Suanzaoren Decoction for the treatment of chronic insomnia: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Suanzaoren decoction (SZRD) in Traditional Chinese Medicine is a common prescription for chronic insomnia. This study systematically and accurately evaluated the safety and efficacy of SZRD in the treatment of chronic insomnia, thus providing a reference for its clinical application.

MATERIALS AND METHODS: From the establishment of the corresponding database until May 2022, we systematically queried EMbase, PubMed, Cochrane Library, Web of Science, CNKI, VIP, and Wanfang Database. Randomized control trials (RCTs) were included in this study, and the results that qualified for inclusion were screened and cross-checked by two researchers. After the relevant data were extracted, a meta-analysis was performed using RevMan 5.3 software.

RESULTS: A total of 1,311 patients with chronic insomnia from 12 RCTs were enrolled in the meta-analysis, showing that the use of SZRD alone or in combination was superior to the control group in improving the clinical effective rate (RR=1.22, 95%CI [1.16, 1.29], p<0.00001), reducing the recurrence rate (RR=0.47, 95%CI [0.28, 0.80], p=0.005), and lowering the Pittsburgh Sleep Quality Index (PSQI) scores ($MD_{SZRD+W-M}$=-3.35,95%CI [-5.22, -1.47], p<0.00001); (MD_{SZRD}=-1.94, 95%CI [-3.80, -0.07], p = 0.04). SZRD also could reduce the adverse effects rate (RR=0.30, 95% CI [0.22, 0.40], p<0.00001).

CONCLUSIONS: It was therefore concluded that SZRD alone or in combination with Western medicine can increase the clinical effective rate, reduce the recurrence rate, improve the quality of life of chronic insomnia patients, and decrease the incidence of adverse effects. However, studies included in this analysis varied in quality, and more large-sample, high-quality, multi-center RCTs are still needed to verify the above conclusions.

Key Words:
  Suanzaoren decoction, Chronic insomnia, Meta-analysis.

Introduction

Insomnia is characterized by difficulty in falling asleep or maintaining a sustained state of sleep at night, which affects social functioning during the day. Insomnia can lead to various other problems, including acute myocardial infarction, stroke, and mental disorders. It can also accelerate the progression of several neurodegenerative diseases[1-4]. Chronic insomnia is a subtype of insomnia, which induces or aggravates the aforementioned underlying diseases. It is clinically defined as insomnia disorder occurring at least three nights a week over a period of more than three months. At least 5-10% of global adults suffer from chronic (or severe) insomnia, and this rate without a clinical diagnosis may be higher[5]. The condition is most prevalent among women, especially after menopause and late in pregnancy. The prevalence is also high among the elderly[6]. In the United States, nearly about 10-30% of the population suffers from chronic insomnia, which costs ranging between $92.5-107.5 billion in treatment annually[7].

Modern medical treatment for insomnia mainly includes cognitive behavioral therapy (CBT-I) and medication. CBT-I comprises sleep hygiene, relaxation training, cognitive reconstruction, stimulation control, time control, and restricted sleep therapy[7,8]. Due to the lack of specialized training for applying CBT-I in clinical settings, it is not widely used by cognitive therapy physicians for the treatment of chronic insomnia. In the United States, CBT-I may be too expensive for many patients and financially unsustainable for clinicians owing to complex reimbursement systems[9,10]. When a patient shows a poor response to CBT-I, medical treatment can be offered. Moreover, benzodiazepine agonists, orexin receptor antagonists,

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melatonin and antidepressants are commonly administered in the treatment of chronic insomnia[11-13]. However, some individuals suffering from of chronic insomnia, without understanding the gravity of their condition, opt for self-administration of sedative-hypnotic drugs instead of systematic medical treatment, and some of these drugs can cause adverse reactions (for instance, driving risk on the next day, dizziness, headache, and daytime sleepiness), and rebound insomnia. Long-term use can also lead to dependence, and withdrawal symptoms may occur upon terminating the drug use[14,15]. Therefore, to avoid drug abuse and reduce its side effects, it is important to assess treatment options with Traditional Chinese Medicine.

Herbalists use the leaves, barks, stems, seeds, and fruits of various plants to treat insomnia. For example, Suanzaoren decoction (SZRD) comprises several herbs that have been scientifically proven to be effective. Medicinal plants are widely used owing to their low costs, high efficacy, and fewer side effects[15]. SZRD improves the symptoms of insomnia in mice by regulating the homeostasis of the hypothalamic axis and releasing beneficial neurotransmitters by regulating the expression of orexin-A[16]. SZRD reduces the production of gastrin, pepsin, and orexin-A, and increases the expression of MTL and CCK-8 by reducing the pH of gastric acid, resulting in a hypnotic effect[17]. Modern medicine considers hyperarousal (at physical, emotional, and cognitive levels, and the central nervous system) as the primary pathway involved in the pathogenesis of insomnia. However, from the perspective of Traditional Chinese Medicine, the locus of disease is the functional system of the heart, considered the most important organ involved in insomnia due to its role as the "seat of consciousness". SZRD is the first choice for the treatment of insomnia of the experts of Chinese natural medicine[18-21]. SZRD nourishes the blood of the liver and calms the heart. Tuckahoe calms the heart, and some other herbs are effective in the treatment of insomnia. Anemarrhenae rhizoma, which nourishes Yin and has a moistening effect, thus eliminates excess heat and relieves aggravation. Liguisticum wallichii, which regulates liver blood and dredges the liver' qi. licorice, helps to accommodate the effects in combination with various medicines. Furthermore, several randomized controlled trials (RCTs) suggest that SZRD exerts therapeutic effects in chronic insomnia[22-24]. Herein, we systematically evaluated the safety and efficacy of SZRD in the treatment of chronic insomnia, to provide a reference for its clinical application.

