate greater improvement in their insomnia and anxiety symptoms.

2. Materials and Methods

2.1. Study Design and Participants. This study was a single-blind, parallel-group, randomized trial conducted at 2 hospitals located in Heilongjiang Province and Henan Province, China. Patients who fulfilled the study criteria were randomly allocated to either the herbal combination treatment (ZRASC and alprazolam) or the control group (alprazolam). All participants were followed up at the hospitals at 2-week and 4-week after the treatment (Figure 1), and they were required to pick up the empty ZRASC cartridges they had taken at the follow-up visits.

The inclusion criteria of the study were as follows: (1) aged between 18 and 65 years old; (2) Hamilton anxiety scale score ≥17; (3) insomnia severity index ≥14; and (4) receiving treatment with alprazolam. The exclusion criteria were as follows: (1) liver or kidney dysfunction; (2) taking other medications that would affect sleep quality; (3) having other severe psychiatric disorders such as schizophrenia; (4) having a chronic medical condition that was not suitable for the study as suggested by the clinician; (5) being the shift worker; and (6) having a history of allergy to the herbal medication.

The study has been granted ethical approval by the hospital ethics committee (No. 2018-KL-002-03), and the trial was registered in the Chinese Clinical Trial Registry (ChiCTR1800019913). Written informed consent was obtained from every participant before entering the trial.

2.2. Randomization and Blinding. Participants were randomly assigned to either the intervention group or the control group in a 1:1 ratio. A researcher generated a randomization sequence without stratification based on the computer-generated numbers. Researchers and clinicians were blind to treatment assignments. Only the nurse responsible for delivering the medication was aware of the group allocation.

2.3. Intervention. Participants in the intervention group were provided with ZRASC and alprazolam. ZRASC is a CHM formula composed of the herbs Suan zao ren (Ziziphi spinosae Semen), Wu wei zi (Schisandrae chinensis Fructus), and Dan shen (Salviae miltiorrhizae Radix et Rhizoma). ZRASC is widely used in China for the treatment of insomnia. The effectiveness and safety of ZRASC for the treatment of insomnia have been confirmed by the State Food and Drug Administration on July 10, 2002. The participants in the intervention group were instructed to take 5 ZRASC (Sinopharm Group Tongjiang (Guizhou) Pharmaceutical Co., Ltd.) every day for 4 weeks before bedtime together with alprazolam.

2.4. Measures. The primary outcome in the study was insomnia symptoms measured by the insomnia severity index (ISI). The ISI is a 7-itemself-report questionnaire to assess perceived insomnia symptoms, with a score of 0–4 for each item and a total score of 0–28. The score of ISI is positively associated with insomnia severity. A cutoff score of 14 was used to define the diagnosis of insomnia in this study. If the ISI score was less than 14, then the patient was defined as having remission of insomnia. The ISI questionnaire was completed by the participant under the guidance of medical staff.

The secondary outcome was anxiety symptoms measured with the Hamilton anxiety rating Scale (HAMA). HAMA is a 14-itemclinician-rated scale used to assess both psychiatric and somatic anxiety symptoms. Each item is scored from 0 (not present) to 4 (severe), and the total score indicates the level of severity with the following cutoff: less than 17 indicates mild severity, 18–24 mild to moderate severity, and 25–30 moderate to severe severity. If the HAMA score was less than 25, the patient would be defined as having remission from anxiety. These two scales have been proven to have acceptable interrater reliability [30].
2.5. Sample Size. The standard deviation of the total ISI score for the insomnia population was 4.1 in a previous study [31]. The sample size in this study was calculated based on a statistical power of 90% and a type I error of 5%. A sample size of 316 participants was obtained from the calculation. We therefore recruited 334 patients (167 participants per group) to account for any dropouts.

2.6. Statistical Analysis. Demographic data and clinical characteristics between groups were compared using the independent t-test and chi-square test for continuous and categorical variables, respectively. The interaction effects between time and treatment were explored using linear mixed models. The linear mixed model enables us to include all participants in the model despite their missing follow-up assessments. It also allows us to adjust the dependency of the repeated observations within the individual by adding a random intercept to the model.

The linear mixed model is constructed as

\[ Y_{it} = \beta_0 + \beta_1 \text{Time}_{1it} + \beta_2 \text{Time}_{2it} + \beta_3 \text{Time}_{1it} \times \text{Treatment}_{it} + \beta_4 \text{Time}_{2it} \times \text{Treatment}_{it} + \mu_i + \epsilon_{it}. \]  

Here, \( Y_{it} \) refers to the score of ISI or HAMA. Treatment, which represents whether the participant is in the ZRASC group or the control group, is binary. \( \mu_i \) is the random intercept for each participant. \( \text{Time}_1 \) and \( \text{Time}_2 \) are two dummy variables that represent the 2-week follow-up and 4-week follow-up, respectively. \( \beta_3 \) and \( \beta_4 \) are the coefficients of interest, which represent the treatment effect at the two time points.

The generalized estimating equation (GEE) model was used to estimate the effect on the remission proportion of insomnia and anxiety. Poisson family with log link was selected to directly estimate incidence rate ratios (IRR).

