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Efficacy and safety of *Shugan Jieyu* capsules in combination with zolpidem for insomnia disorder with depressive symptoms: a double-blind randomized controlled trial

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Abstract

Objective Insomnia disorder with depressive symptoms (IDDS) represents a significant clinical phenotype, with a bidirectional relationship where insomnia both contributes to and results from depression. This study aimed to assess the efficacy and safety of combining zolpidem with *Shugan Jieyu* in treating IDDS.

Methods In a double-blind, randomized trial, 60 IDDS patients were assigned to zolpidem plus *Shugan Jieyu* (ZS) or zolpidem plus placebo (ZP) for 8 weeks, with 59 completing the study. Assessments included the Insomnia Severity Index (ISI), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 7 (GAD-7), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), polysomnography (PSG), and sleep diary. Mixed-model repeated-measures (MMRM) analysis was performed to assess the least squares means difference (LSMD) among the groups after 4 and 8 weeks of treatment. Subgroup analysis was performed on patients with sleep fragmentation (WASO ≥ 30 min).

Results Both groups showed significant improvements in ISI, PSQI, ESS, GAD-7, and PHQ-9, with no between-group differences. For the primary outcome (ISI), the between-group difference at week 8 was − 1.68 points (95% CI: -4.49 to 1.14; $p = 0.238$), corresponding to a small effect size (Cohen's d = 0.42). ZS significantly reduced WASO and increased TST at 8 weeks, whereas ZP showed no significant changes in these measures within the group. ZS reduced subjective sleep latency (sSL) significantly more than ZP at weeks 4 (LSMD − 12.21 min, 95% CI -22.54 to -1.87; $p = 0.021$; d = 0.23) and 8 (LSMD − 12.17 min, 95% CI -21.99 to -2.35; $p = 0.016$; d = 0.25). In the sleep fragmentation subgroup, ZS improved sSL and subjective sleep efficiency (sSE). Both treatments were well-tolerated.

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Conclusion Compared with taking zolpidem alone, the combination of zolpidem with *Shugan Jieyu* did not significantly improve insomnia, but showed preliminary non-objective signals in improving patients' perception of falling asleep, particularly in patients with sleep fragmentation.

Trial registration The study is registered in the ClinicalTrials.gov (NCT05764798). Date registered: 30 November 2022.

Keywords Insomnia, Depression, Sleep disorders, Polysomnography, Complementary therapies

Introduction

Insomnia is a prevalent sleep disorder characterized by difficulties in falling asleep or maintaining sleep, or premature or intermittent waking [1]. A significant clinical challenge is the frequent co-occurrence of insomnia with depressive symptoms, Insomnia Disorder with Depressive Symptoms (IDDS). The prevalence of insomnia is estimated at 10%–60% of the population [2]. Insomnia is often accompanied by depressive symptoms. Previous studies have revealed a bidirectional relationship between insomnia and depression, suggesting that insomnia is not just a consequence but also a predictor of depression [3–6]. Current evidence demonstrates that approximately 66% of depressed patients experience comorbid insomnia [7], while 25% of insomnia patients develop depressive symptoms [4, 8]. A 2024 large-scale Chinese study (N = 51,774) further quantified this overlap, showing insomnia patients had 11.3-fold higher odds of depression (95% CI: 9.58–13.29) compared to non-insomnia controls [9]. Insomnia symptoms may persist even after remission in depression, which increases the risk of depression recurrence [6]. IDDS is a common condition in the clinical population and interventions for IDDS need to consider both insomnia and depressive symptoms that lead to improvement in insomnia and prevention of full-blown depression [10, 11].

Medications are increasingly used in clinical practice for the treatment of insomnia. Zolpidem is a commonly used new generation of non-benzodiazepine sedatives for the treatment of insomnia [12, 13]. However, clinical studies indicate that many patients with insomnia disorder and comorbid depressive symptoms (IDDS) continue to experience persistent depressive symptoms despite zolpidem treatment [6]. This is partly due to zolpidem's limited efficacy in addressing the mood-related aspects of IDDS and its potential for tolerance and dependence with long-term use. Additionally, the sedative effects of zolpidem can sometimes exacerbate the cognitive and emotional symptoms of depression [6].

Antidepressants are widely prescribed for IDDS, with Selective Serotonin Reuptake Inhibitors (SSRIs)/Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (e.g., escitalopram) accounting for ~ 45% of prescriptions and sedating antidepressants (e.g., trazodone) for ~ 30%, despite limited Food and Drug Administration (FDA) approval for insomnia indications, reflecting real-world reliance on their dual mood-sleep effects [14–16]. According to Everitt, some antidepressants improve sleep latency (SL) and may improve patients' sleep fragmentation [17]. However, since depressive symptoms are not equivalent to depression, antidepressants are a bit extravagant when used to improve depressive symptoms. Furthermore, antidepressants can cause undesirable side effects such as weight gain, sexual dysfunction, and sedation, and may lead to withdrawal symptoms upon discontinuation, which can deter long-term adherence [18, 19]. This underscores the need for alternative therapies that can address both sleep and mood disturbances without such side effects. In addition, the use of antidepressants might have side effects and withdrawal reactions after discontinuation [20, 21]. Therefore, it is necessary to use a drug with high safety and effectiveness to improve depressive symptoms in insomnia.

Chinese medicine prescriptions have a long history in the treatment of depression, with significant curative effects and few adverse reactions [22, 23]. *Shugan Jieyu* capsules, a Chinese herbal medicine mainly composed of *Hypericum perforatum* and *Acanthopanax senticosus*, is a commonly used medication approved by the National Medical Products Administration (NMPA) of the People's Republic of China to treat mild to moderate depression [24]. Previous research provides a mechanistic rationale for the use of *Shugan Jieyu* capsules in treating insomnia, depression, and anxiety symptoms. Animal studies have demonstrated that *Shugan Jieyu* reverses depression-like behaviors by enhancing phosphorylation levels in the medial prefrontal cortex and hippocampal CA3 region, as well as upregulating cyclic adenosine monophosphate response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) expression [25]. Clinical evidence supports these findings, with randomized controlled trials (RCTs) showing that *Shugan Jieyu* capsules significantly improved insomnia, depression, and anxiety in various populations, including post-COVID-19 convalescence patients [26]. Additionally, Zhang et al. (2014) conducted a systematic review confirming *Shugan Jieyu* capsules' efficacy in major depressive disorder (MDD) which used data from 7 RCTs highlighting its superior therapeutic effects and safety compared to placebo [27]. Furthermore, combination therapy with venlafaxine has been shown to enhance depression remission rates compared to venlafaxine

alone [27]. Recent studies also indicate that *Shugan Jieyu* capsules can alleviate post-stroke depression-related cognitive impairment and emotional disturbances [28]. In addition, it has higher safety profiles for use in a combination regimen. Therefore, *Shugan Jieyu* capsules can be considered in combination therapy to improve IDDS.

In the current study, we conducted a double-blind, parallel-group randomized controlled trial to examine the efficacy of the combination of *Shugan Jieyu* capsules and zolpidem in IDDS.

Materials and methods

Participants and eligibility criteria

Patients with a diagnosis of IDDS were identified from the outpatient department. The participants were recruited in March 2023, and the last assessment was completed by October 2023. All of the subjects provided written informed consent, and the study was approved by Nanfang Hospital, Southern Medical University, China.