Materials and Methods

This study has been registered on PROSPERO (Registration Number: CRD42022339065; https://www.crd.york.ac.uk/prospero/#recordDetails).

Literature Retrieval Strategy
(1) The following seven databases, EMbase, PubMed, Cochrane Library, Web of Science, CNKI, VIP and Wanfang Database were queried.

(2) The retrieval period was from the database's construction to May 2022.

(3) Chinese search terms were "suanzaoren decoction", and "chronic insomnia". The English search strategy: (((((Sleep Initiation and Maintenance Disorders [MeSH Terms])) OR (Sleep Initiation and Maintenance Disorders [Title/Abstract])) OR (chronic insomnia [Title/Abstract])) OR (intractable insomnia [Title/Abstract])) AND ((suanzaoren decoction [Title/Abstract])).

Literature Inclusion Criteria
(1) study type: published RCTs;

(2) subjects: patients diagnosed with chronic insomnia according to the relevant diagnostic criteria specified in the International Classification of Sleep Disorders (ICSD-3) and the third edition of the European Guidelines published by the European Sleep Society in 2017[25], with no restrictions on age, gender, or the source of medical records of the study subjects;

(3) intervention measures: used SZRD or combination therapy with SZRD in the treatment group and conventional treatment with Western medicine in the control group.

(4) outcomes: clinical efficacy rate, recurrence rate, Pittsburgh Sleep Quality Index (PSQI) scores, and rate of adverse effects (dizziness, headache, drug resistance, and symptoms of gastrointestinal discomfort).

Literature Exclusion Criteria
The exclusion criteria were as follows: (1) non-clinical RCTs; (2) repeated publications, reviews, or case reports; (3) missing or incomplete data; (4) interventions which did not meet inclusion criteria; (5) conference publications or reviews.

Literature Screening and Data Extraction

Two researchers independently searched and screened the literature, extracted the data, and cross-checked the included results. In cases of disagreement, both parties communicated for resolution, or a third party assisted in judgment. After the screening, Excel was used to sort the baseline characteristics of the included literature, mainly the authors of the study, year of publication, sample content, gender, age of subjects, intervention measures, course of treatment, and outcomes.

Quality Evaluation

Two researchers assessed the quality of the included studies using the Cochrane Reviewers Handbook 5.3 risk bias assessment tool, and three types of risk biases were defined: "low risk", "high risk", and "unclear risk". Both researchers sorted out any differences of opinion, and a third researcher was present to discuss and judge when necessary.

Statistical Analysis

The Review Manger 5.3 software (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark) was used for meta-analysis.

(1) Dichotomous variables were represented by relative risk (RR), and continuous variables were represented as mean difference (MD). All combined effect sizes were expressed with their 95% confidence intervals (95% CI). $p<0.05$ was considered statistically significant, and a forest map was plotted.

(2) The I^2 test was used for determining statistical heterogeneity. At $p>0.1$ and $I^2<50\%$, the heterogeneity among studies was small, and the fixed effects model was used. At $p<0.1$ and $I^2>50\%$, and the heterogeneity was large, and the random effects model was employed.

Subgroup analysis

To reduce the heterogeneity among studies, the PSQI score was used for classification into a single medication group and a combined medication group according to different interventional measures to improve the accuracy of our results.

Sensitivity analysis

Sensitivity analysis was performed to assess and analyze the stability and reliability of the results of the meta-analysis. Sensitivity analysis can be performed if the heterogeneity of the combined results is high, to find the source of heterogeneity and the main factors that affect the stability and authenticity of the results, thereby improving the credibility of the combined results. Following the removal of literature contributing to high heterogeneity, the results of the remaining studies were examined to assess any significant changes. If there was no significant change after elimination, although the heterogeneity was large, the result was considered stable.

Results

Literature Retrieval Results

The retrieval approach was used to extract data from 300 references. There were 66 relevant studies in CNKI, 145 in the Wanfang Database, 34 in VIP, 11 in PubMed, 14 in EMbase, 5 in the Cochrane Library, 25 in Web of Science, and 0 in other resources. After removing the duplicate records, 243 references were screened by reading the title and abstract and were further included or excluded references based on the criteria stated above, leaving 140 full text articles to be assessed for eligibility, of which 128 were excluded, and 12 were finally included. The screening process is shown in Figure 1. The baseline characteristics are shown in Table I.