All statistical analyses were conducted using Stata software, version 17.0 MP (StataCorp LLC). A p value of less than 0.05 was considered to be statistically significant.
3. Results and Discussion

3.1. Baseline Characteristics. Figure 1 shows the recruitment progress of the study. A total of 334 participants were enrolled in the study. The baseline characteristics of the study population are given in Table 1. Of them (mean (SD) age, 44.4 (12.8) years; 43.1% female) were assigned to the control group, while 167 (mean (SD) age, 46.0 (13.4) years; 43.7% female) were in the ZRASC group, of whom 97.6% of the intervention group attended 2-week follow-up and 91.6% attended a 4-week follow-up, while for the control group, 98.2% and 86.2% attended 2-week and 4-week follow-up, respectively. Lost to 4-week follow-up was significantly higher in the intervention group relative to the control group (p < 0.05). Among the participants at baseline, 85.6% were married and 44.9% had a college education or above in the ZRASC group; 88.6% were married and 53.9% had a college education or above in the control group. There was no significant difference between gender and age between the two groups (p > 0.05). The mean (SD) baseline score on the ISI (minimum score, 0; maximum, 28) was 16.3 (2.0) in the ZRASC group and 16.4 (2.1) in the control group. The mean (SD) baseline score on the HAMA was 18.5 (3.6) in the ZRASC group and 17.9 (2.5) in the control group.

3.2. Efficacy Outcomes. Table 2 shows the estimated treatment effect of ZRASC on the ISI and HAMA scores. The mixed-effects model for insomnia and anxiety showed no significant treatment group main effect (p > 0.05), indicating no differences in remission proportions of insomnia and anxiety between the groups at baseline. ZRASC intervention had no effect on remission of insomnia and anxiety at a 2-week follow-up (p > 0.05). However, compared with the baseline, the incidence rates of remission of insomnia and anxiety were 2.65 (p < 0.01) and 2.126 (p < 0.001) times higher in the ZRASC group than in the control group at the 4-week follow-up, respectively. Furthermore, we calculated the marginal effects of ZRASC on the remission of insomnia and anxiety to transform the regression coefficient into probability or proportion, and the results are shown in Figure 3. The estimated proportions of remission of insomnia and anxiety in the ZRASC group were significantly higher than those in the control group at the 4-week follow-up (p < 0.001). At the 4-week follow-up, the

### Table 1: Baseline characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention group, n = 167</th>
<th>Control group, n = 167</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.0 (13.4)</td>
<td>44.4 (12.8)</td>
</tr>
<tr>
<td>Sex, female, no. (%)</td>
<td>73 (43.7)</td>
<td>72 (43.1)</td>
</tr>
<tr>
<td>Marital status, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>143 (85.6)</td>
<td>148 (88.6)</td>
</tr>
<tr>
<td>Divorced</td>
<td>6 (3.6)</td>
<td>8 (4.8)</td>
</tr>
<tr>
<td>Widowed</td>
<td>5 (3.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Single</td>
<td>13 (7.8)</td>
<td>10 (6.0)</td>
</tr>
<tr>
<td>Education, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>92 (55.1)</td>
<td>77 (46.1)</td>
</tr>
<tr>
<td>College or above</td>
<td>75 (44.9)</td>
<td>90 (53.9)</td>
</tr>
<tr>
<td>ISI score</td>
<td>16.3 (2.0)</td>
<td>16.4 (2.1)</td>
</tr>
<tr>
<td>HAMA score</td>
<td>18.5 (3.6)</td>
<td>17.9 (2.5)</td>
</tr>
</tbody>
</table>

ISI, the insomnia severity index; scores range from 0 to 28; higher scores indicate more severe insomnia. HAMA, the Hamilton anxiety rating scale; scores range from 0 to 56; higher scores indicate more severe anxiety; 0–17 indicates mild severity, 18–24 mild to moderate severity, and 25–30 moderate to severe.

### Table 2: The effect of ZRASC on the ISI and HAMA scores: mixed effect model.

<table>
<thead>
<tr>
<th></th>
<th>ISI</th>
<th>HAMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (reference group: the control group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZRASC group</td>
<td>-0.108 (0.760)</td>
<td>0.593 (0.179)</td>
</tr>
<tr>
<td>Time (reference group: baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-week follow-up</td>
<td>-3.269**</td>
<td>-3.163***</td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
</tr>
<tr>
<td>4-week follow-up</td>
<td>-2.793***</td>
<td>-3.105***</td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
</tr>
<tr>
<td>Interaction with time (reference group: ZRASC group # baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZRASC group #</td>
<td>-0.173 (0.626)</td>
<td>-0.748 (0.069)</td>
</tr>
<tr>
<td>2-week follow-up</td>
<td>-2.542***</td>
<td>-2.563***</td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
</tr>
<tr>
<td>4-week follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>_cons</td>
<td>16.36***</td>
<td>17.88**</td>
</tr>
<tr>
<td></td>
<td>(0.000)</td>
<td>(0.000)</td>
</tr>
</tbody>
</table>

P values in parentheses. *p < 0.05, **p < 0.01, ***p < 0.001. ZRASC, Zao Ren An Shen capsule. ISI, the insomnia severity index; scores range from 0 to 28; higher scores indicate more severe insomnia. HAMA, the Hamilton anxiety rating scale; scores range from 0 to 56; higher scores indicate a greater severity of anxiety symptoms.