The inclusion criteria for this study were as follows:

1. Insomnia disorder, diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria;
2. Depressive symptoms, defined as Patient Health Questionnaire-9 (PHQ-9) score ≥ 10 points, but not fulfilling the DSM-5 criteria for Major Depressive Disorder (MDD);
3. Age 18–60 years;
4. No previous medication for insomnia or depression was used within the last month.

The exclusion criteria were as follows:

5. Allergy to specified substances, prior unsuccessful use of certain medications, recent use of specific medications affecting liver metabolism, substance or alcohol dependence, recent drug abuse, and medical conditions impacting drug metabolism;
6. Recent participation in other drug studies;
7. Chronic physical illness or mental disorders;
8. Sleep apnea (apnea-hypopnea index [AHI] ≥ 15 events/hour) or periodic limb movement disorder (periodic limb movement index [PLMI] > 15 events/hour) during baseline polysomnography;
9. Night and shift workers;
10. Pregnancy or lactation;
11. Individuals with serious suicidal behavior or plans;
12. Any other conditions deemed unsuitable for inclusion in the study.

Polysomnographic study

Nocturnal polysomnography (PSG) assessments were conducted at baseline, 4 weeks, and 8 weeks. Standard PSG recordings included EEG (F4-M1, F3-M2, C4-M1, C3-M2, O2-M1, O1-M2), electrooculography (EOG: LE-A2, RE-A1), submental electromyography (EMG), bilateral anterior tibialis EMG, electrocardiography (ECG), nasal airflow pressure, thoracic and abdominal respiratory effort sensors, pulse oximetry for oxygen saturation, breathing sound recording, and body position monitoring. All sleep parameters were determined through visual scoring of recordings according to established criteria. An experienced PSG technologist, who remained blinded to the study protocol, performed quality control of all computerized sleep data. Sleep staging, respiratory events, and periodic limb movements were analyzed in 30-second epochs following current AASM guidelines [29]. During baseline screening, participants exhibiting significant periodic limb movement disorder (PLMI ≥ 15 events/hour) or obstructive sleep apnea (AHI ≥ 15 events/hour) were excluded from study participation.

Randomization and blinding

In this study, block randomization was used. Statisticians independent of the study used SAS 9.4 to generate four-block randomization sequences. Then, blinding managers, independent of the study, prepared boxes containing either *Shugan Jieyu* capsules or a placebo for 60 participants. The boxes were labeled with random numbers so that the researchers and the participants were blinded to the treatments. The researchers then distributed the capsules based on those numbers.

Study design

The design entailed randomized (1:1), parallel-group, double-blind assignment of patients to *Shugan Jieyu* capsules in combination with zolpidem (the experimental group, ZS group) or zolpidem in combination with placebo (the control group, ZP group) for 8 weeks. The study design and reporting adheres to the CONSORT guidelines.

Intervention

In the ZS group, the participants received *Shugan Jieyu* capsules (Batch Number: 220106, oral 0.72 g twice daily) in combination with zolpidem (Batch Number: 220201, oral 10 mg once daily) for 8 weeks. In the ZP Group, the participants received a placebo in combination with zolpidem (oral 10 mg once daily) for 8 weeks. *Shugan Jieyu* capsules and placebo (the main ingredient was inert starch) were completely consistent in sensory properties such as color, shape, smell, and taste. During the intervention period, other psychotropic drugs or any other related treatment within 8 weeks were not allowed.

Sample size calculation

This study was a clinical trial with an 8-week duration, employing a 1:1 random allocation to the ZS group and the ZP group. Since no prior data existed for the combination therapy, we conservatively estimated the effect size using published monotherapy results: *Shugan Jieyu* capsules can reduce Insomnia Severity Index (ISI) scores by − 11.2 [30], and zolpidem can reduce ISI scores by − 6.8 [31]. Assuming no synergistic effects, we projected an intergroup difference of 4.4 (11.2–6.8) with a standard deviation of 4.5. With a two-sided α of 0.05 and 85% power, each group required 23 subjects. Considering a dropout rate of 20%, each group would need 30 subjects, resulting in a total estimated requirement of 60 subjects.

Outcome measures and measurements

The primary outcome measure for the study was the change in ISI score at week 8, which was determined as the reduction in ISI score from baseline, providing a patient-reported outcome measure of insomnia severity [32].

The secondary outcome measures were as follows:

13. PHQ-9 to assess depressive symptoms [33],
14. Generalized Anxiety Disorder 7 (GAD-7) to assess anxiety symptoms [34],
15. Epworth sleepiness scale (ESS) to assess excessive daytime sleepiness [35],
16. The Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality [36],
17. Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) to assess the quality of life [37],
18. Polysomnography (PSG) parameters, including total sleep time (TST), SL, wake after sleep onset (WASO), and sleep efficiency (SE), for objective sleep evaluation [38],
19. Sleep diary–extracted parameters, including subjective SL (sSL), subjective WASO (sWASO), subjective SE (sSE), and subjective TST (sTST), for subjective sleep evaluation.

All outcomes were evaluated from baseline to weeks 4 and 8. All adverse events that occurred or worsened between dosing day 1 and week 8 were recorded.

Statistical analysis

Descriptive statistics, including means and standard deviations for continuous variables and frequencies with percentages for categorical variables, were reported. Results were reported in line with the CONSORT guidelines [39]. Primary efficacy analyses were conducted on a per-protocol evaluable population consisting of all randomized participants who: (1) received ≥ 1 dose of study medication, (2) completed baseline assessments, and (3) provided ≥ 1 post-baseline efficacy evaluation (n = 59/60). One participant withdrew before any post-baseline assessments and was excluded from all analyses. Two-tailed tests were used in all statistical analyses in SAS (version 9.4), with $p < 0.05$ indicating statistical significance. Mixed-model repeated-measures (MMRM) analysis on the final value of each measure (at baseline, week 4, and week 8), with group, baseline total score, time, and time × group interaction, was performed to assess the least squares means difference (LSMD) among the groups after 4 and 8 weeks of treatment. Effect sizes (Cohen's d) were calculated for between-group comparisons (LSMD divided by pooled baseline standard deviation (SD)) and within-group changes (mean change divided by baseline SD), with interpretation thresholds of 0.2 (small), 0.5 (medium), and 0.8 (large). The analysis was applied to determine whether the overall course of change over the 8 weeks was different between the two groups. The mixed model is similar to ordinary least squares regression but has the advantage of using all the data. Furthermore, a t-test was carried out to evaluate the difference between the groups at 4 weeks and 8 weeks. Given that sleep fragmentation is a key feature of insomnia, a subgroup analysis was carried out in IDDS with sleep fragmentation. The analysis was an exploratory, non-prespecified analysis using the same analytical methods to investigate potential differential treatment effects in this clinically relevant subgroup.

Results

Participants

A total of 60 patients were initially enrolled and randomly assigned to treatment. Of these, one patient dropped out before receiving the minimum 4 weeks of treatment to qualify for the evaluable sample. The reason for dropping out was a change in medication requested by the patient. A total of 59 patients completed the requirements of the protocol. There were no significant differences in subject retention at the trial endpoint (week 8: ZS, 30/30; ZP, 29/30; $\chi^2 = 1.017$, df = 1, $p = 0.313$). The study flow diagram is shown in Fig. 1.

Table 1 provides descriptive statistics for baseline characteristics of the ZS and ZP groups. Fifty-nine participants diagnosed with IDDS completed the trial, with a mean age of 27.5 ± 6.7 years. Among them, 39.0% were male. A total of 48 (81.36%) were found to have a WASO score of at least 30 min.