Quality Evaluation

Among the 12[23-24,26-35] included studies, 9[23-24,26,28-31,33,35] employed the random number table method. Only one[26] mentioned the word "random". One study[32] showed grouping according to the order of visits. One[34] mentioned use of the blind method and a concrete implementation plan. None of these studies had missing data or suffered from selective reporting. One[23] reported the number of people who dropped out or declined along with the reasons (Figures 2 and 3).

Clinical Effective Rate

A total of 11 RCTs[24,26-35] reported the clinical effective rate for chronic insomnia. No significant heterogeneity among the studies ($p=0.27$, $I^2=19\%$) was observed. A fixed effects model was used for meta-analysis. There were some statistically significant differences (RR=1.22, 95% CI [1.16, 1.29], $p<0.00001$). Compared with the control group, the clinical effective rate in the treatment group increased by 22% (Figure 4).

Recurrence Rate

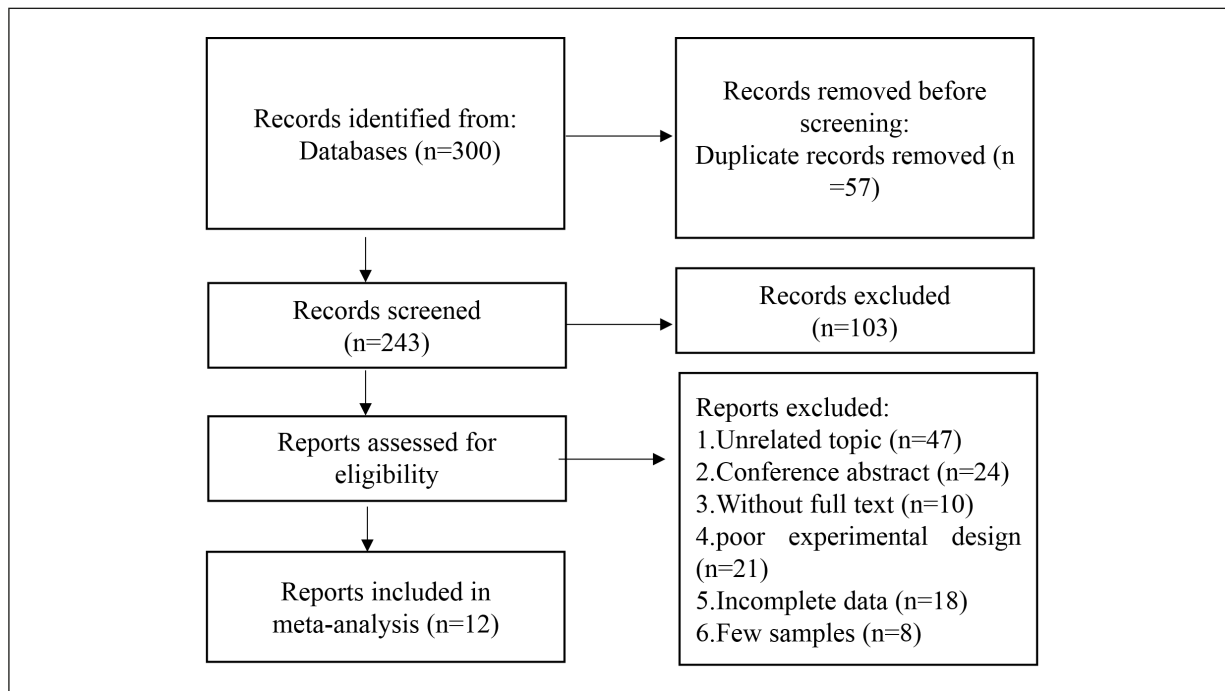A total of three[29-30,35] RCTs for chronic insomnia treatment were analyzed. No heterogeneity

Figure 1. Flow diagram of the study selection process for the meta-analysis.

