

Research Article

The Efficacy and Safety of Zaoren Anshen Capsule in Combination with Zolpidem for Insomnia: A Multicentre, Randomized, Double-Blinded, Placebo-Controlled Trial

Xiangzhen Zhu,¹ Ming Tao,² Haoyu Hu,³ Jingfang Gao ¹, Jiong Chen,⁴ Tiaotiao Lu,⁵ Xiaole Wang,¹ Wei Kong,⁵ Lijun Lv,³ and Minjun Wei⁴

¹The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), Hangzhou, China

²Zhejiang Chinese Medical University, Hangzhou, China

³Jinhua Hospital of Traditional Chinese Medicine, Jinhua, Zhejiang, China

⁴Tongde Hospital of Zhejiang Province, Hangzhou, China

⁵The Second Affiliated Hospital of Zhejiang Chinese Medical University (Xinhua Hospital of Zhejiang Province), Hangzhou, China

Correspondence should be addressed to Jingfang Gao; gjingfang@hotmail.com

Received 6 May 2022; Accepted 9 September 2022; Published 23 November 2022

Academic Editor: Slim Smaoui

Copyright © 2022 Xiangzhen Zhu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. Insomnia is the most common sleep disorder with high rate of prevalence, persistence, and leads to negative consequences. The mainstays of insomnia treatment have limitations due to either the side effects of hypnotics or limited accessibility to cognitive behavioral therapy. This study aims to compare the efficacy and safety of the traditional Chinese medicine (TCM) Zaoren Anshen capsule alone or as an adjunct treatment with different doses of the nonbenzodiazepine medication zolpidem tartrate in treating insomnia. **Method.** This randomized, double-blind, multicentre placebo control trial was conducted in 131 patients with chronic insomnia. The patients were randomly assigned to one of the following four regimen groups: Group ZA + Z5: Zaoren Anshen capsule and 5 mg zolpidem tartrate ($n = 32$); Group Z5: 5 mg zolpidem tartrate and placebo capsule ($n = 35$); Group Z10: 10 mg zolpidem tartrate and placebo capsule ($n = 32$); Group ZA: Zaoren Anshen capsule and placebo pill ($n = 32$). The drugs were administered for 4 weeks. All patients were evaluated by the Insomnia Severity Index (ISI) at 0, 2, 4, 5, and 6 weeks, and adverse events were recorded. **Result.** There are significant differences in the comparison between the four groups at each treatment stage ($P < 0.05$). Repeated measurement analysis of variance (ANOVA) of ISI scores in each treatment stage of the four groups exhibits significant differences in time effect, intergroup effect, and interaction effect ($P < 0.05$). After four weeks of drug administration, the treatment efficacy is similar in Groups ZA + Z5 and Z10 (93%) and in Groups Z5 and ZA (62% and 65%, respectively). Groups ZA + Z5 and Z10 present significantly lower ISI scores compared with Groups Z5 and ZA ($P < 0.05$), which indicates better treatment response of Groups ZA + Z5 and Z10. No significant difference was observed in the incidence of adverse events between the groups. **Conclusion.** Zaoren Anshen capsule can effectively treat insomnia disorder either alone or in combination with zolpidem tartrate. A preferred combination of TCM Zaoren Anshen capsule with zolpidem can provide a magnified therapeutic efficacy with fewer side effects than zolpidem-only management, clinical trial registration number: Chinese Clinical Trial Registry ChiCTR-IPR-1600969.

1. Introduction

Insomnia is the most common sleep disorder with an estimated prevalence of 10–20% in the general population [1]. The occurrence of insomnia increases with age. It is reported that 30%–48% of the elderly population has ever experienced symptoms related to insomnia, which can be partially attributed to developmental changes in sleep architecture [2].

Besides being prevalent, insomnia is also highly persistent and recurrent. The persistence rate of insomnia over a 5-year duration can reach up to 40%. Patients with insomnia exhibit high risk of physical and mental illness such as cardiovascular disease [3, 4], diabetes [5–7], and chronic kidney disease [8, 9]. Insomnia is also associated with chronic pain [3, 10], dementia [11], anxiety [12, 13], and depression [14–16]. All of the conditions will further impair the quality of life and increase morbidity and mortality [17, 18]. Impaired attention and awareness secondary to poor sleep have been reported to significantly increase accidents and injuries [19, 20]. The distress associated with insomnia is now a public health concern. Thus far, tremendous direct and indirect costs associated with insomnia impose a heavy financial burden on both individuals and society [21–23]. Initiating safe and effective treatment in a timely manner is appreciated because it can not only reduce the functioning disability caused directly by insomnia, but also prevent the associated negative physical and psychological consequences.

Current mainstay of insomnia treatment includes both pharmacological and nonpharmacological approaches [24–26]. However, in clinical practice, both approaches have limitations. Drugs commonly used to treat insomnia such as benzodiazepine receptor agonists cause adverse effects such as hangovers, dizziness, and fatigue [27–29]. The long-term use of these drugs may lead to drug dependence as well as withdrawal when discontinued inappropriately [30]. Due to the limitations and side effects, hypnotic medication should be used under the care of a physician for short periods. When it comes to the nonpharmacological approach, cognitive behavioral therapy for insomnia (CBT-I) has been proven to be effective and recommended as the first-line treatment for insomnia. Studies have shown that CBT-I exhibits short-term effects similar to those of medication, whereas the therapeutic gains could be sustained for a longer time period with CBT-I [31, 32]. However, there are various conditions limiting patients from receiving efficacious CBT-I treatment, such as poor geographical accessibility to healthcare, lack of trained therapists, and relatively high cost [32, 33].

