ORIGINAL RESEARCH

Clinical Efficacy of the Chinese Herbal Medicine Shumian Capsule for Insomnia: A Randomized, Double-Blind, Placebo-Controlled Trial

Suzhen Chen [1,2], Zhi Xu[1,2], Yinghui Li[1,2], Tianyu Wang [1,2], Yingying Yue[1,2], Zhenghua Hou[1,2], Linlin You[1,2], Na Lu[1,2], Yingying Yin[1,2], Xiaoyun Liu[1,2], Liangliang Tan[1,2], Houcheng Ji[3], Yaoran Shi[1,2], Xiaoyun Xin[1,2], Wenhao Jiang[1,2], Yonggui Yuan [1,2]

[1]Department of Psychosomatics and Psychiatry, ZhongDa Hospital, School of Medicine, Southeast University, Nanjing, People's Republic of China; [2]Institute of Psychosomatics, School of Medicine, Southeast University, Nanjing, People's Republic of China; [3]Department of Psychiatry, The Second People's Hospital of Jiangning District, Nanjing, People's Republic of China

Correspondence: Yonggui Yuan, Department of Psychosomatics and Psychiatry, ZhongDa Hospital, School of Medicine, Southeast University, No. 87 Dingjiaqiao, Gulou District, Nanjing, 210009, People's Republic of China, Tel +86-25-83285124, Email yygylh2000@sina.com

Purpose: Shumian capsule (SMC) is a patent Chinese herbal medicine that can soothe the liver and relieves depression, quiet the spirit. Here, we aimed to investigate the efficacy of SMC for treating insomnia using both scales and polysomnography (PSG).

Patients and Methods: A randomized, double-blind, placebo-controlled trial was performed. Twenty-six insomnia patients randomly received SMC (n = 11) or placebo (n = 15) for four weeks. Pittsburgh Sleep Quality Inventory (PSQI), Insomnia Severity Index (ISI), 9-items Patient Health Questionnaire (PHQ-9), 7-items Generalized Anxiety Disorder (GAD-7), 17-item Hamilton Depression Rating Scale (HAMD-17), and Hamilton Anxiety Rating Scale (HAMA) were applied at the baseline and the 2nd, 4th week after treatment. Treatment Emergent Symptom Scale was used to assess adverse reactions. We used PSG to record and analyze sleep features at baseline and after four weeks.

Results: PSQI, ISI, PHQ-9, HAMD-17, and HAMA scores decreased significantly after SMC treatment. Also, the total sleep time, rapid-eye-movement (REM) sleep latency, stage 2 sleep, deep sleep, REM sleep, and sleep efficiency improved significantly after SMC treatment. In the placebo group, the only significant change was the decrease of PHQ-9 at week-2. Furthermore, both SMC and placebo reported no adverse events.

Conclusion: SMC could safely improve sleep quality with depression and anxiety remission in insomnia patients.

Keywords: Chinese herbal medicine, shumian capsule, insomnia, polysomnography, clinical trial, randomized and double-blind method

Introduction

Insomnia is a widespread sleep disorder that can lead someone with sufficient sleep time hard to fall asleep, frequent awakening, waking up too early, and falling asleep again hard after waking up. According to a report of JAMA, the prevalence of insomnia disorder is nearly 10% to 20%, of which about 50% have a chronic course, which further affects their mood, social functioning, and quality of life.[1,2] Consistent with this, a survey from the Chinese Ministry of Health also shows that the insomnia rate is as high as 10% to 20%, and the insomnia people in China have reached 1.2 million to 1.4 million person-time.[3]

Insomnia is a risk factor for functional impairments, other medical and mental disorders development, and healthcare costs increasing.[1] Insomnia can increase the risk of depression and anxiety.[4–6] Baglioni et al[7] pointed out that non-depressed people with insomnia have a twofold risk of developing depression compared to people with no sleep difficulties. Also, insomnia can predict suicidality and substance use.[8,9] In addition, a study found that 40% of insomnia patients have a combined mental disorder,[10] while 40% of patients with depression, anxiety, and comorbidity reported insomnia;[11] and the effective treatment of insomnia in patients with depression would positively affect mood.[12] Except for mental disorders, insomnia is also an

independent risk factor for acute myocardial infarction,[13] coronary heart disease,[14] heart failure,[15] hypertension,[16] and diabetes.[17] Therefore, insomnia has become a worldwide public health problem and a main induced cause of various diseases.

Cognitive behavioral therapy (CBT) and pharmacotherapy are effective treatments for insomnia.[18] CBT is strongly recommended as the first choice for the few side effects, and it is cost-effective.[19] However, it also has inevitable limitations, including a shortage of trained therapists and a relatively low response rate.[20] Two-thirds of insomniacs might fail to reach full remission after CBT, and 19–26% even have no response.[21] Moreover, the efficacy of CBT highly depends on patients' commitment and self-efficacy,[22] suggesting that CBT is not suitable for everyone. That is, in some cases, CBT may not be a compelling enough treatment to improve insomnia nor suitable for widespread use. Instead, benzodiazepines have become the first treatment choice over the past three decades and are widely used for insomnia because of their quick onset and apparent effects. However, their use has been limited currently due to drug resistance, dependence, "hangover effect", psychomotor impairment, cognitive impairment, withdrawal reaction, and many other adverse reactions. Thus, a new treatment with fewer side effects and a higher benefit ratio is needed for insomnia.

Chinese herbal medicine (CHM) originated in ancient China and has treated insomnia for thousands of years. Currently, CHM is recognized as good treatment effect, fewer side effects,[23,24] and alternative medication choice.[25] With the continuous improvement of CHM dosage forms and technical levels, many CMH patents are widely used in clinical practice. Shumian capsule (SMC) is a common CHM for treating insomnia whose effectiveness has been demonstrated by several randomized controlled clinical trials (RCT).[26] However, all these studies included only scales to assess insomnia and treatment effects. None of the RCT in the SMC used polysomnography (PSG) to assess subjects' sleeping features, though PSG is considered the gold standard for detecting sleep-related disorders and evaluation.[27,28] Therefore, this study aimed to evaluate the clinical efficacy of SMC for treating insomnia using both scales and PSG to measure sleep improvement.