Table I. Baseline characteristics

Study	Study Type	Sample Size	Gender (%F)	Age [mean (SD)]	Course of Disease (a)	Intervention	Dose (HM)/ Duration (days)	Out comes
Wang et al[32]	RCT	60	65	T:46.3±7.4 C:44.1±8.2	T:6.3±2.1 C:6.1±1.7	T:SZRD+Estazolam C:Estazolam	1dose, bid/30	①④
Jiang et al[28]	RCT	80	NA	T:66.66±3.68 C:66.35±3.67	T:3.18±1.41 C:3.26±1.35	T:SZRD+Eszopiclone C:Eszopiclone	1dose, bid/30	①③
Ou et al[31]	RCT	102	48.04	T:44.72±3.81 C:44.80±3.75	T:8.32±1.74 C:8.35±1.79	T:SZRD+Alprazolam C:Alprazolam	1dose,bid/14	①
Li et al[30]	RCT	122	62.29	T:72.32±7.58 C:71.37±8.29	T:5.72±6.26 C:5.83±6.14	T:SZRD C:Estazolam	1dose, bid/30	①②
Bai et al[26]	RCT	82	NA	T:37.24±6.13 C:37.53±6.22	T:3.75±1.07 C:3.81±1.13	T:SZRD C:Diazepam	150 ml, bid/45	①②③
Yu et al[35]	RCT	130	50	T:45.38±6.23 C:45.38±6.23	T:7.16±0.87 C:7.16±0.87	T:SZRD C:Estazolam	1dose, bid/30	①②③④
Wang et al[33]	RCT	60	58.33	T:61.22±3.89 C:61.01±4.22	T:2.12±0.91 C:2.03±0.84	T:SZRD+Eszopiclone C:Eszopiclone	180 ml, bid/30	①③
Cai et al[24]	RCT	90	50	T:35.32±2.37 C:34.98±2.41	NA	T:SZRD+TMOL C:TMOL	1dose, bid/30	①
Jing et al[29]	RCT	92	46.74	T:55.6±11.9 C:54.9±11.5	T:3.1±0.6 C:3.5±0.4	T:SZRD+Eszopiclone C:Eszopiclone	1dose, bid/28	①②③④
Jia et al[27]	RCT	96	60.20	T:50.2±5.7 C:49.9±6.7	T:4.3±0.6 C:4.2±0.5	T:SZRD+Alprazolam C:Alprazolam	1dose, bid/30	①③④
Wu et al[34]	RCT	270	74.07	NA	NA	T:SZRD+Alprazolam C:Alprazolam	1dose, bid/14	①④
Wu et al[23]	RCT	67	53.73	T:44.76±10.41 C:45.03±9.19	NA	T:SZRD C:Estazolam	200 ml, bid/48	③④

a: Years; TMOL: Tianmeng; T: Treatment group; C: Control group. ① clinical efficacy; ② Recurrence rate; ③ PSQI score; ④ Incidence of adverse events.

was observed among the studies (p=0.64, I^2=0%). A fixed effects model was used for meta-analysis. There were some statistical differences (RR=0.47, 95% CI [0.28, 0.80], p=0.005). which indicated that there was a greater reduction in the recurrence rate in the treatment group than the control group (Figure 5).

PSQI Scores

Seven studies[23,26-29,33,35] evaluated PSQI scores. The results showed a greater reduction in PSQI scores in the treatment group relative to the control group (MD=-2.74, 95% CI [-4.00, -1.49], p<0.0001) (Figure 6). However, the heterogeneity among the studies was markedly high (p<0.00001, I^2=94%). To reduce heterogeneity among studies, subgroup analyses and sensitivity analyses were performed by different interventions, sample sizes, and treatment courses.

Subgroup and sensitivity analyses

The intervention measures in four[27-29,33] studies were SZRD + Western medicine (WM), compared to Western medicine only. There was significant heterogeneity among the studies (p<0.00001, I^2=96%), and the random effects model was used. The difference between the two groups was statistically significant (MD$_{SZRD+WM}$=-3.35, 95%CI [-5.22, -1.47], p = 0.0005). SZRD + WM showed a greater reduction in the PSQI score as compared to Western medicine alone (Figure 7). After further analysis to determine the cause of heterogeneity, the exclusion of one[33] study could be due to the smaller sample size compared to the other three studies (<80 cases). The heterogeneity was significantly reduced (p=0.30, I^2=18%). The results were in conformity with the original analysis results (MD=-3.90, 95%CI [-4.54, -3.27], p<0.00001) (Figure 8).

Three interventional studies[23,26,35] were conducted by comparing SZRD with Western medicine. The heterogeneity among studies was high (p = 0.0007, I^2=86%), and the effect sizes were pooled using the random effects model. The difference between the two groups was statistically significant (MD$_{SZRD}$=-1.94, 95%CI [-3.80, -0.07], p=0.04). SZRD caused a greater reduction in the PSQI score relative to Western medicine (Figure 7). Upon further analysis to determine the cause of heterogeneity, one[23] study was excluded. The analysis found that the outcome index was negative and there was no significant difference in the scores after treatment between the two groups, which could be due to the fact that the treatment

Figure 2. Methodological quality evaluation of included articles.

period of the intervention population was longer than the other two studies[26,35]. As a result, the heterogeneity reduced significantly (p=0.46, I^2=0%). The results were in line with the original findings (MD=-2.97, 95% CI [-3.71, -2.24], p < 0.00001) (Figure 8).