As is shown in Table 3, the GEE models for insomnia and anxiety showed no significant treatment group main effect (p > 0.05), indicating no differences in remission proportions of insomnia and anxiety between the groups at baseline. ZRASC intervention had no effect on remission of insomnia and anxiety at a 2-week follow-up (p > 0.05). However, compared with the baseline, the incidence rates of remission of insomnia and anxiety were 2.65 (p < 0.01) and 2.126 (p < 0.001) times higher in the ZRASC group than in the control group at the 4-week follow-up, respectively. Furthermore, we calculated the marginal effects of ZRASC on the remission of insomnia and anxiety to transform the regression coefficient into probability or proportion, and the results are shown in Figure 3. The estimated proportions of remission of insomnia and anxiety in the ZRASC group were significantly higher than those in the control group at the 4-week follow-up (p < 0.001). At the 4-week follow-up, the
proportions of remissions were 74.93% \((p < 0.001)\) for insomnia and 85.80% \((p < 0.001)\) for anxiety in the ZRASC group, while the proportions of remissions were 32.9% for insomnia and 45.3% for anxiety in the control group.

### 4. Discussion

The findings demonstrated that the combination of ZRASC and alprazolam is effective in reducing both insomnia and anxiety symptoms compared to patients who took alprazolam alone at a 4-week follow-up. In addition, both insomnia and anxiety remission rates were also higher in the herbal treatment group at the 4-week follow-up, suggesting that the ZRASC capsule had the potential to alleviate these symptoms and had an additional effect when combined with the usual medication treatment. The effect was consistent with previous studies that investigated the effect of ZRASC in treating insomnia [32, 33]. However, the majority of previous studies used ZRASC decoction [29, 34], and limited evidence was available on the ZRASC capsule. The study provides evidence that the ZRASC capsule had an additional effect when added to the usual treatment received by anxiety patients.

The current study added to the existing literature that the ZRASC capsule is not only able to reduce insomnia symptoms but also has a positive effect on anxiety. Many of the previous studies exploring the treatment effects of ZRASC only focused on sleep disturbances without consideration of mood symptoms, despite their close association. Therefore, the findings of the current study have
provided some evidence that ZRASC is also able to reduce mood symptoms. However, the mechanism remains unknown.

It is well documented that ZRASC has sedative and hypnotic effects through the GABAergic and serotonergic systems [26, 35] and has been used for treating insomnia for a long time [26], which is further confirmed by our study. Our results showed that the effect seemed to emerge at the 4-week follow-up, which indicated that the herbal medicine takes a slightly longer time to be effective. Although the slightly delayed effect of ZRASC was contrary to our expectations, a previous study also demonstrated similar results [29]. In addition, the improvement of anxiety symptoms in this study has suggested that ZRASC can also be used to reduce anxiety symptoms. However, the exact reasons for the improvement of anxiety symptoms were not able to be demonstrated in our current study design. The improvement may be mediated by the improvement of insomnia symptoms, which is one of the diagnostic criteria for anxiety disorders.

One of the strengths of this study is that it had a large sample size recruited in a multicenter study, which increases the generalizability of the study findings. In addition, the assessors were blinded to the allocation of the treatment conditions, which could limit the potential bias of assessors. This study has the following limitations: first, psychiatric histories such as the onset of anxiety disorder and medications that might potentially affect the treatment effects were not recorded. Second, only subjective measurement of insomnia symptoms was included in the study; it might be helpful to include actigraphy and a sleep diary to measure other sleep parameters that are closely related to insomnia.

Third, possible adverse events were not recorded in the study, which might raise concerns about the safety of the ZRASC capsule, although it has been widely used in the clinical setting. Moreover, the large age range included in the current study might also potentially lead to heterogeneity in treatment effects.

In summary, Chinese medicine has been widely used to treat insomnia. The current study provided evidence that the ZRASC capsule is also able to improve anxiety symptoms. Future studies are needed to confirm its effectiveness and to indicate what properties ZRASC has that may contribute to its ability to reduce mood symptoms. It is necessary to conduct a randomized controlled trial with a more robust design that includes objective measurements of both sleep and mood to evaluate the effectiveness of ZRASC in reducing symptoms of insomnia and anxiety.

5. Conclusions

This study provided some evidence on the effectiveness of the ZRASC capsule in improving both insomnia and anxiety symptoms. Future studies that use a more robust study design with objective measurements are warranted to further demonstrate its efficacy.

Data Availability

The data used to support the findings of this study are available from the corresponding author (Chenggang Jin) upon request.
Disclosure

Ge Yu and Xi Cheng are the co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Ge Yu and Xi Cheng contributed equally to this work. Ge Yu contributed to investigation and writing the original draft. Xi Cheng contributed to writing the original draft and review and editing. Chenggang Jin contributed to data analysis and review and editing. All the authors read and approved the final manuscript.

Acknowledgments

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References