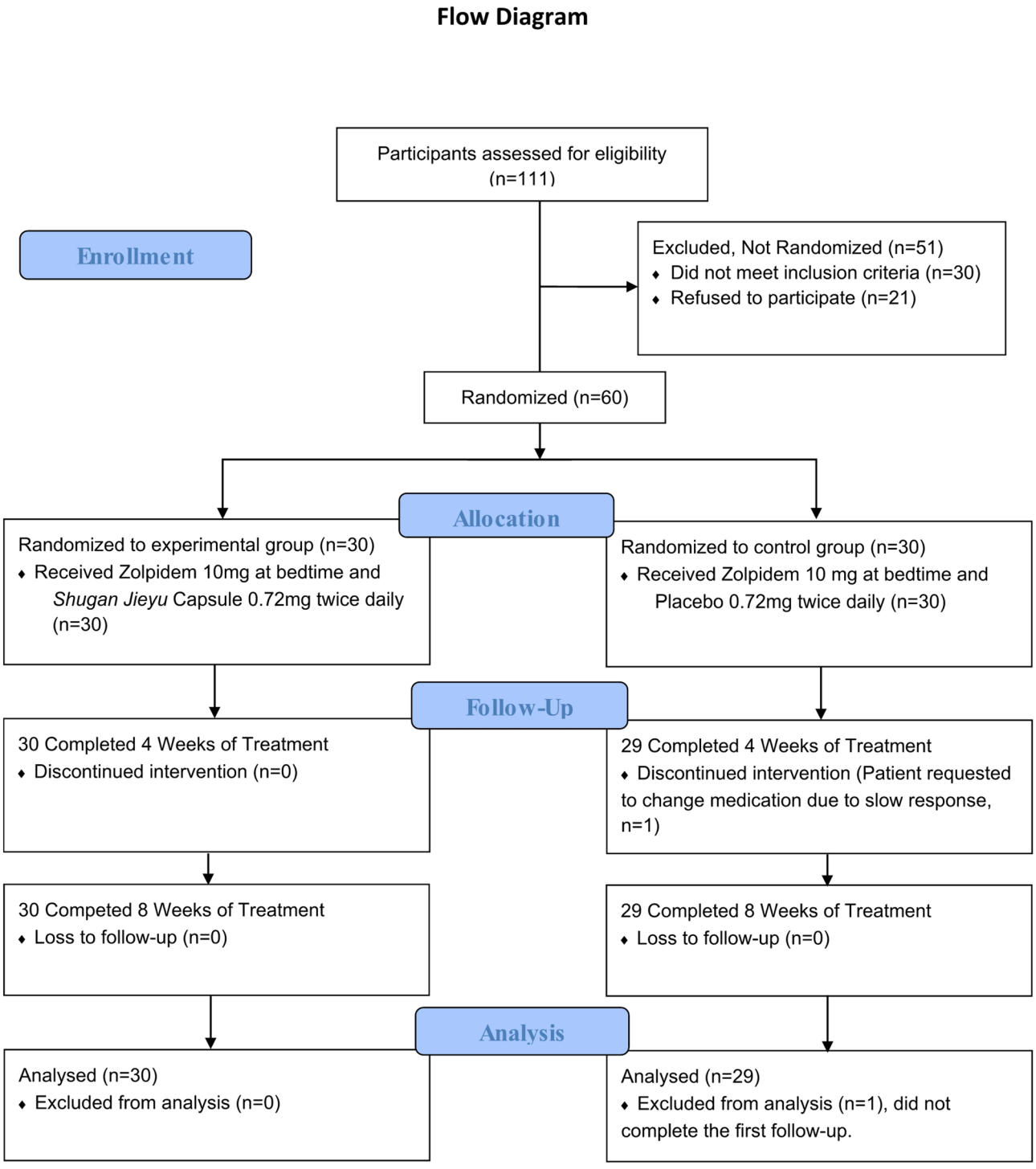

Fig. 1 Consolidated CONSORT study flow diagram

Clinical scales, PSG, and sleep diary outcomes between the ZS and ZP groups

Clinical scales

Table 2 shows the least squares mean differences (MD) for patient-reported outcomes between groups. For the primary outcome (ISI), the within-group changes from baseline to week 8 were −10.01 points (95% CI −11.98 to −8.04; $p < 0.001$; Cohen's d = 2.29) in the ZS group and −8.33 points (95% CI −10.34 to −6.33; $p < 0.001$; d = 2.31) in the ZP group, with a between-group difference of −1.68 points (95% CI −4.49 to 1.14; $p = 0.238$; d = 0.42). Secondary outcomes showed similar patterns:

Table 1 Baseline demographic and clinical characteristics in the ZS and ZP groups

Characteristic	*n* (%) or mean ± SD		*P* value
	ZS group (*n* = 30)	ZP group (*n* = 29)	
Age, years	28.50 ± 7.78	26.50 ± 5.28	0.267
Male	14 (46.7)	9 (31.0)	0.218
BMI, kg/m^2	21.42 ± 2.95	20.59 ± 2.84	0.273
Education (bachelor and above)	20 (66.7)	21 (72.4)	0.632
Marital status (unmarried)	22 (73.3)	25 (86.2)	0.219
History of smoking (yes)	5 (16.7)	4 (13.8)	0.759
History of treatment (yes)	17 (56.7)	13 (44.8)	0.363
History of other illnesses (yes)	1 (3.3)	1 (3.4)	0.981
Self-harm (yes)	7 (23.3)	4 (13.8)	0.347
Family history of insomnia (yes)	8 (26.7)	7 (24.1)	0.824
Clinical scales			
ISI	18.70 ± 4.38	18.90 ± 3.64	0.826
PHQ-9	15.17 ± 3.21	15.72 ± 4.04	0.561
GAD-7	11.60 ± 3.93	11.52 ± 4.99	0.944
PSQI	11.70 ± 3.19	12.31 ± 3.33	0.475
ESS	10.17 ± 5.29	10.90 ± 4.69	0.577
Q-LES-Q-SF	42.30 ± 5.79	41.10 ± 7.50	0.507
PSG			
TST, min	380.7 ± 67.92	414.1 ± 86.96	0.105
SL, min	21.60 ± 26.63	27.02 ± 83.39	0.736
WASO ≥ 30 minutes[a], min	90.4 ± 44.63	69.3 ± 33.57	0.075
SE (%)	78.77 ± 10.30	83.23 ± 15.26	0.192

n Frequency, *SD* Standard deviation, *ZS* Zolpidem and *Shugan Jieyu* capsules, *ZP* Zolpidem and placebo, *BMI* Body mass index, *ISI* Insomnia severity index, *PHQ-9* Patient Health Questionnaire-9, *GAD-7* Generalized Anxiety Disorder 7, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *Q-LES-Q-SF* Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form, *PSG* Polysomnography, *TST* Total sleep time, *SL* Sleep latency, *WASO* Wake after sleep onset, *SE* Sleep efficiency

[a], ZS, n = 26, ZP, n = 29;

[a]baseline WASO duration ≥ 30 min (sleep fragmentation subgroup)

PSQI (within-group d = 0.57–1.07), ESS (d = 0.35–0.63), PHQ-9 (d = 1.52–2.54), GAD-7 (d = 0.84–1.51), and Q-LES-Q-SF (d = 0.85–1.93) all demonstrated significant within-group improvements ($p < 0.05$) but no significant between-group differences (all $p > 0.05$; between-group d = 0.01–0.42).