Adverse Effects Rate

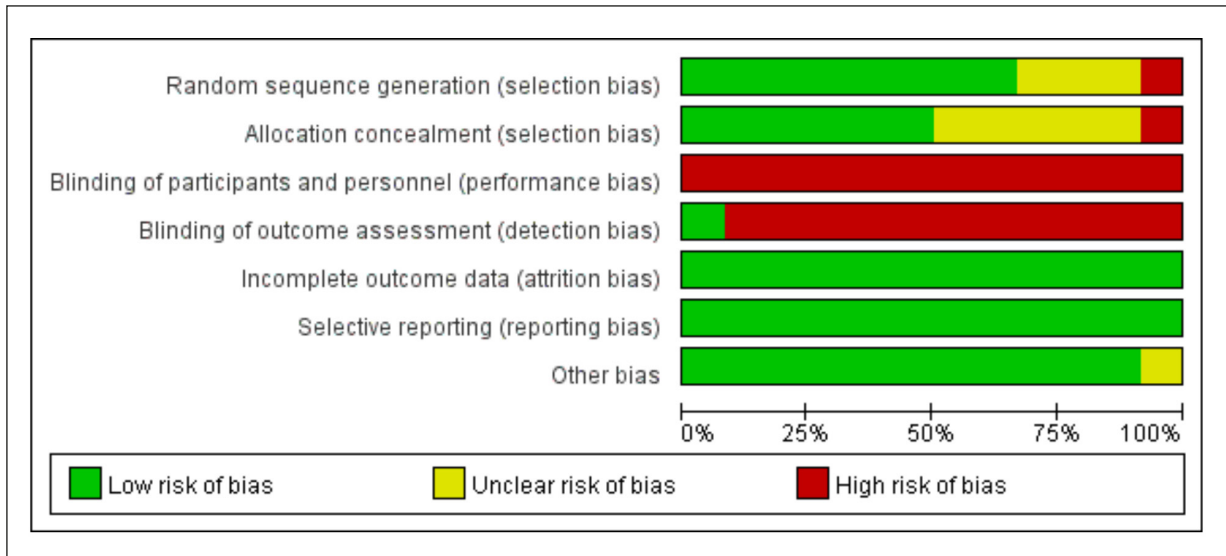The adverse effects rate reported in the treatment of chronic insomnia in seven[23,26,27,29,32,34,35]

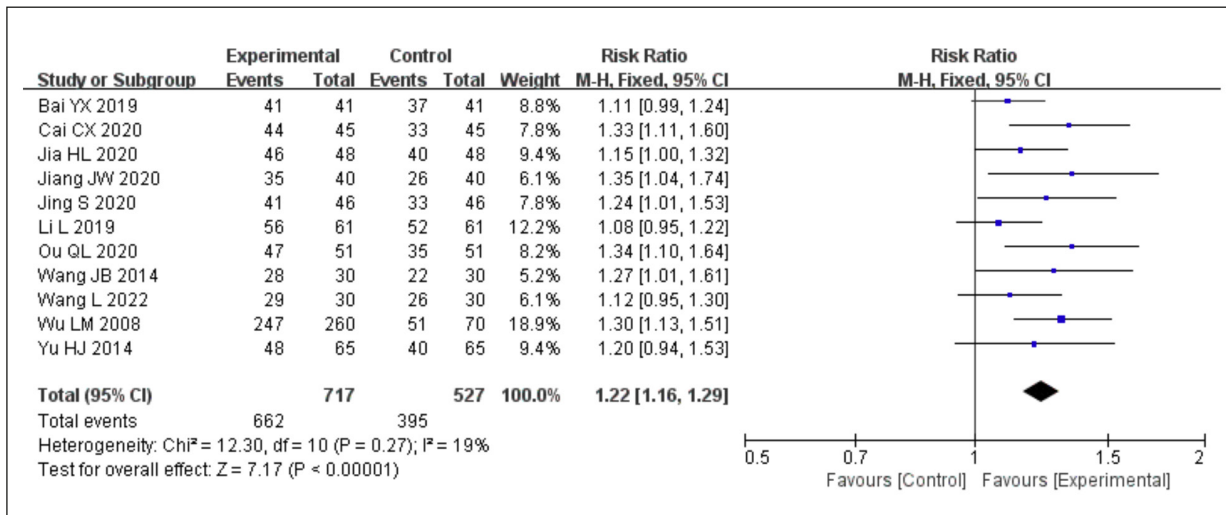**Figure 3.** Methodological quality evaluation of included articles.

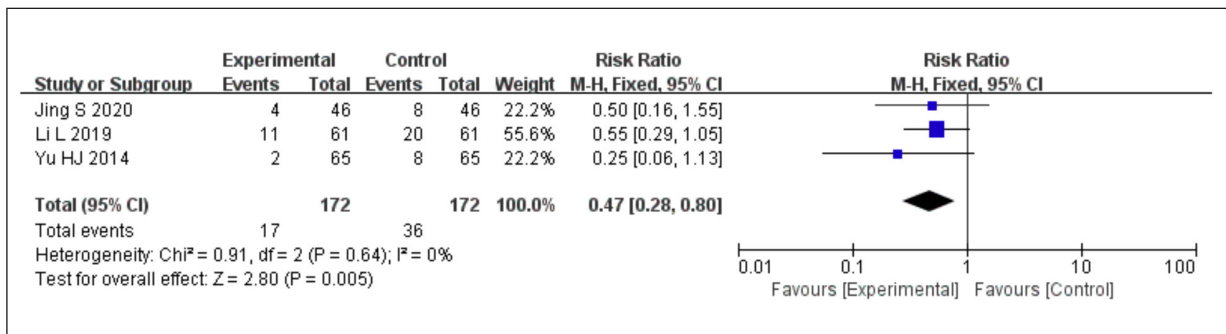**Figure 4.** Forest plot for the meta-analysis of total clinical response rate.