Methods
Trial Design
This clinical study was a randomized, double-blind, placebo-controlled trial, and the double-blind treatment lasted for four weeks and was conducted between June 2019 and May 2021 in the Affiliated ZhongDa Hospital of Southeast University, Nanjing, China. The trial used the two-group parallel design. Patients who met the inclusion and exclusion criteria were planned to randomly assign 1:1 to either the SMC group or placebo group to receive the corresponding treatment for a total of four weeks. The patients would receive SMC or placebo capsules immediately according to the randomization schedule as soon as they were recruited. Unfortunately, however, we had to stop the study early because of the coronavirus disease 2019 (COVID-19), and only 26 insomnia patients were recruited at the end, among whom were 11 patients in the SMC group and 15 patients in the placebo group. Patients' subjective sleep and mood changes were assessed using the scales at baseline and 2- and 4-week after treatment. Meanwhile, objective sleep was measured using the PSG test at baseline and 4-weeks after treatment. According to the Helsinki Declaration, all the participants were given a detailed description of the study and then written informed consent was obtained. The Ethical Committee of the Affiliated ZhongDa Hospital of Southeast University approved the protocol of this study (Approved number: 2019ZDSYLL054-P01), and the study was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR1900024117).

Subjects
Subjects were from insomniacs who came to ZhongDa hospital because of insomnia or were recruited through recruitment advertisements, and they also met the following inclusion criteria: (1) aged between 18–65 years old; (2) the diagnosis of insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (3) Pittsburgh Sleep Quality Inventory (PSQI) ≥ 8 and 17-item Hamilton Depression Rating Scale (HAMD-17) < 17 and Hamilton Anxiety Rating Scale (HAMA) < 14; (4) had no other serious systemic complications; (5) have not taken any medication that may affect sleep before the trial for two months; (6) must sign the written informed consent before the trial. The exclusion criteria were as follows: (1) secondary insomnia (caused by or co-morbid with moderate depression or anxiety or acute stressful events et al) and other sleep disorder such as sleep apnea syndrome; (2) pregnant or lactating women; (3) a history of alcohol or drug dependence or

abuse; (4) serious physical diseases such as malignant tumors, severe abnormal heart, liver or renal function; (5) had been taken antidepressants, anti-anxiety or hypnotic medications; (6) allergic to any component of SMC.

Intervention

According to a random number table, all enrolled subjects received either SMC or identical placebo capsules randomly for four weeks treatment and were required back to the hospital every two weeks for evaluation. All patients were instructed to take three capsules respective after supper and one hour before going to bed. The 4-week dose of SMC or placebo capsules were distributed to patients in two separate rounds, one on the day of enrollment and one at the end of two weeks' treatment, by other personnel not participating in the patients' enrollment and evaluation. SMC and shumian simulation capsules that are provided by Guizhou Dalong Pharmaceutical Co. Ltd.; batch numbers are 20190307 and 20190308, respectively. Shumian simulation capsule contains the same color but nonpharmacological brown powder as SMC. In addition, any drugs (including herb medicine), health care products, foods or drinks that may cause hypnotic or insomnia effects were not allowed to use during the treatment.

Assessment of the Severity of Insomnia, Depression, and Anxiety

The PSQI,[29] the Insomnia Severity Index (ISI),[30] the 9-items Patient Health Questionnaire (PHQ-9),[31] and the 7-items Generalized Anxiety Disorder (GAD-7)[32] were self-rating scales, and the first two scales were employed to assess the patients' severity of insomnia while the last two were applied to respectively evaluate the severity of depression and anxiety. While the HAMD-17[33] and Hamilton Anxiety Rating Scale (HAMA)[34] were used for researchers to assess the patients' severity of depression and anxiety, respectively, the Treatment Emergent Symptom Scale (TESS)[35] was used to assess treatment safety. All these scales were administered at baseline and 2- and 4-weeks after beginning treatment.

Polysomnography (PSG)

All the insomnia patients underwent overnight PSG (580-G2CGSS, Bio-Logic, USA), and the recordings were analyzed according to the American Academy of Sleep Medicine (AASM) criteria.[36] The main PSG monitoring measurements included the sleep latency, the sleep efficiency, the sleep maintenance efficiency, the rapid-eye-movement (REM) sleep latency, the total sleep time, and the time of each sleep stage (stage 1 and 2 sleep, deep sleep and REM sleep). The PSG monitoring was performed twice at baseline and four weeks after treatment for each subject, and every monitoring time must be no less than eight hours.

Statistical Analysis

All data were analyzed by SPSS 22.0 (IBM, Armonk, NY, USA). Data were examined for normality using the Kolmogorov–Smirnov test. As applicable, the numerical variables were described as mean ± standard error (M ± SE) or median (interquartile range). Independent-samples t-test and Mann–Whitney U-test were used to compare the normally distributed and nonnormally distributed data between the SMC and placebo groups. At the same time, the paired-sample t-test was applied to compare the numerical data within the group. Categorical variables were expressed as numbers and were compared by chi-square (x^2) between the two groups. Differences were considered statistically significant at a two-tailed $P < 0.05$.