PSG

Table 3 shows LSMD for objective sleep parameters between the ZS and ZP groups at 4 and 8 weeks. PSG results showed both groups achieved significant within-group improvements in TST at week 4 (ZS: −12.1 min, d = 0.45; ZP: −9.0 min, d = 0.11) and week 8 (ZS: −9.6 min, d = 0.34; ZP: −11.9 min, d = 0.14). The ZS group demonstrated significant WASO reduction at week 8 (−18.9 min, d = 0.60) and maintained SE gains at both timepoints (week 4: +5.9%, d = 0.57; week 8: +5.4%, d = 0.52). Between-group differences were non-significant for all parameters (all $p > 0.05$), with effect sizes ranging from negligible to small (d = −0.12 to 0.11).

Subjective sleep diary outcomes

Figure 2 shows the means ± standard error of measurements in the sleep diary. sTST and sSE increased in both groups, and sSL and sWASO decreased in both groups (Fig. 2). The results of LSMD analysis for subjective sleep diary outcomes between the ZS and ZP groups from 1 to 8 weeks showed no differences in sWASO, sSE, and sTST between the ZS and ZP groups ($p > 0.05$) (Supplementary Table 1). For sSL, the ZS group showed significantly greater reductions than ZP at week 4 (LSMD −12.21 min, 95% CI −22.54 to −1.87; $p = 0.021$; Cohen's d = 0.23) and week 8 (LSMD −12.17 min, 95% CI −21.99 to −2.35; $p = 0.016$; d = 0.25).

MMRM analysis confirmed sustained between-group differences in sSL reduction favoring ZS at week 4 ($p = 0.021$, d = 0.23), week 5 ($p = 0.030$), week 6 ($p = 0.035$), and week 8 ($p = 0.016$, d = 0.25) (Fig. 3).

Clinical scales, PSG, and sleep diary outcomes between the ZS and ZP groups in IDDS with sleep fragmentation

Clinical scales and PSG

Table 4 shows the LSMD for outcomes among the individuals with PSG WASO ≥ 30 min over 4 and 8 weeks. For the primary and secondary outcomes, the results were similar to the original groups. However, ESS improvements were significant in both groups at 8 weeks (all $p < 0.001$), but only the ZP group showed significant improvement at 4 weeks (ZP: $p = 0.048$; ZS: $p = 0.059$).

In PSG, the ZS group showed a significant increase in TST and SE at both 4 and 8 weeks (all $p < 0.05$) compared with the ZP group (all $p > 0.05$). However, there was a reduction in WASO at 4 weeks in the ZP group ($p = 0.044$), but it was not sustained at 8 weeks ($p = 0.060$), and WASO in the ZS group demonstrated significant reductions at 8 weeks only ($p = 0.006$). There were no significant between-group differences.

Subjective sleep diary outcomes in IDDS with sleep fragmentation

In IDDS with sleep fragmentation, the LSMD for subjective sleep diary outcomes between the ZS and ZP groups from 1 to 8 weeks showed no significant between-group differences in sWASO and sTST ($p > 0.05$). In the subgroup analysis of IDDS with sleep fragmentation, we found statistically significant between-group differences in the reduction of sSL at week 5 ($p = 0.018$), week 6 ($p = 0.007$), and week 8 ($p = 0.017$), and increase in sSE at week 6 ($p = 0.022$) (Fig. 4).

Safety

No significant serious adverse events were noted in any of the trial groups. The reported adverse events at 4 and 8 weeks are shown in Table 5. In both groups, a comparable proportion of patients reported adverse events

Table 2 Analysis of least squares means differences in clinical scales outcomes among the ZS and ZP groups

Characteristics		Difference from baseline							
		Week 4				Week 8			
		MD	95% CI	P value	Cohen's d	MD	95% CI	P value	Cohen's d
ISI	ZS vs. ZP	−0.95	−3.56, 1.67	0.471	0.24	−1.68	−4.49, 1.14	0.238	0.42
	ZS	−8.11	−9.94, −6.28	**< 0.001**	1.85	−10.01	−11.98, −8.04	**< 0.001**	2.29
	ZP	−7.16	−9.03, −5.3	**< 0.001**	1.97	−8.33	−10.34, −6.33	**< 0.001**	2.31
PSQI	ZS vs. ZP	0.07	−1.43, 1.58	0.922	0.02	−0.25	−1.90, 1.40	0.763	0.07
	ZS	−1.81	−2.86, −0.76	**0.001**	0.57	−3.41	−4.57, −2.25	**< 0.001**	1.07
	ZP	−1.88	−2.96, −0.81	**< 0.001**	0.56	−3.16	−4.34, −1.98	**< 0.001**	0.95
ESS	ZS vs. ZP	−0.22	−2.22, 1.78	0.827	0.04	−0.38	−2.55, 1.80	0.731	0.07
	ZS	−1.85	−3.25, −0.45	**0.010**	0.35	−3.32	−4.84, −1.80	**< 0.001**	0.63
	ZP	−1.63	−3.06, −0.21	**0.025**	0.35	−2.94	−4.49, −1.40	**< 0.001**	0.63
PHQ-9	ZS vs. ZP	−0.15	−2.38, 2.08	0.893	0.04	0.60	−1.64, 2.84	0.591	0.16
	ZS	−6.29	−7.85, −4.73	**< 0.001**	1.96	−8.16	−9.73, −6.59	**< 0.001**	2.54
	ZP	−6.14	−7.73, −4.56	**< 0.001**	1.52	−8.76	−10.36, −7.17	**< 0.001**	2.17
GAD-7	ZS vs. ZP	0.03	−2.31, 2.37	0.980	0.01	−0.46	−2.67, 1.74	0.677	0.10
	ZS	−4.17	−5.81, −2.53	**< 0.001**	1.06	−5.94	−7.49, −4.39	**< 0.001**	1.51
	ZP	−4.20	−5.87, −2.53	**< 0.001**	0.84	−5.48	−7.05, −3.90	**< 0.001**	1.10
Q-LES-Q-SF	ZS vs. ZP	0.3	−3.5, 4.08	0.870	0.04	0.2	−4.7, 5.24	0.922	0.03
	ZS	6.8	4.2, 9.5	**< 0.001**	1.12	11.7	8.2, 15.2	**< 0.001**	1.93
	ZP	6.5	3.8, 9.2	**< 0.001**	0.85	11.5	7.9, 15.0	**< 0.001**	1.52

MD Least squares means difference, *ZS* Zolpidem and *Shugan Jieyu* capsules, n = 30*; ZP* Zolpidem and placebo, n = 29*; ISI* Insomnia Severity Index, *PHQ-9* Patient Health Questionnaire-9, *GAD-7* Generalized Anxiety Disorder 7, *PSQI* Pittsburgh Sleep Quality Index, *ESS* Epworth Sleepiness Scale, *Q-LES-Q-SF* Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form

Bold indicates significant

Table 3 Analysis of least squares means differences in PSG outcomes among the ZS and ZP groups