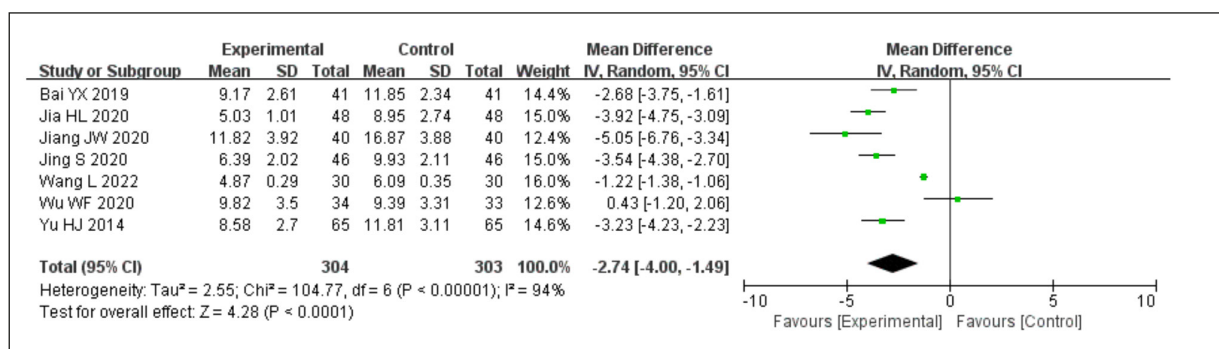**Figure 5.** Forest plot for the meta-analysis of recurrence rate.

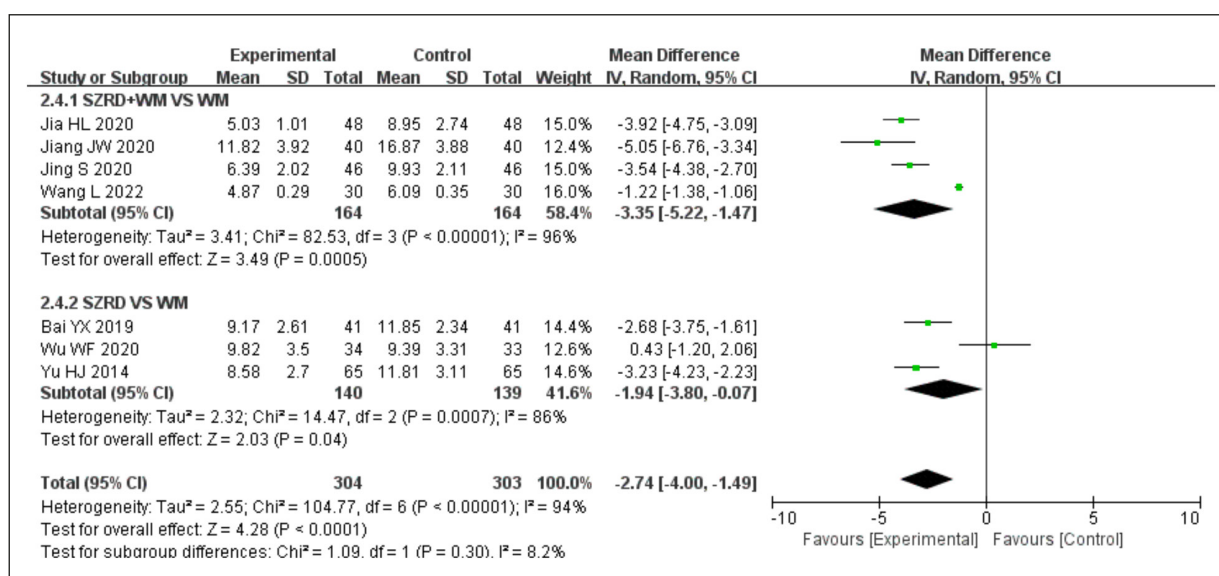**Figure 6.** Forest plot for the meta-analysis of PSQI scores.