Due to the side effects of hypnotics and limited accessibility to CBT-I, alternative approaches such as traditional Chinese medicine (TCM) have become viable complementary strategies [34, 35]. TCM exhibits a long history in Chinese medical practice and is progressively being recognized in the world. Systematic analyses of randomized controlled studies on TCM for insomnia have demonstrated the safety and efficacy in improving sleep quality [36–38]. Zaoren Anshen capsule is a Chinese patent medication that has been made in accordance with the standards of

a nonbenzodiazepine sedative hypnotic to treat insomnia. The capsule comprises three TCM ingredients, namely Suan Zao Ren (*Ziziphi Spinosa* Semen, 417 mg/capsule), Wu Wei Zi (*Schisandrae Chinensis* Fructus, 70 mg/capsule), and Dan Shen (*Salviae Miltiorrhizae* Radix et Rhizoma, 167 mg/capsule) [39]. Clinical studies have suggested that Zaoren Anshen capsule has higher efficacy than that of placebo and that it produces a similar effect as benzodiazepines with fewer side effects [40, 41]. Unfortunately, these studies have methodological limitations such as lack of an active control group, small sample size, and lack of long-term follow-up. In addition, it remains unclear whether the combination of TCM with drugs can provide additional therapeutic gains. Thus, a study with a robust design is required to evaluate TCM Zaoren Anshen capsule's efficacy in treating insomnia.

This study aims to compare the efficacy and safety of the TCM Zaoren Anshen capsule alone or as an adjunct treatment with different doses of the nonbenzodiazepine medication zolpidem tartrate in treating insomnia.

2. Methods

2.1. Study Design. The present randomized, double-blind, and parallel placebo-controlled study was conducted in 135 participants recruited from four hospitals (Zhejiang Provincial Hospital of Traditional Chinese Medicine ($n=50$), Xinhua Hospital in Zhejiang Province ($n=41$), Tongde Hospital in Zhejiang Province ($n=20$), and Jinhua Hospital of Traditional Chinese Medicine ($n=24$)) in Zhejiang Province of China from December 2016 to December 2018. After baseline assessment, the participants received a 4-week intervention, requiring assessment during weeks 2 and 4, and reassessment at weeks 5 and 6. The study was approved by the Ethics Committee of Zhejiang Provincial Hospital of Traditional Chinese Medicine (number: 2016-KL-009-01) and registered at the Chinese clinical trial registry (registration number: ChiCTR-IPR-16009669).

2.2. Randomization and Blinding. The participants were blinded to the group allocation. The random coding table was established by the clinical research data management and statistical unit. The blinding code was sealed and submitted to the responsible clinical research unit and sponsor for proper preservation. A statistical professional who did not have contact with the participants during the study period conducted the randomization procedure. The entire drug coding process was documented by a person unrelated to the present clinical study. The assessors who were responsible for drug prescription and assessments were also blinded to the group allocation. The randomization list was kept confidential throughout the study period unless any adverse event was reported.

2.3. Participants. The participants were recruited from four hospitals in Zhejiang. These participants' age varied from 18 to 65, educated beyond grade 3, and diagnosed with insomnia disorder according to the Diagnostic and Statistical Manual of Mental Disorders version 5, and with a Pittsburgh

Sleep Quality Index (PSQI) score >7. Participants with following conditions were excluded from the study: ① patients who were professional drivers or aerial workers; ② patients who were already on sleep medications; ③ pregnant and lactating women; ④ patients with severe chronic diseases such as cancer, cardiovascular diseases, and kidney dysfunction; ⑤ those allergic to zolpidem tartrate or Zaoren Anshen capsules; ⑥ patients with mental disorders or with severe epilepsy; ⑦ patients with psychiatric disorders such as depression (Hamilton Depression Rating Scale-17 (HAMD) ≥ 17), anxiety (Hamilton Anxiety Rating Scale (HAMA) ≥ 14), and alcohol or drug abuser; ⑧ those who had participated in other drug clinical trials within 3 months of enrollment; and ⑨ those who were unable to provide informed consent were excluded from the study.

2.4. Interventions. Eligible participants were randomly assigned to one of the following four groups: Group ZA + Z5: Zaoren Anshen capsule and 5 mg zolpidem tartrate; Group Z5: placebo capsule and 5 mg zolpidem tartrate; Group Z10: Placebo capsule and 10 mg zolpidem; and Group ZA: Zaoren Anshen capsule and placebo pill.

After randomization, the participants were administered the therapy as per their assigned regimen once a day before bedtime for 4 weeks. After 4 weeks, the drug was discontinued and the withdrawal reaction was observed. The participants were provided with health education during the treatment.

During the trial, drugs other than those specified in the dosing regimen such as other TCMs, Western medicine for insomnia, and external treatment methods were not used as these drugs may affect drug efficacy evaluation. All the participants had to comply with the combined medication regulations during the period from drug initiation to the assessment of efficacy and safety.

The blinding code could be broken urgently when an emergency occurred during the study (such as a serious adverse event), or when a patient without any former treatment recorded need to be rescued in the study. Emergency blindness breaking must be decided by the main investigators. The cause, time, and place of breaking the code need to be recorded in detail and signed.