Results

Baseline Clinical Data of Subjects

A total of 26 insomnia patients were finally included in the study, among whom 11 patients were assigned to the SMC group and 15 patients to the placebo group; the detailed flow was described in Figure 1. One patient in the SMC group and two patients in the placebo group dropped out for lacking efficacy after two weeks of treatment, and the dropout rates were not significantly different between the two groups (9.09% vs 13.33%, $P = 0.369$). There were respective another two (both were due to self-withdrawal) and two (one for self-withdrawal, the other for protocol violation) patients in the SMC and placebo groups who dropped out after four weeks of treatment, and the difference of the dropout rate was also not significant (27.27% vs 26.67%, $P = 0.973$). Ultimately, eight patients in the SMC group and 11 in the placebo groups
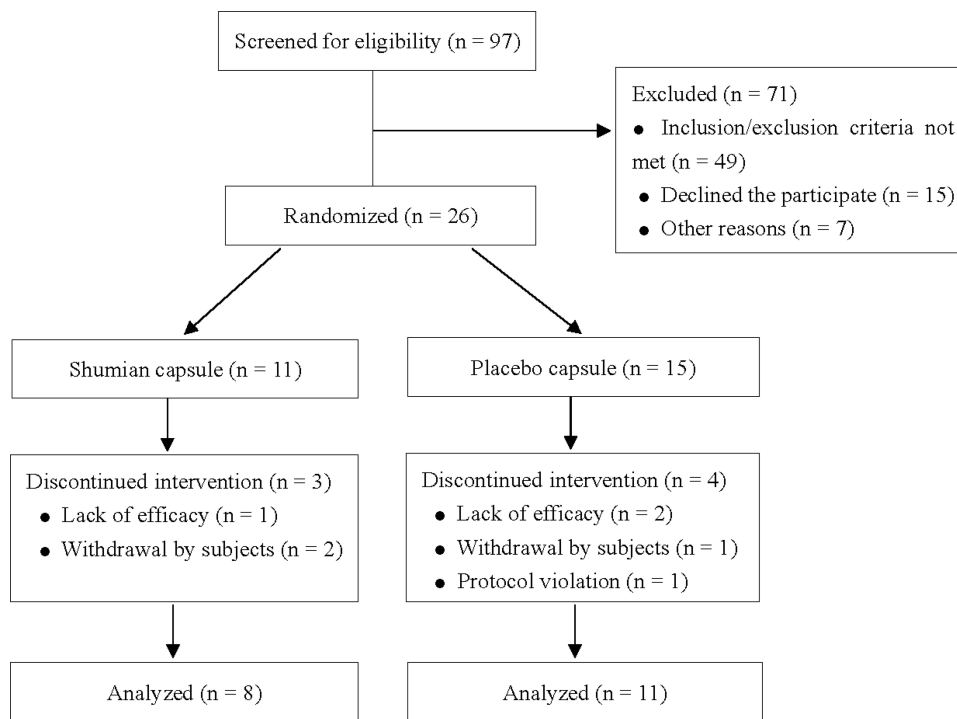
Figure 1 Flow diagram of the progress through the phases of a parallel randomized trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis).

completed all three-time assessments and two PSG monitoring sessions, among whom the efficacy analysis was performed.

The baseline demographic and clinical data of all enrolled subjects are shown in Table 1. There were no significant differences between the two groups in terms of sex, age, education years, marital status, age of onset, insomnia duration, family history of insomnia or other mental disorders, scores of various scales including PSQI, ISI, PHQ-9, GAD-7, HAMD-17 and HAMA, and the PSG-related indicators including the sleep latency, sleep efficiency, REM sleep latency, total sleep time, and time of stage 1 and 2 sleep, deep sleep, and REM sleep ($P > 0.05$). However, the sleep maintenance efficiency of patients in the placebo group was found significantly better than that of patients in the SMC group ($P = 0.002$).

Comparison of Efficacy and Safety

Subjective Sleep Measurements

As presented in Figure 2 and Table 2, the PSQI scores in the SMC group were significantly decreased after 2- and 4-weeks treatment ($P < 0.001$ and $P = 0.040$, respectively), while the ISI scores were only significantly decreased after 2-weeks treatment ($P = 0.002$). However, within the placebo group, whether the scores of PSQI and ISI after 2 weeks or 4 weeks treatment, there were both no statistical differences compared with the scores at baseline ($P > 0.05$).

Objective Sleep (PSG) Measurements

After treatment for 4-weeks, none of the PSG indicators was significantly changed in the placebo group (Figure 3 and Table 3; all $P > 0.05$). As expected, however, several PSG indicators in the SMC group improved significantly. Specifically, the total sleep time, stage 2 sleep time, deep sleep time, REM sleep time, and sleep efficiency were significantly increased ($P < 0.05$), while REM sleep latency was significantly shortened ($P = 0.021$), as shown in Figure 3 and Table 3.

Table 1 Baseline Clinical Data of Study Subjects

Variable	SMC Group	Placebo Group	$t/Z/x^2$	P-value
Sex (Female/Male)[a]	6/5	12/3	3.346	0.067
Age[b]	51.64 ± 3.71	44.53 ± 3.53	1.364	0.185
Education years[b]	12.27 ± 1.38	15.33 ± 1.07	−1.782	0.087
BMI[b]	22.89 ± 0.90	23.86 ± 1.86	−0.419	0.679
Age of onset[b]	42.73 ± 3.69	38.73 ± 3.25	0.809	0.426
Marital status (Single/ Married)[a]	1/10	4/11	1.262	0.261
Insomnia duration (month)[b]	107.25 ± 34.24	72.27 ± 22.74	0.886	0.385
Family history of insomnia or other mental disorders (yes/no)[a]	2/9	6/9	1.418	0.234
PSQI_0W (score)[b]	21.91 ± 1.86	20.80 ± 1.38	0.490	0.628
ISI_0W (score)[b]	15.73 ± 1.71	15.07 ± 1.12	0.338	0.739
PHQ-9_0W (score)[b]	8.55 ± 1.32	8.60 ± 1.40	−0.027	0.978
GAD-7_0W (score)[b]	5.18 ± 1.67	5.73 ± 1.54	−0.240	0.812
HAMD-17_0W (score)[b]	8.64 ± 0.66	7.80 ± 1.17	0.133	0.579
HAMA_0W (score)[b]	7.45 ± 0.53	7.13 ± 1.11	0.261	0.797
Total sleep time_0W (min)[b]	361.64 ± 15.27	351.93 ± 21.77	0.338	0.738
Sleep latency_0W (min)[c]	27.70 (27.70)	33.90 (85.10)	−0.289	0.772
REM sleep latency_0W (min)[c]	104.50 (135.63)	79.00 (49.00)	−1.115	0.265
Stage 1 sleep_0W (min)[c]	33.75 (23.75)	33.00 (40.00)	−0.495	0.620
Stage 2 sleep_0W (min)[b]	211.18 ± 14.10	235.37 ± 19.52	−0.935	0.359
Deep sleep_0W (min)[b]	28.45 ± 6.88	30.83 ± 6.13	−0.257	0.800
REM sleep_0W (min)[c]	60.25 (20.25)	34.5 (43.50)	−1.899	0.058
Sleep efficiency_0W (%)[c]	74.40 (16.93)	84.90 (19.90)	−1.239	0.215
Sleep maintenance efficiency_0W (%)[b]	75.22 ± 3.38	88.41 ± 2.19	−3.422	0.002

Note: The normally distributed data were expressed as mean ± standard error and the nonnormally distributed data were expressed as median (interquartile range); [a]chi-square test; [b]independent-samples t test; [c]Mann–Whitney U-test.
Abbreviations: SMC, Shumian capsule; PSQI, Pittsburgh Sleep Quality Inventory; ISI, Insomnia Severity Index; PHQ-9, 9-items Patient Health Questionnaire; GAD-7, 7-items Generalized Anxiety Disorder; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; REM, rapid-eye-movement.