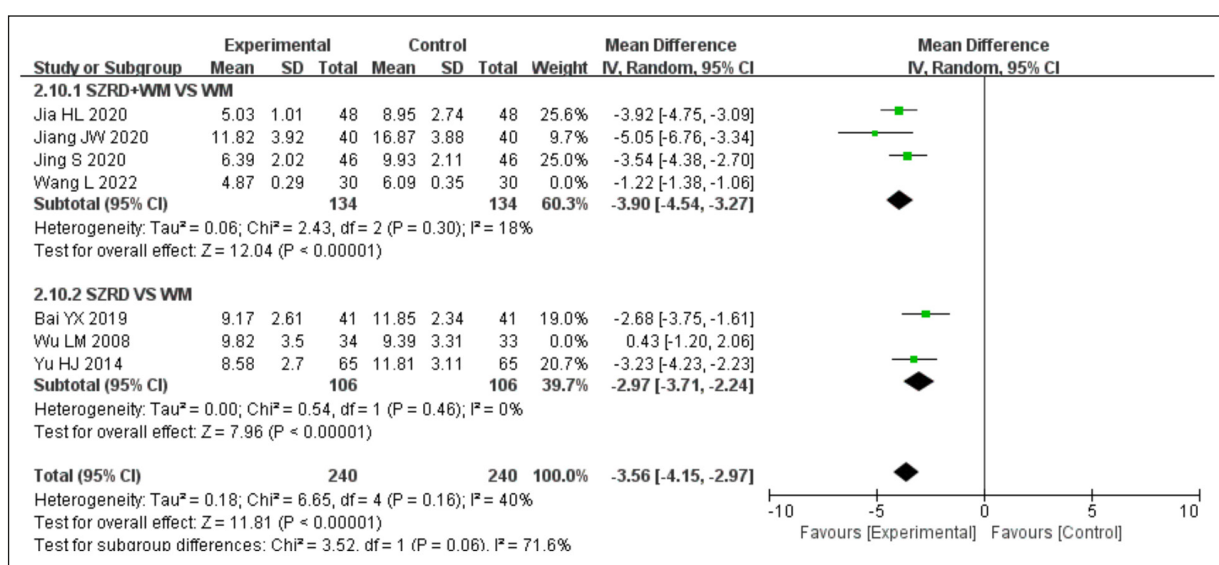

Figure 7. Subgroup analysis of PSQI scores.

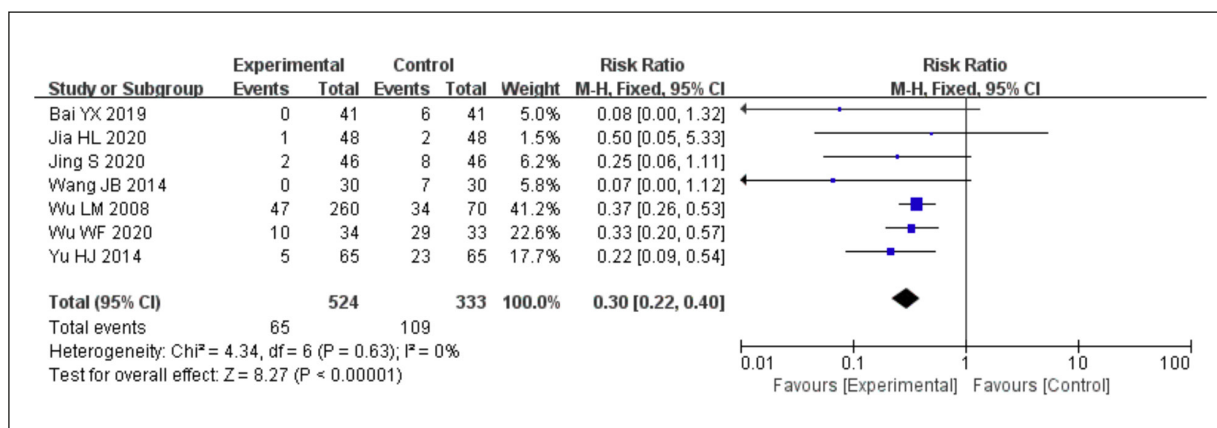**Figure 8.** Sensitivity analysis of PSQI scores.

Figure 9. Forest plot for the meta-analysis of adverse event rate.

RCTs were reported. No heterogeneity was present among the studies (p=0.63, I^2=0%). A fixed effects model was used for meta-analysis. A statistically significant difference (RR=0.30, 95% CI [0.22, 0.40], p<0.00001) indicated that the reduction in adverse effects rate (dizziness, headache, drug resistance, and symptoms of gastrointestinal discomfort) in the treatment group relative to the control group. These results indicated that SZRD was safer than Western medicine (Figure 9).