2.5. Efficacy Evaluation. Insomnia symptoms were measured using the Insomnia Severity Index (ISI). ISI is a 7-item self-reported questionnaire that assesses the insomnia severity over 2 weeks. The treatment efficacy was measured by changes in the pre- and postintervention ISI score.

ISI decline rate = (pre-post ISI score difference)/pre-ISI score $\times 100\%$.

The clinical significance and parameters of the treatment were defined as follows: ① recovery: decline rate $\geq 95\%$; ② significant effect: decline rate is 60%–94%; ③ effective: decline rate is 30%–59%; and ④ no change: decline rate <30%. Effective rate = (the number of cured cases + the number of significant cases + the number of effective cases)/the total number of cases in this group $\times 100\%$.

2.5.1. Adverse Events. Adverse events reported by patients during the intervention and follow-up period were recorded using an adverse event form. A description of the adverse events, time duration, severity, seriousness, adverse event outcome, and relationship with the experimental procedure were recorded. The number of adverse events was used to assess the safety of experimental drugs.

2.6. Statistical Analysis. All statistical tests were two-sided, and P values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 22.0. Continuous data were analyzed with ANOVA and repeated measurement ANOVA. Mean, standard deviation, effect size, and the P value were recorded. The pairwise t -test was used to compare between the pre- and posttreatment changes in the groups and baseline values in the screening period. The data that did not meet the normal distribution were represented by median (upper quartile and lower quartile). Rank-sum tests were used for comparison between the groups. Counting data of each visit in different treatment groups were described statistically by frequency (composition ratio). Pre- and posttreatment changes between the two groups were analyzed using the χ^2 test or nonparametric test.

2.6.1. Full Analysis Set. The full analysis set (FAS) refers to the ideal subject set as close as possible to the intent analysis principle (main analysis should include all randomized subjects). The data set was eliminated in the smallest and most reasonable method from all randomized subjects. The missing ISI, PSQI, HAMD, and HAMA values were estimated by carrying forward the last observation data carry-over method (LOCF) to the place where the study data were missing. The result was consistent with those in the beginning of the study. The FAS population was used for the analysis of primary and partial secondary efficacy indicators.

2.6.2. Per Protocol Set. Patients with drug dosage of 80%–120% exhibited superior compliance, did not use prohibited drugs during the study period, withdrew the drug early for 2 weeks without any change or exacerbation, and completed the CRF regulations. The per protocol set (PPS) population was used for analyzing primary and secondary efficacy indicators.

2.6.3. Safety Set (SS). All patients using at least one study drug with at least one safety evaluation record constituted the safety analysis population in the present study. Safety population is the main population for safety evaluation in this study.

3. Result

3.1. Enrollment and Completion. All the participants from Groups ZA + Z5 and Z5 completed the study, whereas one patient from Group Z10 and three patients from Group ZA