Depression and Anxiety Measurements

Figure 4 and Table 2 displayed the changes of various scales related to the mood of patients in the SMC group and the placebo group. The scores of PHQ-9, HAMD-17, and HAMA in the SMC group were significantly decreased both after
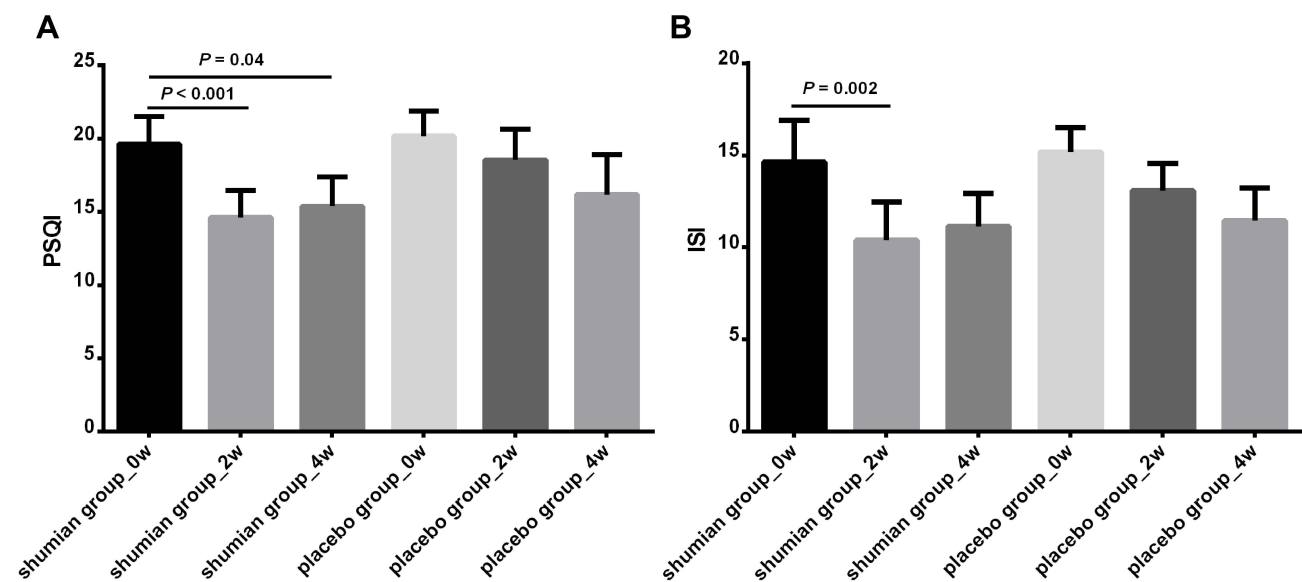
Figure 2 The scores of (**A**) PSQI and (**B**) ISI in the shumian group and the placebo group pre- and post-treatment.
Abbreviations: PSQI, Pittsburgh Sleep Quality Inventory; ISI, Insomnia Severity Index.
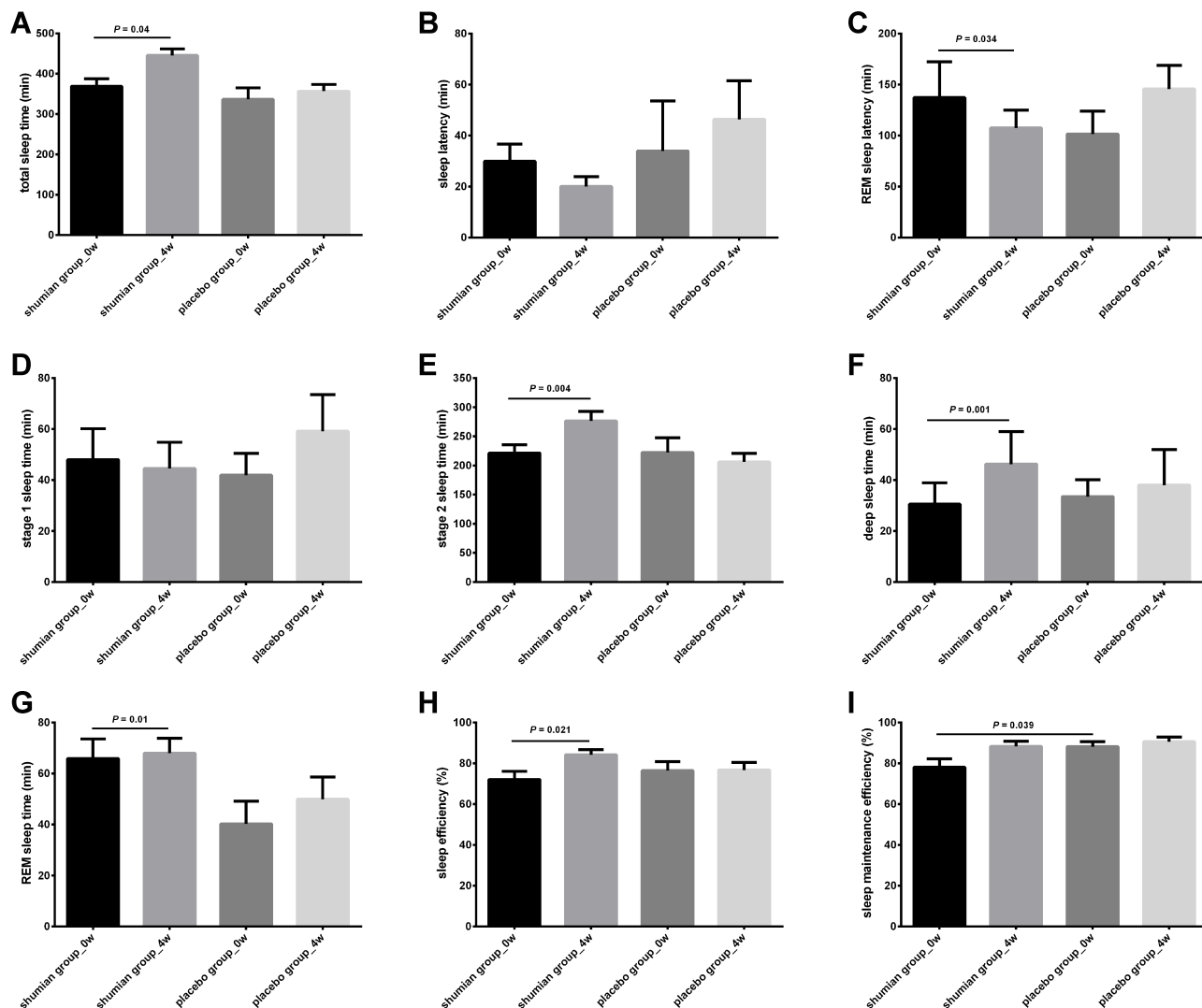
Table 2 The Scores of Various Scales of Pre- and Post-Treatment in the Shumian Capsule Group and the Placebo Capsule Group