Characteristics		Difference from baseline							
		Week 4				Week 8			
		MD	95% CI	P value	Cohen's d	MD	95% CI	P value	Cohen's d
TST, min	ZS vs. ZP	−3.0	−10.9, 4.76	0.438	−0.06	2.2	−7.9, 12.38	0.660	0.04
	ZS	−12.1	−17.5, −6.6	**< 0.001**	0.45	−9.6	−16.7, −2.5	**0.009**	0.34
	ZP	−9.0	−14.6, −3.5	**0.002**	0.11	−11.9	−19.1, −4.6	**0.002**	0.14
SL, min	ZS vs. ZP	−3.0	−10.9, 4.76	0.438	−0.06	2.2	−7.9, 12.38	0.660	0.04
	ZS	−12.1	−17.5, −6.6	**< 0.001**	0.45	−9.6	−16.7, −2.5	**0.009**	0.34
	ZP	−9.0	−14.6, −3.5	**0.002**	0.11	−11.9	−19.1, −4.6	**0.002**	0.14
WASO, min	ZS vs. ZP	5.6	−23.5, 34.8	0.700	0.11	−5.8	−31.8, 20.3	0.659	−0.12
	ZS	−14.7	−34.9, 5.5	0.151	0.31	−18.9	−36.9, −0.9	**0.040**	0.60
	ZP	−20.3	−40.9, 0.2	0.053	0.55	−13.1	−31.5, 5.2	0.157	0.36
SE, %	ZS vs. ZP	0.1	−6.2, 6.46	0.964	0.01	0.7	−4.7, 6.10	0.803	0.05
	ZS	5.9	1.5, 10.3	**0.010**	0.57	5.4	1.6, 9.2	**0.006**	0.52
	ZP	5.7	1.2, 10.2	**0.013**	0.37	4.7	0.9, 8.6	**0.017**	0.31

MD Least squares means difference, *ZS* Zolpidem and *Shugan Jieyu* capsules, n = 30*; ZP* Zolpidem and placebo, n = 29*; PSG* Polysomnography, *TST* Total sleep time, *SL* Sleep latency, *WASO* Wake after sleep onset, *SE* Sleep efficiency

Bold indicates significant

throughout the trial, namely a total of 25 (86.2%) in the ZP group and 23 (76.7%) in the ZS group. All intervention-related AEs were categorized as "possibly related" after investigator assessment and all reported AEs were Grade 1 (mild) in severity. Drowsiness, dizziness, nausea and vomiting were the common side effects reported. There was no increase in side effects after combining *Shugan Jieyu* capsules with zolpidem.

Discussion

The main finding of this study was that the combination of *Shugan Jieyu* capsules and zolpidem significantly decreased sSL in IDDS. For patients with sleep fragmentation, the combination regimen improved sSE in addition to sSL. In PSG, the combination regimen showed within-group improvement in TST and WASO at 8 weeks. This study's primary outcome, that is change in ISI, showed no significant difference between zolpidem

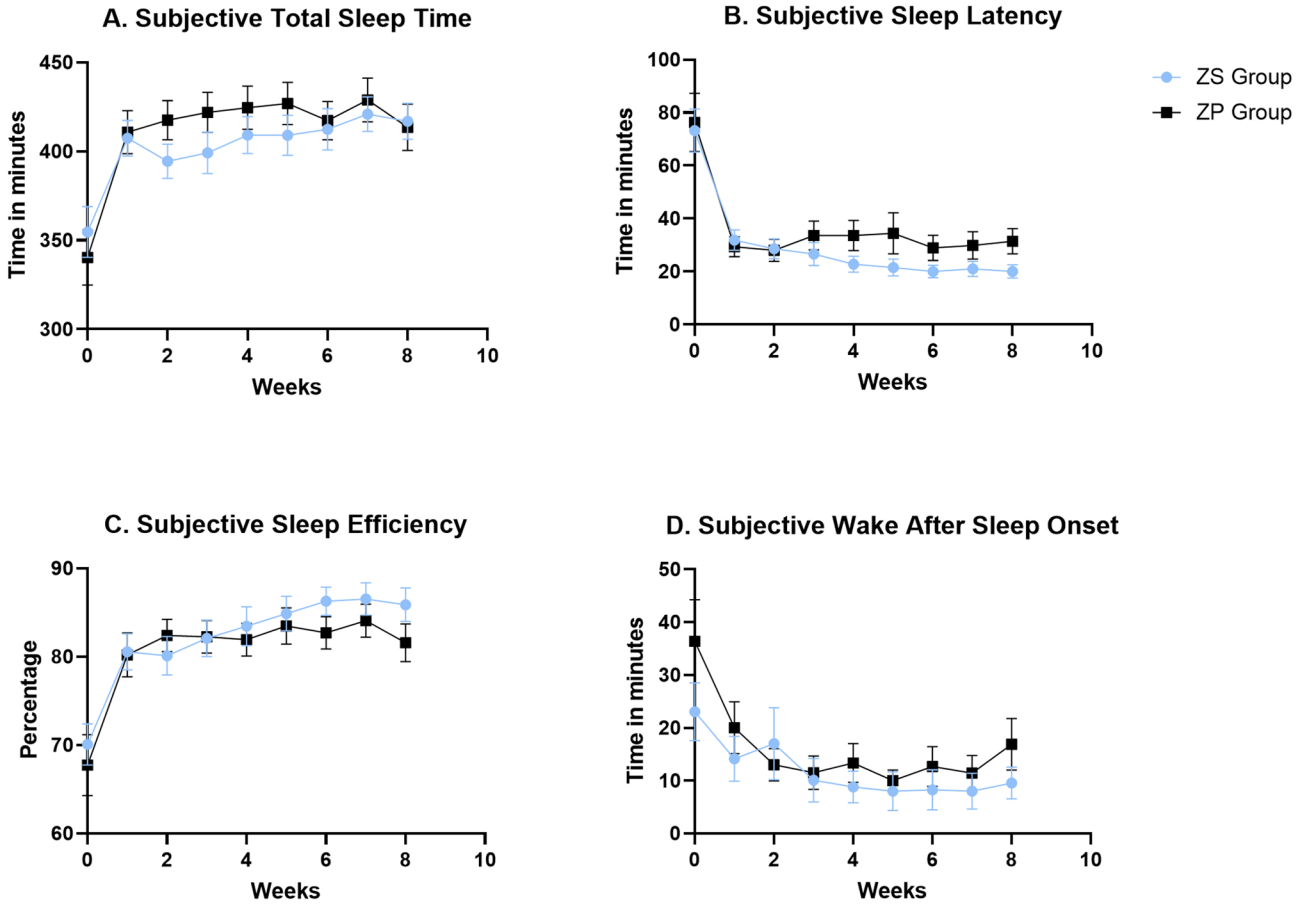

Fig. 2 Plot of sleep diary measurement recorded over 8 weeks. ZS group, Zolpidem and *Shugan Jieyu* group, ZP group, Zolpidem and Placebo group. The error bars represent the standard error of the mean (SEM) for ZS ($n=30$) and ZP ($n=29$) groups

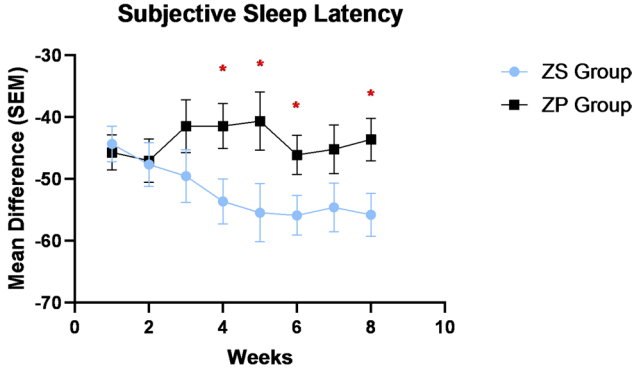

Fig. 3 Change in sleep diary measurements over 8 weeks in IDDS. ZS group ($n=30$), zolpidem and *Shugan Jieyu* group; ZP group ($n=29$), zolpidem and placebo group. *, $p<0.05$ denoting nominal p-values. The error bars represent the standard error of the mean difference (SEM)

monotherapy and combination therapy with Shugan Jieyu. Both groups showed significant improvements in insomnia severity (ISI), sleep quality (PSQI), excessive daytime sleepiness (ESS), anxiety symptoms (GAD-7), depressive symptoms (PHQ-9), and quality of life (Q-LES-Q-SF).