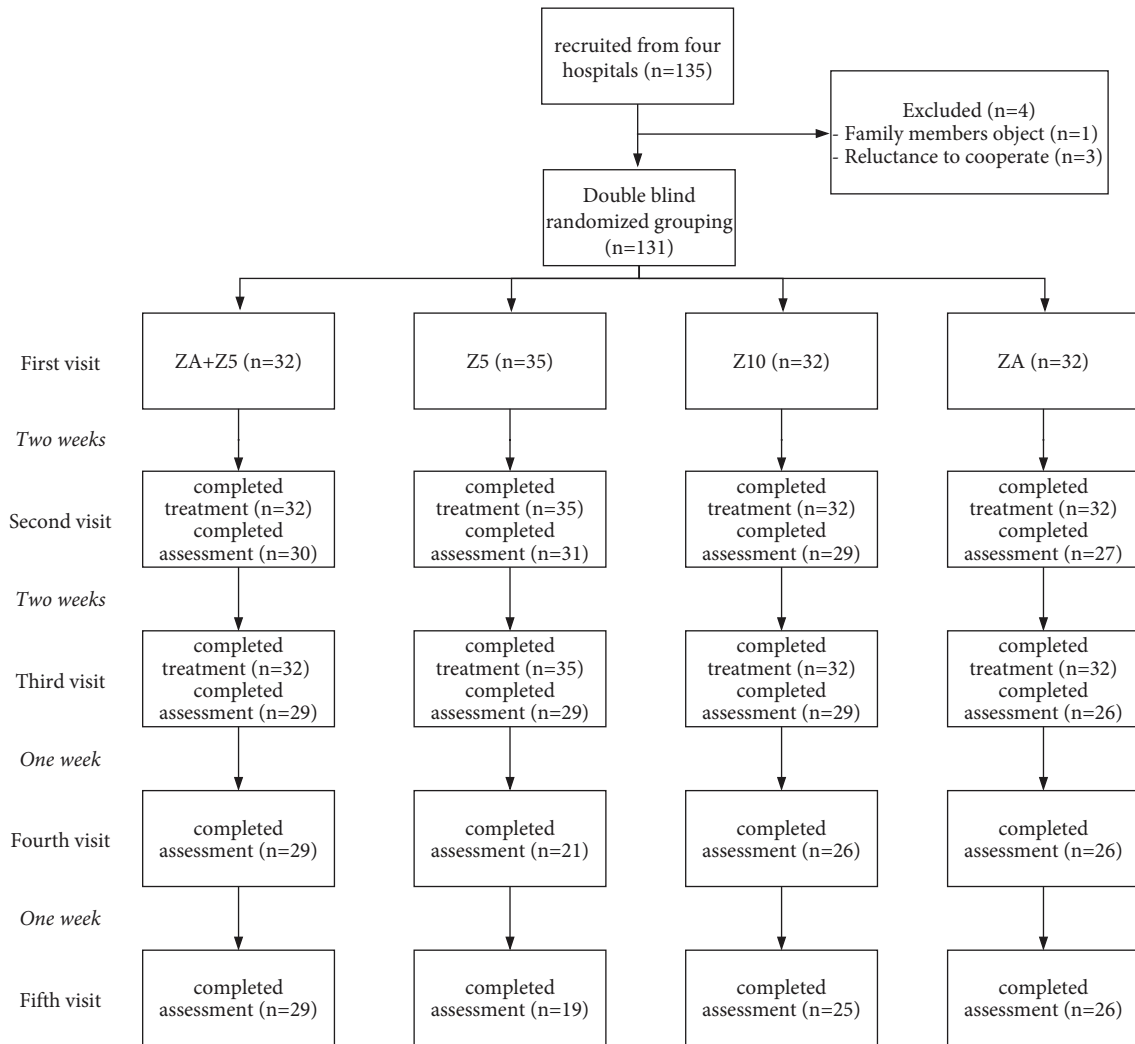


FIGURE 1: Flowchart of recruitment and randomization processes.

TABLE 1: Participant characteristics by group.

Demographics	ZA + Z5 (N = 32)	Z5 (N = 35)	Z10 (N = 32)	ZA (N = 32)	Statistics	P values
Age (y) mean (SD)	48 (12)	44 (13)	47 (14)	51 (13)	$F = 1.58$	0.20
Height (cm) mean (SD)	164 (8)	162 (7)	163 (8)	163 (7)	$F = 0.23$	0.88
Weight (kg) mean (SD)	58 (9)	56 (8)	59 (11)	61 (9)	$F = 1.68$	0.17
Sex					$\chi^2 = 1.91$	0.59
Male	10	10	14	11		
Female	22	25	18	21		

dropped out of the study. The overall shedding rate was 2.96%. Figure 1 shows the recruiting and randomization processes.

3.2. Participant Characteristics. Participant characteristics are presented in Table 1. The four groups did not differ in terms of age, gender, height, and weight ($P > 0.05$).

3.3. Clinical Efficacy. ISI scores of the four groups at each treatment stage are presented in Table 2. No significant difference was observed in the ISI scores between the groups

in baseline ($P > 0.05$). However, a significant difference was observed between the groups during weeks 2, 4, 5, and 6 ($P > 0.05$). The conclusions of FAS and PPS datasets were consistent (Table 2).

Since the medication had been discontinued by 5 and 6 weeks, many patients were reluctant to come to the hospital, resulting in an increase in missing data, but none of these patients had significant adverse effects and were able to sleep well according to our telephone visits.

Repeated measurement ANOVA of ISI in each treatment stage of the four groups exhibited significant differences in

TABLE 2: Intention-to-treat analysis of ISI scores.

	Mean values (SD)				Between group differences			
	ZA + Z5 (n = 32)	Z5 (n = 32)	Z10 (n = 32)	ZA (n = 32)	FAS (n = 131)		PPS (n = 98)	
					F values	P values	F values	P values
Baseline	14.03 (2.57)	14.09 (4.00)	13.31 (3.82)	14.53 (3.84)	0.62	0.60	0.62	0.60
Week 2	6.80 (2.38)	9.84 (4.57)	6.72 (5.13)	11.11 (3.99)	8.74	<0.001	8.07	<0.001
Week 4	5.34 (2.91)	9.03 (3.78)	5.62 (3.55)	9.04 (4.42)	9.39	<0.001	8.78	<0.001
Week 5	5.34 (2.78)	8.59 (3.97)	5.04 (4.39)	8.24 (3.07)	8.28	<0.001	6.68	<0.001
Week 6	5.14 (3.32)	7.74 (3.83)	4.84 (3.80)	7.15 (2.62)	6.82	<0.001	4.24	0.01

TABLE 3: Repeated measure ANOVA results of ISI scores of the four groups.

Items	FAS (n = 131)		PPS (n = 98)	
	F	P	F	P
The time effect	164.390	<0.001	168.875	<0.001
The intergroup effect	8.267	<0.001	5.560	0.001
The interaction effect	4.083	<0.001	3.960	<0.001

time effect, intergroup effect, and interaction effect ($P < 0.05$). The conclusions of the FAS and PPS datasets were consistent (Table 3).

The ISI scores were compared between the two groups through repeated measurement ANOVA at each treatment stage. Significant differences were observed between Group ZA + Z5 and Group Z5, Group ZA + Z5 and Group ZA, Group Z5 and Group Z10, and Group Z10 and Group ZA ($P < 0.05$). On the other hand, no significant difference was observed between Group Z5 and Group ZA and Group ZA + Z5 and Group Z10 ($P > 0.05$). The conclusions of FAS and PPS datasets were consistent (Table 4).

Four weeks after treatment, similar treatment efficacy was observed between Groups ZA + Z5 and Z10 (93%) and between Groups Z5 and ZA (62% and 65%, respectively) (Figure 1). Groups ZA + Z5 and Z10 exhibited better treatment efficacy than Groups Z5 and ZA ($P < 0.05$). The conclusions of FAS and PPS datasets were consistent. No statistically significant difference was observed between Groups Z5 and ZA ($P > 0.05$) and between Groups ZA + Z5 and Z10 ($P > 0.05$). The FAS and PPS datasets were consistent. Figure 2 shows the treatment efficacy between 4 groups.