Variable	Shumian Capsule Group (n =8)			Placebo Capsule Group (n=11)			P_1	P_2	P_3	P_4	P_5
	Pre-Treatment	Week-2	Week-4	Pre-Treatment	Week-2	Week-4					
PSQI	19.63±5.37	14.63±5.21	15.38±5.66	20.18±5.67	18.55±6.92	16.18±9.02	< 0.001	0.040	0.218	0.081	0.832
ISI	14.63±6.39	10.38±5.88	11.13±5.11	15.18±4.38	13.09±4.87	11.45±5.85	0.002	0.111	0.066	0.073	0.824
PHQ-9	8.13 ± 4.58	5.63 ±3.93	5.38 ± 3.70	8.18 ± 4.26	6.91 ±3.94	6.18 ± 4.17	0.008	0.034	0.046	0.199	0.978
GAD-7	2.00 (11.00)	0.50 (6.75)	1.50 (4.25)	4.00 (9.00)	5.00 (4.00)	2.00 (6.00)	0.052	0.097	0.500	0.534	0.881
HAMD-17	8.88 ± 2.42	6.25 ±3.62	4.63 ± 2.67	8.00 ± 3.90	6.91 ±3.67	5.82 ± 4.49	0.013	0.004	0.140	0.117	0.583
HAMA	7.50 (3.25)	6.00 (4.00)	4.00 (3.50)	6.00 (6.00)	5.00 (3.00)	4.00 (6.00)	0.003	0.001	0.557	0.222	0.793

Note: The normally distributed data were expressed as mean ± standard error and the nonnormally distributed data were expressed as median (interquartile range). P_1, comparison of various scales between pre-treatment and week-2 in the Shumian capsule group; P_2, comparison of various scales between pre-treatment and week-4 in the Shumian capsule group; P_3, comparison of various scales between pre-treatment and week-2 in the placebo group; P_4, comparison of various scales between pre-treatment and week-4 in the placebo group; P_5, comparison of various scales between the Shumian capsule group and the placebo group before treatment.
Abbreviations: PSQI, Pittsburgh Sleep Quality Inventory; ISI, Insomnia Severity Index; PHQ-9, 9-items Patient Health Questionnaire; GAD-7, 7-items Generalized Anxiety Disorder; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

2- and 4-week of treatment ($P < 0.05$). However, in the placebo group, only PHQ-9 scores declined at the end of week-2 compared with the scores at baseline ($P = 0.046$). The scores of GAD-7 in both the SMC and the placebo groups were not changed significantly after 2 weeks and 4 weeks treatment (all $P > 0.05$).

Figure 3 The PSG indicators in the shumian group and the placebo group pre- and post-treatment. The PSG indicators are respective (**A**) Total sleep time. (**B**) Sleep latency. (**C**) REM sleep latency. (**D**) Stage 1 sleep time. (**E**) Stage 2 sleep time. (**F**) Deep sleep time. (**G**) REM sleep time. (**H**) Sleep efficiency. (**I**) Sleep maintenance efficiency.
Abbreviations: PSG, polysomnography; REM, rapid-eye-movement.

Table 3 The PSG Indicators of Pre- and Post-Treatment in the Shumian Capsule Group and the Placebo Group

Variable	Shumian Capsule Group (n =8)		Placebo Capsule Group (n=11)		P_1	P_2	P_3
	Pre-Treatment	Post-Treatment	Pre-Treatment	Post-Treatment			
Total sleep time, min	368.88 ± 18.65	445.31 ± 16.31	336.64 ± 28.27	356.73 ± 16.87	0.040	0.081	0.496
Sleep latency, min	27.70 (27.70)	20.05 (21.23)	33.90 (85.10)	46.30 (78.40)	0.111	0.073	0.239
REM latency, min	104.50 (135.63)	89.50 (61.13)	79.00 (49.00)	131.00 (59.50)	0.034	0.199	0.474
Stage 1 sleep, min	33.75 (23.75)	47.00 (42.25)	33.00 (40.00)	53.00 (57.50)	0.097	0.534	0.678
Stage 2 sleep, min	221.31 ± 13.95	276.38 ± 16.26	222.36 ± 25.37	205.86 ± 14.88	0.004	0.117	0.972
Deep sleep, min	30.50 (15.00)	46.25 (48.63)	33.50 (31.00)	38.00 (41.50)	0.001	0.222	0.882
Stage REM, min	60.25 (20.25)	64.75 (10.25)	34.5 (43.50)	43.50 (43.00)	0.010	0.130	0.053
Sleep efficiency, %	74.40 (16.93)	85.60 (12.23)	84.90 (19.90)	75.00 (22.70)	0.021	0.937	0.495
Sleep maintenance efficiency, %	78.04 ± 4.11	88.30 ± 2.50	88.15 ± 2.45	90.58 ± 2.22	0.056	0.158	0.039

Note: The normally distributed data were expressed as mean ± standard error and the nonnormally distributed data were expressed as median (interquartile range). P_1, comparison of various PSG indicators between pre- and post-treatment in the Shumian capsule group; P_2, comparison of various PSG indicators between pre- and post-treatment in the placebo group; P_3, comparison of various PSG indicators between the Shumian capsule group and the placebo group before treatment.
Abbreviations: PSG, polysomnography; REM, rapid-eye-movement.

Adverse Events

No adverse events were reported during the study period in either the SMC or placebo groups. In addition, among seven patients who dropped out of the study, none of them were due to adverse events.