In this study, both subjective and objective sleep parameters were improved. However, the patients from the ZS group reported a significant decrease in sSL, while objective sleep parameters did not reflect this change. This is in line with the well-documented phenomenon of subjective-objective sleep discrepancy in insomnia, where patient-reported sleep improvements often occur independently of changes in objective polysomnographic measures [40, 41]. Objective and subjective sleep measures often diverge in insomnia patients. Previous research has shown that patients with insomnia often report their sleep characteristics as being more severe than indicated by objective measurements. As sleep improves, the patient's perception of sleep also improves, significantly shortening the sSL. However, the first-night effect (FNE) may influence objective results [42, 43]. The quantitative criteria for insomnia define insomnia as occurring at least three nights per week. Hence, one night of PSG is likely to be insufficient to fully capture insomnia symptoms [44, 45]. In addition, when our bodies try to enter a resting state in an unfamiliar environment, one hemisphere of the brain will be more alert than usual in PSG. This is a balancing mechanism generated

Table 4 Analysis of least squares means difference in outcomes among the ZS ($n=26$) and ZP ($n=22$) groups with WASO ≥ 30 min

Characteristics		Difference from baseline							
		Week 4				Week 8			
		MD	95% CI	*P* value	Cohen's d	MD	95% CI	*P* value	Cohen's d
Clinical Scales									
ISI	ZS vs. ZP	0.53	−2.36, 3.42	0.714	0.11	−0.87	−4.26, 2.53	0.610	−0.19
	ZS	−7.49	−9.44, −5.53	**< 0.001**	1.66	−9.56	−11.86, −7.27	**< 0.001**	2.12
	ZP	−8.02	−10.14, −5.89	**< 0.001**	2.39	−8.70	−11.19, −6.21	**< 0.001**	2.65
PSQI	ZS vs. ZP	0.49	−1.21, 2.19	0.567	0.15	−0.03	−1.97, 1.91	0.975	−0.01
	ZS	−1.38	−2.52, −0.24	**0.019**	0.43	−3.03	−4.34, −1.73	**< 0.001**	0.94
	ZP	−1.87	−3.11, −0.62	**0.004**	0.57	−3.00	−4.43, −1.58	**< 0.001**	0.98
ESS	ZS vs. ZP	0.22	−2.16, 2.59	0.854	0.04	−0.13	−2.45, 2.18	0.907	−0.03
	ZS	−1.55	−3.15, 0.06	0.059	0.30	−3.35	−4.92, −1.79	**< 0.001**	0.65
	ZP	−1.76	−3.51, −0.02	**0.048**	0.36	−3.22	−4.92, −1.52	**< 0.001**	0.67
PHQ-9	ZS vs. ZP	0.15	−2.42, 2.73	0.905	0.04	0.55	−2.09, 3.19	0.679	0.12
	ZS	−6.14	−7.87, −4.40	**< 0.001**	2.01	−8.29	−10.07, −6.51	**< 0.001**	2.71
	ZP	−6.29	−8.18, −4.40	**< 0.001**	1.42	−8.84	−10.77, −6.90	**< 0.001**	2.00
GAD-7	ZS vs. ZP	0.09	−2.55, 2.72	0.948	0.02	0.05	−2.40, 2.50	0.967	0.01
	ZS	−4.65	−6.42, −2.87	**< 0.001**	1.16	−5.96	−7.61, −4.30	**< 0.001**	1.49
	ZP	−4.73	−6.67, −2.80	**< 0.001**	0.94	−6.01	−7.80, −4.21	**< 0.001**	1.19
Q-LES-Q-SF	ZS vs. ZP	−2.1	−6.3, 2.09	0.319	−0.28	−1.9	−7.7, 4.00	0.527	−0.18
	ZS	6.6	3.8, 9.4	**< 0.001**	1.09	11.0	7.1, 15.0	**< 0.001**	1.76
	ZP	8.7	5.6, 11.7	**< 0.001**	1.06	12.9	8.6, 17.2	**< 0.001**	1.57
PSG									
TST, min	ZS vs. ZP	5.2	−42.1, 52.6	0.825	0.08	35.1	−2.9, 73.0	0.069	0.53
	ZS	34.2	2.7, 65.8	**0.034**	0.49	29.6	4.5, 54.7	**0.022**	0.42
	ZP	29.0	−5.4, 63.4	**0.096**	0.54	−5.4	−32.8, 21.9	0.691	−0.10
SL, min	ZS vs. ZP	−3.4	−12.6, 5.89	0.468	−0.15	0.1	−11.9, 12.03	0.992	0.00
	ZS	−3.8	−10.0, 2.4	0.226	0.15	−1.4	−9.5, 6.7	0.735	0.06
	ZP	−0.4	−7.2, 6.4	0.898	0.02	−1.4	−10.2, 7.4	0.745	0.08
WASO, min	ZS vs. ZP	4.4	−31.1, 39.9	0.803	0.09	−7.8	−37.5, 21.8	0.597	−0.16
	ZS	−22.2	−46.0, 1.6	0.067	0.50	−28.5	−48.2, −8.7	**0.006**	0.84
	ZP	−26.6	−52.5, −0.7	**0.044**	0.79	−20.6	−42.2, 0.9	0.060	0.61
SE, %	ZS vs. ZP	1.6	−6.2, 9.44	0.679	0.18	2.8	−4.0, 9.61	0.407	0.24
	ZS	6.4	1.2, 11.5	**0.018**	0.65	6.2	1.7, 10.7	**0.008**	0.63
	ZP	4.7	−0.9, 10.4	0.099	0.67	3.4	−1.5, 8.3	0.170	0.48

MD Least squares means difference, *WASO* Wake after sleep onset, *ZP* Zolpidem and placebo group with PSG WASO ≥ 30 min, n = 26; *ZS* Zolpidem and *Shugan Jieyu* capsules group with PSG WASO ≥ 30 min, n = 22; *PSG* Polysomnography, *TST* Total sleep time, *SL* Sleep latency, *SE* Sleep efficiency

Bold indicates significant

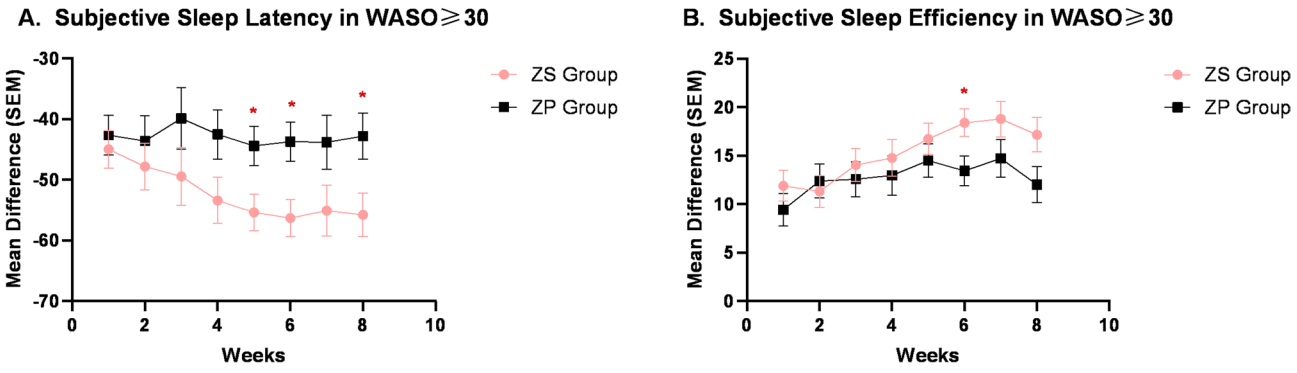

Fig. 4 Change in sleep diary measurements over 8 weeks in IDDS with sleep fragmentation. ZS, zolpidem plus *Shugan Jieyu*; ZP, zolpidem plus placebo; *, ZS vs. ZP, $p<0.05$ denoting nominal p-values. Panels A and B show the least squares means difference (MD) with standard error of the MD (SEM) from baseline in sleep latency (SL) and sleep efficiency (SE) in the ZS ($n=26$) and ZP (29) groups with PSG wake after sleep onset (WASO) ≥ 30 minutes