3.4. Adverse Events. Adverse reactions were observed in 19 participants (Table 5). There were three participants of Group ZA + Z5 (9%), six participants of Group Z5 (17%), eight participants of Group Z10 (25%), and two participants of Group ZA (6%). No significant difference was observed in the incidence of adverse events between the groups (Table 6).

4. Discussion

More and more evidences show that complementary and alternative medicine (CAM) can supplement other medicine besides mainstream medicine [42–44]. About 12% people taking insomnia have TCM as complement or alternative [36, 37]. TCM is efficacious in insomnia with a mean

TABLE 4: Repeated measurement ANOVA of ISI scores of the four groups.

Comparison between two groups	FAS P values	PPS P values
ZA + Z5-Z5	0.002	0.013
ZA + Z5-Z10	0.719	0.857
ZA + Z5-ZA	0.001	0.003
Z5-Z10	0.001	0.010
Z5-ZA	0.665	0.755
Z10-ZA	<0.001	0.002

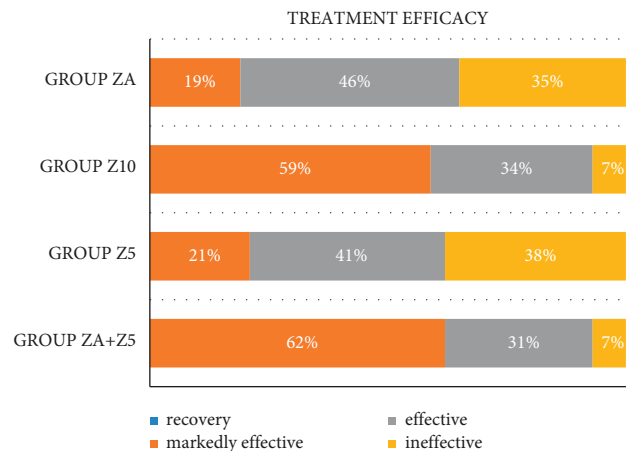


FIGURE 2: Comparison of the treatment efficacy among the four groups (PPS).

difference of 3.1 points in Pittsburgh Sleep Quality Index score between TCM and placebo according to a recent systematic review [38].

The treatment efficacy in the four groups is in the order (ZA + Z5 = Z10) > (Z5 = ZA), indicating that Zaoren Anshen capsule alone is as effective as 5 mg of zolpidem in treating insomnia. The combination of Zaoren Anshen capsule and 5 mg zolpidem tartrate is as effective as 10 mg Zolpidem alone. This combination not only enhances the curative effect of Zaoren Anshen capsule but also reduces the amount of zolpidem needed to treat insomnia, which is beneficial in minimizing the adverse reactions caused by zolpidem.

The incidence rates of adverse events over the 6-week study period in Groups ZA + Z5, Z5, Z10, and ZA were 9%, 17%, 25%, and 6%, respectively. The incidence of adverse events in Groups ZA + Z5 and ZA was less than 10%, whereas that in Groups Z5 and Z10 was more than 10%. No

TABLE 5: Details of the reported adverse events (SAS).

Serial number	Groups	Subject codes	Adverse events	Duration	Severity	Serious adverse events	Turnover	Measures taken for drug test	Corrective treatment	Exit tests	Test drug caused
1	ZA + Z5	1032	Dizzy	3 days	Mild	No	Disappear	Continue	No	No	Suspicious
2	ZA + Z5	3021	Dry mouth	3 days	Mild	No	Disappear	Continue	No	No	Suspicious
3	ZA + Z5	4023	Drowsiness	2 days	Mild	No	Disappear	Continue	No	No	Possible
4	Z5	1013	Constipation and urgency of urination	1 day	Mild	No	Disappear	Continue	No	No	Suspicious
5	Z5	1015	Weak waist and drowsiness	4 days	Mild	No	Disappear	Continue	No	No	Suspicious
6	Z5	1033	Gastrointestinal discomfort	1 day	Mild	No	Disappear	Continue	No	No	Possible
7	Z5	1036	Dry mouth and bitter mouth	2 days	Mild	No	Disappear	Continue	No	No	Possible
8	Z5	1037	Head distension	1 day	Mild	No	Disappear	Continue	No	No	Possible
9	Z5	2025	Drowsiness	3 days	Mild	No	Disappear	Continue	No	No	Possible
10	Z10	1003	Headache	8 hours	Moderate	No	Disappear	Continue	No	No	Possible
11	Z10	1025	Dizzy	4 hours	Mild	No	Disappear	Continue	No	No	Possible
12	Z10	1029	Heart tingling	2 days	Moderate	No	Disappear	Cease	No	No	Impossible
13	Z10	1039	Drowsiness	2 days	Mild	No	Disappear	Continue	No	No	Possible
14	Z10	2012	Drowsiness	2 days	Mild	No	Disappear	Continue	No	No	Possible
15	Z10	2026	Dizzy	1 day	Mild	No	Disappear	Continue	No	No	Possible
16	Z10	3028	Nausea	8 hours	Moderate	No	Disappear	Continue	No	No	Possible
17	Z10	4025	Dizzy	1 day	Mild	No	Disappear	Continue	No	No	Possible
18	ZA	3010	Constipation	2 days	Mild	No	Disappear	Continue	No	No	Suspicious
19	ZA	4007	Mild dull pain in the right upper abdomen	3 days	Mild	No	Disappear	Cease	No	Yes	Impossible

TABLE 6: Incidence of adverse events in the four groups.