Discussion

To our knowledge, this is the first randomized, double-blind, placebo-controlled trial using PSG to explore the efficacy of SMC in adult insomnia. In the present study, SMC exhibited better treatment efficacy than placebo after four weeks, and it significantly improved sleep structure. Notably, SMC also improved patients' mood compared with baseline.

The observed treatment effects on insomnia might connect to the herbal formula of SMC. It is formulated from Semen Ziziphi Spinosae, Radix Bupleuri, Radix Paeoniae Alba, Flos Albiziae, Cortex Albiziae, Bombyx Batryticatus, Periostracum Cicadae, and Medulla Junci.[37] The whole formula was believed to soothe the liver, relieve depression, and quiet the heart.[37] The recent study reported that SMC might improve insomnia by increasing γ-aminobutyric acid levels, decreasing glutamate levels in the brain, and up-regulating the hippocampal 5-hydroxytryptamine 1A receptors protein expression.[38] Among all the compounds, Semen Ziziphi Spinosae and Radix Bupleuri were the main ingredients to improve sleep.[39,40] Importantly, the "Guideline for the evaluation and treatment of insomnia in Chinese adults (2017)" pointed out that the essential goals of insomnia treatment should improve sleep quality and structure and avoid adverse effects.[41] The PSG showed that the total sleep, REM sleep latency, stage 2 sleep, deep sleep, REM sleep, and sleep efficiency were significantly improved after 4-weeks of treatment in the SMC group. In addition, we did not record any adverse events. In summary, as CHM, SMC might be a safe choice in addition to current benzodiazepines, which might lead to tolerance and addiction,[41] changes in sleep structure, and declines in sleep quality.[42]

Besides sleep improvement, the present study found significantly decreased PHQ-9, HAMD-17, and HAMA in the SMC group compared with the placebo group after treatment. It indicated that SMC could improve insomnia patients' depressive and anxious moods. The result of a recent study that focused on sleep and mood disorders caused by the COVID-19 also supported our findings, and this study reported that SMC significantly improved depression and anxiety of patients with COVID-19 during the recovery phase.[43] Also, the findings were consistent with a variety of previous clinical studies.[44–47] The mechanism of mood symptoms improvements might be related to the Semen Ziziphi Spinosae, Radix Bupleuri, and Bombyx Batryticatus. These compounds were rich in tryptophan, which was the precursor of serotonin.[48,49] It might indicate that SMC improved serotonin deficiency and balanced the levels of neurotransmitters, then restored patients' autonomous sleep with better quality, and improved depression and anxiety simultaneously.[37,48,49]

The strengths of this study were: (1) We used the scales to assess patients' subjective feelings and applied PSG to evaluate patients' actual sleep changes pre-and post-treatment, which was helpful for a more comprehensive evaluation of the efficacy of SMC. (2) SMC or placebo monotherapy was administered randomly with a double-blind method, which
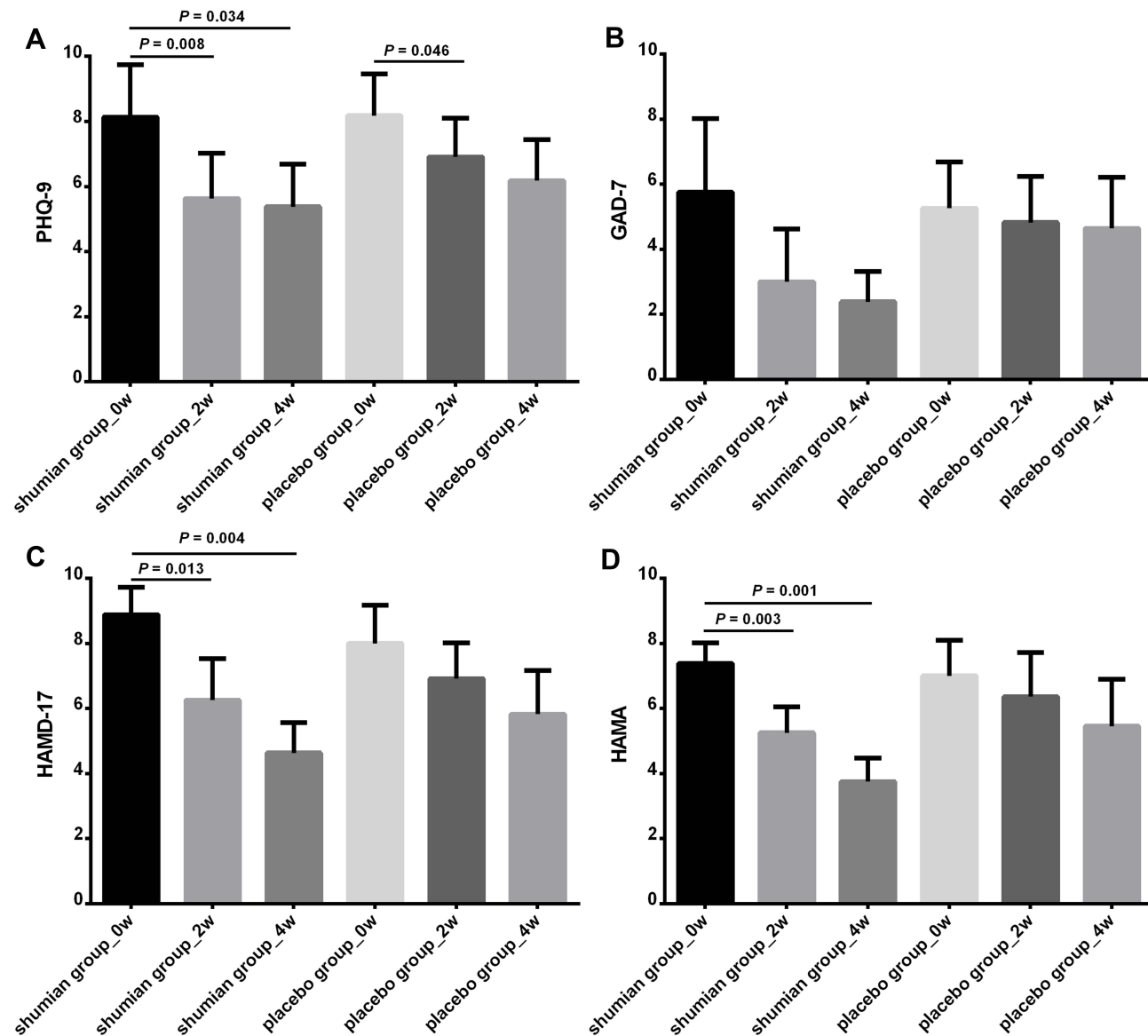
Figure 4 The scores of (**A**) PHQ-9, (**B**) GAD-7, (**C**) HAMD-17, and (**D**) HAMA in the shumian group and the placebo group pre- and post-treatment.
Abbreviations: PHQ-9, 9-items Patient Health Questionnaire; GAD-7, 7-items Generalized Anxiety Disorder; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

could help avoid the effects of sleep-affecting medicine and the subjectivity of the informed evaluators. (3) Only patients with insomnia were enrolled in the present study, which could help ensure more accurate evaluations of efficacy for SMC within a single diagnosis.