Table 5 Incidence of adverse events in the ZS and ZP groups

	ZS group ($n=30$)		ZP group ($n=29$)	
	Week 4	Week 8	Week 4	Week 8
Number of AEs, n (%)	23 (76.67)	18 (60.00)	24 (82.76)	19 (65.52)
Most frequent AEs				
Somnolence, n (%)	19 (63.33)	13 (43.33)	18 (62.07)	14 (48.28)
Headache, n (%)	3 (10.00)	2 (6.67)	5 (17.24)	7 (24.14)
Dizziness, n (%)	10 (33.33)	7 (23.33)	12 (41.38)	13 (44.83)
Nausea (%)	7 (23.33)	2 (6.67)	9 (31.03)	6 (20.69)
Less frequent AEs				
Excitement, n (%)	1 (3.33)	1 (3.33)	1 (3.45)	0 (0.00)
Low mood, n (%)	1 (3.33)	0 (0.00)	3 (10.34)	3 (10.34)
Lethargy, n (%)	1 (3.33)	0 (0.00)	1 (3.45)	1 (3.45)
Sleep disturbances, n (%)	3 (10.00)	2 (6.67)	6 (20.69)	6 (20.69)
Dry mouth, n (%)	0 (0.00)	0 (0.00)	1 (3.45)	1 (3.45)
Nasal congestion, n (%)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.45)
Blurred vision, n (%)	2 (6.67)	0 (0.00)	1 (3.45)	1 (3.45)
Constipation, n (%)	3 (10.00)	1 (3.33)	2 (6.90)	0 (0.00)
Sweating, n (%)	0 (0.00)	0 (0.00)	1 (3.45)	1 (3.45)
Diarrhea, n (%)	4 (13.33)	1 (3.33)	8 (27.59)	2 (6.90)
Loss of appetite, n (%)	0 (0.00)	0 (0.00)	1 (3.45)	0 (0.00)
Other, n (%)	13 (43.33)	10 (33.33)	16 (55.17)	13 (44.83)

ZS Zolpidem and *Shugan Jieyu* capsules, *ZP* Zolpidem and placebo, *AE* Adverse events

Data represent the number of participants experiencing ≥ 1 adverse event (AE). A single participant may have reported multiple AEs. All causal relationships were "possibly related"; All AEs were Grade 1 (mild)

during sleep to guard against potential dangers [46]. Previous studies have shown that zolpidem improves subjective and objective sleep [47], and current combination therapy significantly reduced sSL compared with zolpidem monotherapy. Moreover, the ZS group showed statistically significant within-group improvement in TST and WASO at 8 weeks, which was not observed in the ZP group. This indicates that the combination of *Shugan Jieyu* capsules and zolpidem may have the potential to improve subjective sleep quality and sleep continuity. The sSL finding, while potentially clinically relevant, requires cautious interpretation due to multiple comparisons and lack of objective corroboration.

In addition, our study showed that in IDDS with sleep fragmentation, the combination of *Shugan Jieyu* capsules and zolpidem significantly reduced sSL and enhanced sSE. These results suggest that individuals with more pronounced sleep fragmentation may benefit from a combination with *Shugan Jieyu* capsules, possibly due to the inhibitory effects of *Acanthopanax senticosus* on serotonin synthesis and antioxidative stress damage, contributing to sedation and calming of nerves. This is consistent with a recent meta-analysis confirming that Shugan Jieyu capsule combination therapy significantly improves sleep quality in patients with insomnia [26, 48]. Futhermore, the combination of Shugan Jieyu capsules and non-benzodiazepine drugs improved the overall clinical effectiveness in patients with insomnia [48]. Sleep fragmentation, characterized by frequent awakenings, is a hallmark of insomnia disorder and has been linked to heightened emotional dysregulation and depressive symptoms [6, 49]. Better SE is associated with better subjectively perceived sleep quality [50–52]. This effect may be attributed to the complementary mechanisms of the two interventions: while zolpidem (a short-acting GABAergic hypnotic) primarily facilitates sleep initiation, Shugan Jieyu—through bioactive compounds (e.g., *Acanthopanax senticosus*, *Hypericum perforatum*) —modulates monoaminergic neurotransmission (e.g., serotonin, BDNF) function [12, 13, 25, 53], thereby enhancing sleep continuity and reducing fragmentation.

In this study, we found that both groups showed significant improvements in ISI, PSQI, ESS, GAD-7, PHQ-9, and Q-LES-Q-SF, without between-group differences. Our findings highlight the efficacy of both treatments in reducing insomnia, excessive daytime sleepiness, anxiety symptoms, and depressive symptoms, while also enhancing sleep quality and overall quality of life (all $p < 0.05$ in each group), consistent with prior research. Zolpidem improves subjective and objective insomnia symptoms by acting selectively on the central nervous system ω 1 receptor, producing strong sedative and hypnotic effects, with a mild reduction in anxiety and depressive symptoms [53–56]. In addition, a significant reduction in SL and WASO may lead to a reduction in anxiety and worry at the beginning of sleep and waking up at midnight, thereby further improving anxiety and depressive symptoms [57]. Moreover, due to the improvement in sleep, there might be a reduction in sleep-related anxiety and depressive symptoms by changing their perception of sleep [58, 59]. However, some depressive symptoms may be secondary to poor sleep and, if sleep problems are addressed, depressive symptoms may improve [6, 60]. Those might be the reasons for the improvement of depressive and anxiety symptoms in both groups without between-group differences.