Groups	Occurred		Not occurred		Total	χ^2	P
	n	Percentage (%)	n	Percentage (%)			
ZA + Z5	3	9	29	91	32	5.138	0.163
Z5	6	17	29	83	35		
Z10	8	25	24	75	32		
ZA	2	6	30	94	32		
Total	19	15	112	85	131		

significant difference was observed in the incidence of adverse events between the groups, which may be due to the small sample size of this study.

A heterogeneity analysis of the 13 studies (1175 patients) indicates that the clinical efficacy of the Zaoren Anshen capsule is superior to that of the conventional hypnotic medicine in treating insomnia; however, the difference is statistically nonsignificant (RR = 1.03; 95% CI = 0.97, 1.09); ($P = 0.34$). The adverse reactions caused by Zaoren Anshen capsule treatment are significantly lesser than those caused by conventional hypnotic medicine treatment (RR = 0.20; 95% = (0.14, 0.28), $P < 0.00001$) [41]. Another analysis of 19 studies (1780 patients) indicates that the improvement in sleep quality with Zaoren Anshen capsules is better than that with placebo (RR = -0.90; 95% CI = (-1.56, -0.24); $P = 0.007$). Similar to benzodiazepine receptor agonist (RR = 0.17; 95% = (-0.29, 0.64); $P = 0.46$), Zaoren Anshen capsules cause lesser incidences of adverse events than benzodiazepine receptor agonists (RR = 0.16, 95% CI = (0.12, 0.23); $P < 0.001$) [40]. The results of clinical effectiveness and adverse reaction incidences in the present study are consistent with those of the aforementioned two meta-analyses, further confirming the effectiveness and safety of Zaoren Anshen capsules in treating insomnia.

An Australian study shows that ZRAS capsule is safe, acceptable, and tolerable, yet not more effective than placebo in the treatment of insomnia [45]. Zaoren Anshen capsules used in this study were manufactured by Australian laboratories. The origin and manufacturing process of the medicinal materials were different from those of Zaoren Anshen capsules made in China. In our study, Zaoren Anshen capsules were taken 5 capsules per night, but in the Australian study, 3 capsules were taken. The difference in drug dosage may lead to the difference in the efficacy.

The strength of this study is its strictly randomized, double-blind control design, and the execution of the study strictly according to the established procedures. The study involves a set of detailed management measures such as random allocation method, allocation scheme hiding, blind application, and completeness of the result data, which avoided subject and researcher bias to ensure that the research results were objective, true, and reliable. The placebo group is not included in this study because of ethical considerations. All the subjects are insomnia patients who suffer from insomnia and seek medical treatment in the hospital. After diagnosis, the patients hope to receive treatment as soon as possible. This study ensures that each patient will receive medical treatment after participating in

the study, so as to avoid delaying treatment due to the use of placebo. The side effects of zolpidem are related to its dosage. Therefore, we set up a small dose group and a conventional dose group to observe the difference in the efficacy and side effects.

4.1. Limitations. This clinical trial has some limitations. First, the limitation of the study is the short period of intervention and small sample population. This study can be further improved by future research with a larger sample size. Second, the leakage rate during the follow-up of this study was high, mainly because the patients felt that they spent too much time on the way to the hospital. Future research can improve the follow-up process, such as collecting data through telephone or video interview.

5. Conclusions

In conclusion, this study showed that, Zaoren Anshen capsule can effectively treat insomnia disorder either alone or in combination with zolpidem tartrate. A preferred combination of TCM Zaoren Anshen capsule with zolpidem can provide a magnified therapeutic efficacy with fewer side effects than zolpidem-only management.

Data Availability

The datasets generated during this study are available from the corresponding author on reasonable request.

Ethical Approval

All human studies have been approved by the ethics committee of Zhejiang Hospital of Traditional Chinese Medicine and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent

All persons gave their informed consent prior to their inclusion in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was funded by the Jinhua Public Science and Technology research plan (grant no. 2018-4-100).

References

- [1] D. J. Buysse, "Insomnia," *JAMA*, vol. 309, pp. 706–716, 2013.
- [2] K. Crowley, "Sleep and sleep disorders in older adults," *Neuropsychology Review*, vol. 21, no. 1, pp. 41–53, 2011.
- [3] A. Koyanagi, N. Garin, B. Olaya et al., "Chronic conditions and sleep problems among adults aged 50 years or over in nine countries: a multicountry study," *PLoS One*, vol. 9, no. 12, Article ID e114742, 2014.