However, the strict inclusion criteria and trial requirements resulted in a relatively small sample size. Also, due to the small sample size, we were unable to explore gender differences on the indicators of PSG between male and female insomnia patients, although most researchers state that females are more prone to insomnia than males. In addition, there is a lack of follow-up after withdrawal, making it impossible to know whether the effects of SMC can continue after withdrawal. In the future, repeating the study in a larger sample, dividing patients into different gender groups, and adding a follow-up after drug withdrawal will be very useful for confirming the preliminary findings and whether gender plays an important role in insomnia.

Conclusion

In conclusion, SMC could improve insomnia after four weeks treatment, which was reflected in the subjective scales and the objective sleep indicators, especially in increasing the total sleep and deep sleep time and sleep efficiency. Furthermore, depression and anxiety were also significantly improved after treatment with SMC. During the four-week study period, the patients were well-tolerated in both SMC and placebo groups. Briefly, the present study demonstrated that SMC could improve subjective and objective sleep and the accompanying depression and anxiety symptoms of insomnia patients with low side effects. Future studies should focus on further evaluating the efficacy and safety of SMC in improving insomnia and its concomitant symptoms such as depression and anxiety in a large sample of insomnia patients.

Data Sharing Statement

The data and material supporting the results of this article are included within the article.

Acknowledgment

Author Contributions

Yuan Y was the principal investigator, designed the study protocol, and was involved in the recruitment of subjects and the revise of the manuscript. Chen S collected the samples of the subjects, performed the experiment, analyzed the statistical analysis, and wrote the manuscript. Xu Z, Li Y, Wang T, Yue Y, Hou Z, You L, Lu N, Yin Y, Liu X, Ji H, and Shi Y collected the samples from the subjects. Tan L and Xin X were involved in the experiment. Jiang W revised the manuscript. All authors contributed to data analysis, drafting, or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The study was funded by Guizhou Dalong Pharmaceutical Co. Ltd. However, the funder had no role in the study design, data collection, analysis, and interpretation, in writing the report, or in the decision to submit the article for publication. The authors report no other conflicts of interest in this work.

References

1. Buysse DJ. Insomnia. *JAMA*. 2013;309(7):706–716. doi:10.1001/jama.2013.193
2. Morin CM, Bélanger L, LeBlanc M, et al. The natural history of insomnia: a population-based 3-year longitudinal study. *Arch Intern Med*. 2009;169(5):447–453. doi:10.1001/archinternmed.2008.610
3. Shi Z, Lv J. Research progress of insomnia status. *Guangming J Chin Med*. 2015;30(6):1376–1377. in Chinese.
4. Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: a review on a bidirectional relationship, mechanisms and treatment. *J Cell Mol Med*. 2019;23(4):2324–2332. doi:10.1111/jcmm.14170
5. Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. *BMC Psychiatry*. 2016;16(1):375. doi:10.1186/s12888-016-1075-3
6. Okun ML, Mancuso RA, Hobel CJ, Schetter CD, Coussons-Read M. Poor sleep quality increases symptoms of depression and anxiety in postpartum women. *J Behav Med*. 2018;41(5):703–710. doi:10.1007/s10865-018-9950-7
7. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011;135(1–3):10–19. doi:10.1016/j.jad.2011.01.011
8. de Zambotti M, Goldstone A, Colrain IM, Baker FC. Insomnia disorder in adolescence: diagnosis, impact, and treatment. *Sleep Med Rev*. 2018;39:12–24. doi:10.1016/j.smrv.2017.06.009
9. Ribeiro JD, Pease JL, Gutierrez PM, et al. Sleep problems outperform depression and hopelessness as cross-sectional and longitudinal predictors of suicidal ideation and behavior in young adults in the military. *J Affect Disord*. 2012;136(3):743–750. doi:10.1016/j.jad.2011.09.049
10. McCall WV. A psychiatric perspective on insomnia. *J Clin Psychiatry*. 2001;62(Suppl 10):27–32.
11. Mason EC, Harvey AG. Insomnia before and after treatment for anxiety and depression. *J Affect Disord*. 2014;168:415–421. doi:10.1016/j.jad.2014.07.020
12. Gebara MA, Siripong N, DiNapoli EA, et al. Effect of insomnia treatments on depression: a systematic review and meta-analysis. *Depress Anxiety*. 2018;35(8):717–731. doi:10.1002/da.22776
13. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation*. 2011;124(19):2073–2081. doi:10.1161/CIRCULATIONAHA.111.025858

14. Sands-Lincoln M, Loucks EB, Lu B, et al. Sleep duration, insomnia, and coronary heart disease among postmenopausal women in the Women's health initiative. *J Womens Health*. 2013;22(6):477–486. doi:10.1089/jwh.2012.3918

15. Laugsand LE, Strand LB, Platou C, Vatten LJ, Janszky I. Insomnia and the risk of incident heart failure: a population study. *Eur Heart J*. 2014;35 (21):1382–1393. doi:10.1093/eurheartj/eht019

16. Fernandez-Mendoza J, Vgontzas AN, Liao D, et al. Insomnia with objective short sleep duration and incident hypertension: the penn state cohort. *Hypertension*. 2012;60(4):929–935. doi:10.1161/HYPERTENSIONAHA.112.193268

17. Vgontzas AN, Liao D, Pejovic S, Calhoun S, Karataraki M, Bixler EO. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. *Diabetes Care*. 2009;32(11):1980–1985. doi:10.2337/dc09-0284