Zolpidem is a non-benzodiazepine hypnotic widely used in the treatment of insomnia. It functions by binding to the alpha-1 subunit of the γ-aminobutyric acid type A (GABA-A) receptor, exerting hypnotic effects through neuronal inhibition similar to benzodiazepines. Clinical trial have demonstrated that zolpidem effectively reduces sleep latency by an average of 20 min and sustains these results in the long term [12, 61, 62]. It is available in various formulations, with immediate-release zolpidem being particularly effective at reducing SL and increasing TST. However, zolpidem has been associated with several adverse effects, including complex

sleep-related behaviors like sleepwalking, hallucinations, increased suicidality, and even rare cases of committing homicide [12, 63]. The *Shugan Jieyu* capsules are a herbal remedy primarily composed of extracts from *Hypericum perforatum* (St. John's Wort) and *Acanthopanax senticosus*. *Hypericum perforatum* has been used for centuries as an antidepressant, functioning through mechanisms such as serotonin receptor modulation, monoamine oxidase inhibition, and neuroendocrine and ion channel modulation [53]. Clinical studies have shown that it is significantly more effective than placebo and comparable to standard antidepressants such as fluoxetine and sertraline in treating depressive disorder [64]. The addition of *Acanthopanax senticosus* may enhance the capsules' effectiveness in improving SL and reducing oxidative stress, providing neuroprotection, and calming nerves [53]. Zolpidem and *Shugan Jieyu* both offer unique benefits in treating insomnia, though through different mechanisms. Zolpidem primarily focuses on improving SL and TST through its hypnotic effects, but carries risks of significant neuropsychiatric side effects [12, 63]. In contrast, *Shugan Jieyu*, with its combination of *Hypericum perforatum* and *Acanthopanax senticosus*, provides both antidepressant and sedative effects with a more favorable side effect profile for those with depressive symptoms [53]. Combining zolpidem with *Shugan Jieyu* may offer a superior treatment strategy for patients suffering from both insomnia and depressive symptoms. The rationale for this combination lies in the complementary effects of the two treatments: zolpidem provides immediate relief for sleep initiation [12], while Shugan Jieyu addresses the underlying mood dysregulation and improves sleep continuity [53], potentially leading to more sustained improvements. Furthermore, our study's safety results support this strategy, demonstrating that the combination was well-tolerated with no significant increase in adverse events compared to zolpidem monotherapy (Table 5). This dual approach may not only improve sleep quality, but also address the underlying depression, which is often intertwined with insomnia [65].

While no significant between-group differences were observed in PSG measures, the clinically meaningful improvements in sSL and sSE with *Shugan Jieyu* supplementation are noteworthy. Subjective sleep perception often diverges from objective metrics in insomnia, and patient-reported outcomes are critical determinants of treatment success [66, 67]. The reduction in sSL and enhanced sSE suggest that *Shugan Jieyu* may ameliorate the hyperarousal and cognitive distortions characteristic of insomnia disorder [68], particularly in patients with sleep fragmentation. However, the clinical relevance of this reduction remains uncertain, as the between-group effect sizes were small (Cohen's d = 0.23–0.25) and were not supported by objective PSG measures. While patient-reported outcomes are valuable, a statistically significant but small improvement in sSL may not translate into a meaningful clinical benefit. These subjective improvements align with evidence that perceived sleep quality strongly influences daytime functioning and mood. Thus, even in the absence of PSG-detected changes [58, 68], the alleviation of patient-reported distress may translate to better adherence, reduced depressive symptoms, and improved quality of life in managing insomnia with comorbid depressive features.

Furthermore, there is evidence suggesting that treating insomnia can lead to significant reductions in depressive severity, and these improvements are often maintained during follow-up [65]. Therefore, the combination of zolpidem and *Shugan Jieyu* benefits from the antidepressant and sleep-enhancing properties of *Shugan Jieyu*. This multifaceted approach aligns well with the need for a multidisciplinary strategy in treating insomnia, particularly when comorbid with depressive symptoms [12, 65].

Limitations

Although our research has advantages, there are still some limitations that need to be considered. First, the relatively small sample sizes for each group may have reduced the statistical power to detect more significant group differences. Second, the study was done in a single center. Third, the intervention and follow-up periods in this study were relatively short. Fourth, lack objective biomarker (e.g., serum BDNF) to correlate with clinical outcomes. Short-term follow-up (8 weeks) precluded assessment of relapse rates. Fifth, while we observed improvements in subjective sleep measures, the lack of objective PSG concordance and multiple secondary analyses increase the risk of type I error. These findings should therefore be considered exploratory.

Future directions

Future studies should address the limitations of this study. Specifically, longer intervention and follow-up periods are needed to assess the durability of the effects of zolpidem and *Shugan Jieyu* capsules in insomnia with comorbid depression. Multi-center trials with larger, more diverse samples will improve the generalizability of the findings. Additionally, research into the mechanisms of their synergistic effects, particularly through markers like BDNF and EEG sleep patterns, is warranted to better understand their molecular interactions.

Conclusions

Compared with taking zolpidem alone, the combination of zolpidem with *Shugan Jieyu* did not significantly improve insomnia, but showed preliminary non-objective signals in improving patients' perception of falling asleep, particularly in patients with sleep fragmentation.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
BDNF	Brain-derived neurotrophic factor
CREB	Cyclic adenosine monophosphate response element-binding protein
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiography
EEG	Electroencephalography
EOG	Electrooculography
ESS	Epworth sleepiness scale
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder 7
IDDS	Insomnia Disorder with Depressive Symptoms
ISI	Insomnia Severity Index
LSMD	Least squares means difference
MD	Mean differences
MDD	Major depressive disorder
MMRM	Mixed-model repeated-measures
NMPA	National Medical Products Administration
OAI	Obstructive apnea index
ODI	Oxygen desaturation index
PHQ-9	Patient Health Questionnaire-9
PLMI	Periodic limb movement index
PSG	Polysomnography
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
RCTs	Randomized controlled trials
SD	Standard deviation
SEM	Standard error of the mean
SE	Sleep efficiency
SL	Sleep latency
SNRIs	Serotonin-Norepinephrine Reuptake Inhibitors
sSE	Subjective sleep efficiency
sSL	Subjective sleep latency
SSRIs	Selective Serotonin Reuptake Inhibitors
sTST	Subjective total sleep time
sWASO	Subjective wake after sleep onset
TST	Total sleep time
WASO	Wake after sleep onset
ZP	Zolpidem in combination with placebo
ZS	*Shugan Jieyu* capsules in combination with zolpidem

Supplementary Information

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Supplementary Material 1

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Authors' contributions

Z.B.: Conceptualization, Funding acquisition, Project administration. Q.X.: Methodology, Investigation, Resources, Data curation, Writing - Review & Editing, Validation. D.P.: Visualization, Data curation, Formal analysis, Writing-Original draft preparation. J.Z.: Investigation and Recruiting volunteers. H.W.: Supervision, Investigation, Software, Data Curation. Y. C.: Investigation, Software, Data Curation. Y. X.: Software, Supervision, Project administration, Writing - Review & Editing. R. F.: Investigation, Software, Data Curation. J. J.: Investigation, Software, Data Curation. Y.W.: Investigation, Software, Data Curation.All authors critically reviewed the manuscript and approved the final version submitted.

Data availability

The data will be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Nanfang Hospital, Southern Medical University Research Ethics Committee (protocol NFEC-2023-030). The study was registered at ClinicalTrials.gov (NCT05764798) on 2022-11-30 (Registration Date). The study was conducted in accordance with the Declaration of Helsinki. All human participants provided written informed consent for the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Ethics and dissemination

The study was approved by the Institutional Ethics Committee of Nanfang Hospital, Southern Medical University (No. NFEC-2023-030, Guangzhou, China).

Credit authorship contribution statement

Zhang Bin: Conceptualization, Funding acquisition, Project administration. Qianqian Xin: Methodology, Investigation, Resources, Data curation, Writing - Review & Editing, Validation. Dhirendra Paudel: Visualization, Data curation, Formal analysis, Writing- Original draft preparation. Jiehan Zhang: Investigation and Recruiting volunteers. Huafeng Wei: Supervision, Investigation, Software, Data Curation. Yihong Cheng: Investigation, Software, Data Curation. Yan Xu: Software, Supervision, Project administration, Writing - Review & Editing. Ruichen Fang: Investigation, Software, Data Curation. Jinnong Jiang: Investigation, Software, Data Curation. Yuling Wang: Investigation, Software, Data Curation. All authors critically reviewed the manuscript and approved the final version submitted.

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