- [4] C.-Y. Hsu, Y.-T. Chen, M.-H. Chen et al., "The association between insomnia and increased future cardiovascular events: a nationwide population-based study," *Psychosomatic Medicine*, vol. 77, no. 7, pp. 743–751, 2015.
- [5] B. Zhu, P. E. Hershberger, M. C. Kapella, and C. Fritschi, "The relationship between sleep disturbance and glycaemic control in adults with type 2 diabetes: an integrative review," *Journal of Clinical Nursing*, vol. 26, no. 23–24, pp. 4053–4064, 2017.
- [6] C. L. Lin, W. C. Chien, C. H. Chung, and F. L. Wu, "Risk of type 2 diabetes in patients with insomnia: a population-based historical cohort study," *Diabetes Metabolism Research and Review*, vol. 34, no. 1, Article ID e2930, 2017.
- [7] T. Anothaisintawee, S. Reutrakul, E. Van Cauter, and A. Thakkinstian, "Sleep disturbances compared to traditional risk factors for diabetes development: systematic review and meta-analysis," *Sleep Medicine Reviews*, vol. 30, pp. 11–24, 2016.
- [8] S. Sasaki, E. Yoshioka, Y. Saijo et al., "A prospective cohort study of insomnia and chronic kidney disease in Japanese workers," *Sleep and Breathing*, vol. 22, no. 1, pp. 257–265, 2018.
- [9] J. Li, Z. Huang, J. Hou et al., "Sleep and CKD in Chinese adults: a cross sectional study," *Clinical Journal of the American Society of Nephrology*, vol. 12, no. 6, pp. 885–892, 2017.
- [10] B. Katic, J. Heywood, F. Turek et al., "New approach for analyzing self-reporting of insomnia symptoms reveals a high rate of comorbid insomnia across a wide spectrum of chronic diseases," *Sleep Medicine*, vol. 16, no. 11, pp. 1332–1341, 2015.
- [11] L. Shi, S. J. Chen, M. Y. Ma et al., "Sleep disturbances increase the risk of dementia: a systematic review and meta-analysis," *Sleep Medicine Reviews*, vol. 40, pp. 4–16, 2018.
- [12] E. K. Lee and A. B. Douglass, "Sleep in psychiatric disorders: where are we now?" *Canadian Journal of Psychiatry*, vol. 55, no. 7, pp. 403–412, 2010.
- [13] T. W. Uhde, B. M. Cortese, and A. Vedeniapin, "Anxiety and sleep problems: emerging concepts and theoretical treatment implications," *Current Psychiatry Reports*, vol. 11, no. 4, pp. 269–276, 2009.
- [14] E. O. Johnson, T. Roth, and N. Breslau, "The association of insomnia with anxiety disorders and depression: exploration of the direction of risk," *Journal of Psychiatric Research*, vol. 40, pp. 700–708, 2006.
- [15] D. Neckelmann, A. Mykletun, and A. A. Dahl, "Chronic insomnia as a risk factor for developing anxiety and depression," *Sleep*, vol. 30, no. 7, pp. 873–880, 2007.
- [16] R. Manber and A. S. Chambers, "Insomnia and depression: a multifaceted interplay," *Current Psychiatry Reports*, vol. 11, no. 6, pp. 437–442, 2009.
- [17] J. Scalo, P. Desai, and K. Rascati, "Insomnia, hypnotic use, and health-related quality of life in a nationally representative sample," *Quality of Life Research*, vol. 24, no. 5, pp. 1223–1233, 2015.
- [18] S. Parthasarathy, M. M. Vasquez, M. Halonen et al., "Persistent insomnia is associated with mortality risk," *The American Journal of Medicine*, vol. 128, no. 3, pp. 268–275.e2, 2015.
- [19] D. Léger, V. Bayon, M. M. Ohayon et al., "Insomnia and accidents: cross-sectional study (EQUINOX) on sleep-related home, work and car accidents in 5293 subjects with insomnia from 10 countries," *Journal of Sleep Research*, vol. 23, no. 2, pp. 143–152, 2014.
- [20] C. Morin, H. Ivers, E. Altena et al., "Insomnia and risk of traffic accidents: a 5-year follow up cohort study," *Journal of Sleep Research*, vol. 25, pp. 305–310, 2016.
- [21] M. Daley, C. M. Morin, M. LeBlanc, J. P. Gregoire, and J. Savard, "The economic burden of insomnia: direct and indirect costs for individuals with insomnia syndrome, insomnia symptoms, and good sleepers," *Sleep*, vol. 32, no. 1, pp. 55–64, 2009.
- [22] D. Léger and V. Bayon, "Societal costs of insomnia," *Sleep Medicine Reviews*, vol. 14, no. 6, pp. 379–389, 2010.
- [23] R. C. Kessler, P. A. Berglund, C. Coulouvrat et al., "Insomnia and the performance of US workers: results from the America insomnia survey," *Sleep*, vol. 34, no. 9, pp. 1161–1171, 2011.
- [24] A. Qaseem, D. Kansagara, M. A. Forcica, M. Cooke, and T. D. Denberg, "Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians," *Annals of Internal Medicine*, vol. 165, no. 2, pp. 125–133, 2016.
- [25] M. Ree, M. Junge, and D. Cunnington, "Australasian Sleep Association position statement regarding the use of psychological/behavioral treatments in the management of insomnia in adults," *Sleep Medicine*, vol. 36, pp. S43–S47, 2017.
- [26] D. Riemann, C. Baglioni, C. Bassetti et al., "European guideline for the diagnosis and treatment of insomnia," *Journal of Sleep Research*, vol. 26, no. 6, pp. 675–700, 2017.
- [27] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, American Psychiatric Association, Arlington, TX, USA, 2013.
- [28] American Academy of Sleep Medicine, *International Classification of Sleep Disorders*, American Academy of Sleep Medicine, Darien, IL, USA, 2014.
- [29] J. L. Schroeck, J. Ford, E. L. Conway et al., "Review of safety and efficacy of sleep medicines in older adults," *Clinical Therapeutics*, vol. 38, no. 11, pp. 2340–2372, 2016.
- [30] S. M. Bertisch, S. J. Herzig, J. W. Winkelman, and C. Buettner, "National use of prescription medications for insomnia: nhanes 1999–2010," *Sleep*, vol. 37, no. 2, pp. 343–349, 2014.
- [31] N. Vincent and C. Lionberg, "Treatment preference and patient satisfaction in chronic insomnia," *Sleep*, vol. 24, no. 4, pp. 411–417, 2001.
- [32] J. D. Edinger and W. S. Sampson, "A primary care friendly cognitive behavioral insomnia therapy," *Sleep*, vol. 26, no. 2, pp. 177–182, 2003.
- [33] M. L. Perlis and M. T. Smith, "How can we make CBT-I and other BSM services widely available?" *Journal of Clinical Sleep Medicine*, vol. 4, no. 1, pp. 11–13, 2008.
- [34] J. Y. Ng and N. D. Parakh, "A systematic review and quality assessment of complementary and alternative medicine recommendations in insomnia clinical practice guidelines," *BMC Complement Medicine and Therapies*, vol. 21, no. 1, p. 54, 2021 Feb.
- [35] F. Afrasiabian, M. Mirabzadeh Ardakani, K. Rahmani et al., "Aloysia citriodora Palau (lemon verbena) for insomnia patients: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety," *Phytotherapy Research*, vol. 33, no. 2, pp. 350–359, 2019 Feb.
- [36] K. H. Lee, Y. T. Tsai, J. N. Lai, and S. K. Lin, "Concurrent use of hypnotic drugs and Chinese herbal medicine therapies among Taiwanese adults with insomnia symptoms: a population-based study," *Evidence-based Complementary and Alternative Medicine*, vol. 2013, Article ID 987862, 8 pages, 2013.
- [37] W. F. Yeung, K. F. Chung, K. P. Yung et al., "The use of conventional and complementary therapies for insomnia