Publication Bias

The clinical effective rates for patients with chronic insomnia in more than 10 studies were analyzed to assess potential publication biases (Figure 10). As shown in the funnel plot, studies on both sides are asymmetric and there is potential publication bias, for which there are various possible reasons, including that negative results may not be published, and the inclusion of low-quality small-sample studies.
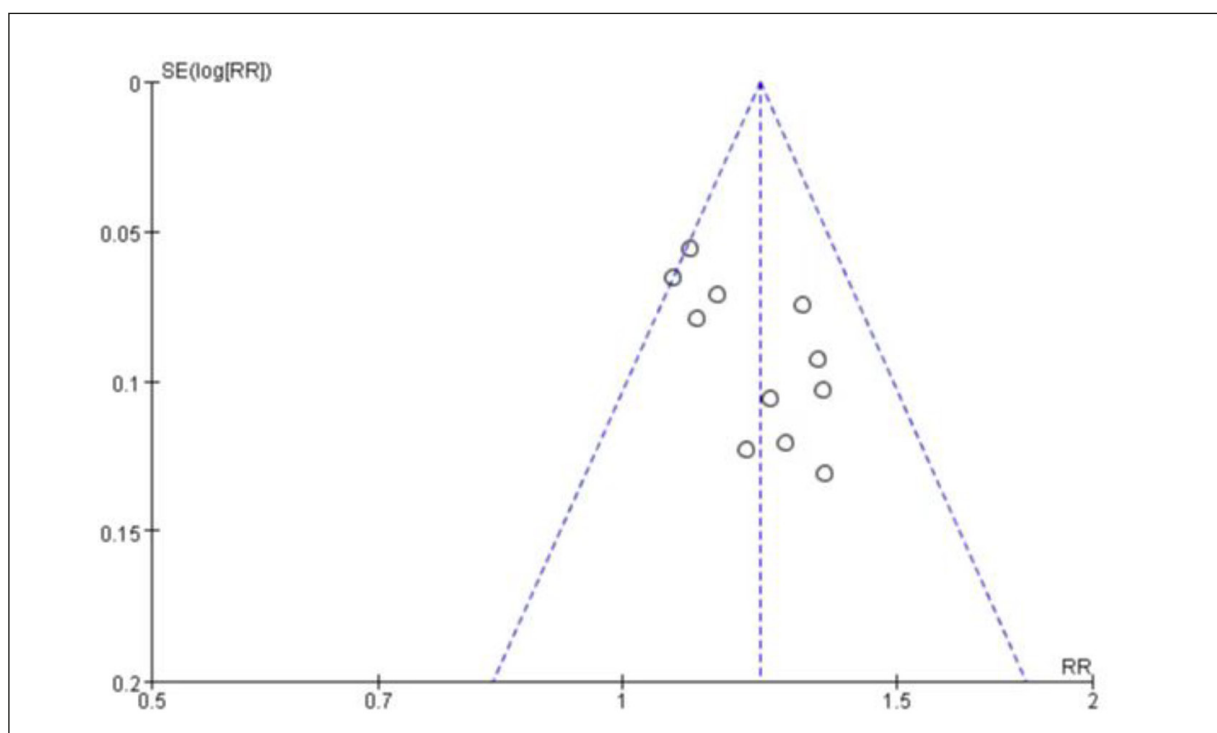

Figure 10. Funnel Plot to evaluate for publication bias regarding clinical effective rates.

Discussion

Chronic (or severe) insomnia occurs in at least 5-10% of adults globally and the rate may possibly be higher owing to clinically undiagnosed individuals[5]. Women mainly suffer from death due to chronic insomnia[36]. Modern medical treatment for insomnia mainly includes CBT-I and medication[37,38]. However, cognitive therapists are expensive. The user of Western medicine is prone to drug dependence and substance abuse[39,40]. SZRD is a pure Chinese medicine preparation with fewer adverse effects and significant hypnotic effects; it can be used to prevent the patients' dependence on Western medicine, and thus, deserves to be promoted in clinical settings. Based on the results of this study, in terms of effectiveness, SZRD alone or in combination with Western medicine in the treatment of chronic insomnia showed better efficacy, as evidenced by increased clinical effective rate, reduced recurrence rate, and improved quality of sleep. In terms of safety, SZRD could reduce the occurrence of adverse reactions, suggesting that SZRD should be combined with conventional treatment for patients with chronic insomnia. However, clinicians should interpret the results of this study carefully along with the actual situation of patients. A comprehensive consideration should be made before applying it in clinical practice.

Limitations

This study has some limitations. (1) In terms of clinical effective rate, 11[24,26-35] studies lacked unified clinical efficacy evaluation criteria. Therefore, the clinical effective rate was combined after processing the data in this study, reducing the strength and credibility of the evidence; (2) differences in applications, prescriptions, medication, courses of treatment, sample sizes, and published data among the included literature may reduce the reliability of the results of this meta-analysis; (3) there were no long-term follow-up visits and no reports on the incidence of end-point events in some of the studies; (4) the funnel plot for clinical effective rate showed asymmetry, and there might have been some selective reporting.

Conclusions

In conclusion, SZRD alone or in combination with Western medicine can highly be effective in the treatment of chronic insomnia. It can also significantly reduce the adverse effects rate. However, due to the uneven quality of the included studies, more large-sample, high-quality, and multicenter RCTs are needed to obtain definitive evidence for treating chronic insomnia with SZRD in clinical settings.

Conflict of Interest
The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

Ethics Approval
Not applicable.

Authors' Contributions
Formal analysis: X.-X. Liu and Y.-Q. Ma.
Methodology: F.-X. Zhong and Y.-G. Wang.
Project administration: Q.-M. Zhang.
Software: X.-X. Liu and F.-X. Zhong.
Validation: Y.-Q. Ma, Y.-G. Wang and X.-P. Yin.
Writing - original draft: X.-X. Liu and Y.-Q. Ma.
Writing - review & editing: X.-X. Liu and Q.-M. Zhang.

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