18. National Institutes of Health. National institutes of health state of the science conference statement on manifestations and management of chronic insomnia in adults, June 13–15, 2005. *Sleep*. 2005;28(9):1049–1057. doi:10.1093/sleep/28.9.1049

19. Tannenbaum C, Diaby V, Singh D, Perreault S, Luc M, Vasiliadis HM. Sedative-hypnotic medicines and falls in community-dwelling older adults: a cost-effectiveness (decision-tree) analysis from a US Medicare perspective. *Drugs Aging*. 2015;32(4):305–314. doi:10.1007/s40266-015-0251-3

20. Pchelina PV, Poluektov MG. [Cognitive-behavioral therapy and pharmacotherapy for chronic insomnia]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2019;119(4.Vyp. 2):22–27. Russian. doi:10.17116/jnevro201911904222

21. Hassinger AB, Bletnisky N, Dudekula R, El-Solh AA. Selecting a pharmacotherapy regimen for patients with chronic insomnia. *Expert Opin Pharmacother*. 2020;21(9):1035–1043. doi:10.1080/14656566.2020.1743265

22. Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract*. 2012;13(1):40. doi:10.1186/1471-2296-13-40

23. Ni X, Shergis JL, Guo X, et al. Updated clinical evidence of Chinese herbal medicine for insomnia: a systematic review and meta-analysis of randomized controlled trials. *Sleep Med*. 2015;16(12):1462–1481. doi:10.1016/j.sleep.2015.08.012

24. Singh A, Zhao K. Treatment of insomnia with traditional Chinese herbal medicine. *Int Rev Neurobiol*. 2017;135:97–115. doi:10.1016/bs. irn.2017.02.006

25. Frass M, Strassl RP, Friehs H, Müllner M, Kundi M, Kaye AD. Use and acceptance of complementary and alternative medicine among the general population and medical personnel: a systematic review. *Ochsner J*. 2012;12(1):45–56.

26. Wang C, Yang Y, Ding X, et al. Efficacy and safety of Shumian capsules in treating insomnia: a systematic review and meta-analysis. *Medicine*. 2021;100(50):e28194. doi:10.1097/MD.0000000000028194

27. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep*. 2005;28(4):499–521. doi:10.1093/sleep/28.4.499

28. Littner M, Hirshkowitz M, Kramer M, et al. Practice parameters for using polysomnography to evaluate insomnia: an update. *Sleep*. 2003;26 (6):754–760. doi:10.1093/sleep/26.6.754

29. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213. doi:10.1016/0165-1781(89)90047-4

30. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601–608. doi:10.1093/sleep/34.5.601

31. Yu X, Tam WW, Wong PT, Lam TH, Stewart SM. The Patient Health Questionnaire-9 for measuring depressive symptoms among the general population in Hong Kong. *Compr Psychiatry*. 2012;53(1):95–102. doi:10.1016/j.comppsych.2010.11.002

32. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166 (10):1092–1097. doi:10.1001/archinte.166.10.1092

33. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62. doi:10.1136/jnnp.23.1.56

34. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55. doi:10.1111/j.2044-8341.1959.tb00467.x

35. Vinar O. Scale for rating treatment emergent symptoms in psychiatry DVP. *Act Nerv Super*. 1971;13(3):238–240.

36. Richard BB, Claude LA, Susan MH, et al. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Version 2.5*. IL, Darien: American Academy of Sleep Medicine; 2018.

37. Xie M, Liao M. Shumian capsule. *Chin J New Drugs*. 2001;10(5):386. in Chinese.

38. Liang F, Zhang X, Jiang X, et al. Experimental study on the effects of Shumian Capsule on sedation and hypnosis and its mechanisms. *J Xi'an Jiaotong Univ*. 2021;42(1):168–174. in Chinese.

39. Jo SY, Jung IH, Yi JH, et al. Ethanol extract of the seed of Zizyphus jujuba var. spinosa potentiates hippocampal synaptic transmission through mitogen-activated protein kinase, adenylyl cyclase, and protein kinase A pathways. *J Ethnopharmacol*. 2017;200:16–21. doi:10.1016/j.jep.2017.02.009

40. Li Y, Su Y, Li T, Yan X. Material basis of Sini Powder with sedative-hypnotic effect. *Chin Tradit Herb Drugs*. 2012;43(7):1361–1365. in Chinese.

41. Neurology CSo, Sleep Disorder Society CSoN. Guideline for the evaluation and treatment of insomnia in Chinese adults (2017). *Chin J Neurol*. 2018;51(5):324–335. in Chinese.

42. Li C, Li D, Zheng H, Li Z, Du H. Influence of Estazolam on the sleep quality and daytime function of patients with insomnia. *J Clin Rehabil Tissue Eng Res*. 2007;11(52):10483–10485.

43. An X, Duan L, Zhang YH, et al. The three syndromes and six Chinese patent medicine study during the recovery phase of COVID-19. *Chin Med*. 2021;16(1):44. doi:10.1186/s13020-021-00454-x

44. Cheng S, Ma H, Zhao Y, Yuan J. Clinical observation on 40 cases of adolescent depression treated by combined Chinese and Western medicine. *Shandong Med J*. 2012;52(4):58–59. in Chinese.

45. Li S, Wang Y, Liu F, Tang Z. Clinical research of Shumian capsule in treating liver stagnancy injuring spirit type insomnia. *China Pharmaceut*. 2014;23(3):6–7. in Chinese.

46. Liang Y, Wang W, Zhang H, et al. A randomized study comparing the efficacy and safety of Shumian capsules and Jieyuanshen capsules in the treatment of insomnia. *Chin J New Drugs*. 2015;24(10):1155–1159. in Chinese.

47. Lv Y. Analysis of paroxetine combined with Shumian capsule in the treatment of anxiety disorder (in Chinese). *World Latest Med Inform*. 2019;19 (4):103–104.

48. Lu A, Pan Y, Cao Y. Control observation of shumian capsule in treating insomnia. *Hainan Med J*. 2008;19(5):70+103. in Chinese.

49. Xia L, Li L, Zhang Q, Wu W, Chen S. Comparison of the therapeutic effects of Shumian capsule and estazolam in the treatment of insomnia. *Anhui Med Pharmaceut J*. 2015;19(2):367–371. in Chinese.