- among Hong Kong Chinese: a telephone survey,” *Complementary Therapies in Medicine*, vol. 22, no. 5, pp. 894–902, 2014.
- [38] X. J. Ni, J. L. Shergis, X. F. Guo et al., “Updated clinical evidence of Chinese Herbal Medicine for insomnia: a systematic review and meta-analysis of randomized controlled trials,” *Sleep Medicine*, vol. 16, no. 12, pp. 1462–1481, 2015.
- [39] Z. Wang, W. Xie, and J. Y. Que, “Research progress on Zaoren Anshen capsules for the treatment of insomnia disorders,” *Chinese Journal of Drug Dependence*, vol. 26, pp. 407–410, 2017.
- [40] Y. Birling, M. Jia, G. Li, J. Sarris, A. Bensoussan, and X. Zhu, “Zao Ren an Shen for insomnia: a systematic review with meta-analysis,” *Sleep Medicine*, vol. 69, pp. 41–50, 2020.
- [41] B. W. Chen, J. Yi, B. Sun, P. Jia, W. J. Zhang, and B. Y. Liu, “Efficacy and safety of Zaoren Anshen capsules in the treatment of insomnia: a meta-analysis of randomized controlled trials,” *Medicine (Baltimore)*, vol. 99, no. 6, Article ID e19033, 2020.
- [42] M. Seyed Hashemi, M. H. Hashempur, M. H. Lotfi et al., “The efficacy of asafoetida (*Ferula assa-foetida*oleo-gum resin) versus chlorhexidine gluconate mouthwash on dental plaque and gingivitis: a randomized double-blind controlled trial,” *European Journal of Integrative Medicine*, vol. 29, Article ID 100929, 2019.
- [43] A. Rahmani, B. Niknafs, M. Naseri, M. Nouri, and A. Tarighat-Esfanjani, “Effect of nigella sativa oil on oxidative stress, inflammatory, and glycemic control indices in diabetic hemodialysis patients: a randomized double-blind, controlled trial,” *Evidence-Based Complementary and Alternative Medicine*, vol. 20229 pages, Article ID 2753294, 2022.
- [44] X. Wan, F. Gen, Y. Sheng et al., “Meta-analysis of the effect of kangfuxin liquid on diabetic patients with skin ulcers,” *Evidence-Based Complementary and Alternative Medicine*, vol. 20219 pages, Article ID 1334255, 2021.
- [45] Y. Birling, X. Zhu, N. Avard et al., “Zao Ren an Shen capsule for insomnia: a double-blind, randomized, placebo-controlled trial,” *Sleep*, vol. 45, no. 2, Article ID zsab266, 2022.
- [46] G. Benbir, A. U. Demir, M. Aksu et al., “Prevalence of insomnia and its clinical correlates in a general population in Turkey,” *Psychiatry and Clinical Neurosciences*, vol. 69, no. 9, pp. 543–552, 2015.
- [47] Z. Mintao, Z. Wei, Z. Tingting, B. An, and J. C. Zhen, “Analysis of drug use in elderly patients with insomnia from 22 hospitals in Beijing,” *Clin Mediat J*, vol. 15, pp. 57–60, 2017.
- [48] B. W. Riedel and K. L. Lichstein, “Insomnia and daytime functioning,” *Sleep Medicine Reviews*, vol. 4, no. 3, pp. 277–298, 2000.
- [49] N. Gunja, “The clinical and forensic toxicology of Z-drugs,” *Journal of Medical Toxicology*, vol. 9, no. 2, pp. 155–162, 2013.