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# Meta-analysis of the efficacy and safety of Huanglian Wendan Decoction alone or combined with western medicine in treating insomnia caused by phlegm-heat internal disturbance

YANG Lei[a], HE Liyun[b*], CHEN Xiao[c], WANG Kaiyue[c], FANG Yongjun[d], LIANG Zhuang[a], YANG Zhao[a]

*a. First Clinical Medical School, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi 712046, China*

*b. Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing 100700, China*

*c. The 9th Department of Encephalopathy, Xi'an TCM Hospital of Encephalopathy, Shaanxi University of Chinese Medicine, Xi'an, Shaanxi 710038, China*

*d. The 3rd Department of Encephalopathy, The Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang, Shaanxi 712000, China*

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ABSTRACT

**Objective** To evaluate the efficacy and safety of Huanglian Wendan Decoction (黄连温胆汤, HLWDD) alone or combined with western medicine in treating insomnia caused by phlegm-heat internal disturbance in recent 10 years.

**Methods** The randomized controlled trials of HLWDD alone or combined with western medicine in treating insomnia caused by phlegm-heat internal disturbance from January 1, 2012 to April 1, 2022 were searched in China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database, China BioMedical Literature Database (CBM), PubMed, Web of Science, Embase, and Cochrane Library databases. After being screening, the included literature was analyzed to evaluate the effective rate, Pittsburgh Sleep Quality Index (PSQI) score, traditional Chinese medicine (TCM) syndrome score, and adverse reactions of HLWDD on insomnia caused by phlegm-heat internal disturbance. The subgroup analyzed the effect of HLWDD after different treatment courses, and compared the therapeutic effects of HLWDD alone and HLWDD combined with western medicine.

**Results** Twenty-seven randomized controlled trials were finally included, with a total of 2 395 patients. The results of the meta-analysis showed that the curative effect of HLWDD alone or combined with the western medicine group was better than that of the western medicine group [RR = 1.14, 95% CI (1.06, 1.22), $P = 0.000$]. The PSQI score [SMD = – 0.31, 95% CI (– 0.42, – 0.20), $P = 0.000$], TCM syndrome score [SMD = – 0.40, 95% CI (– 0.67, – 0.12), $P = 0.005$], and adverse reaction rate [RR = 0.21, 95% CI (0.15, 0.29), $P = 0.000$] of HLWDD alone or combined with western medicine group were significantly reduced compared with the western medicine group. The subgroup's analysis showed that the curative effect of HLWDD alone or combined with western medicine group of 4 weeks treatment course was better than that of the western medicine group [RR = 1.14, 95% CI (1.03, 1.26), $P < 0.05$]. The TCM syndrome score of HLWDD alone or combined with the western medicine group of 4 weeks treatment course decreased more obviously than that of the western medicine group [SMD = – 0.60, 95% CI

*Corresponding author: HE Liyun, Professor, E-mail: 415740904@qq.com.

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(– 0.96, – 0.25), $P < 0.05$]. There were no significant differences between HLWDD alone or combined with western medicine group and western medicine group with different treatment courses based on PSQI score and adverse reaction rate. Based on the effective rate, the comparison between the HLWDD alone group and the western medicine group [RR = 1.09, 95% CI (1.00, – 1.20) $P < 0.05$], and between the HLWDD combined with western medicine group and the western medicine group [RR = 1.15, 95% CI (1.03, 1.29), $P < 0.05$] was the same. PSQI score [SMD = – 0.44, 95% CI (– 0.59, – 0.30), $P < 0.05$] and TCM syndrome score [SMD = – 1.10, 95% CI (– 1.59, – 0.61), $P < 0.05$] of HLWDD combined with western medicine group were significantly lower than those of the western medicine group. There were no significant differences of adverse reaction rate between HLWDD alone group [RR = 0.08, 95% CI (0.04, 0.17), $P < 0.05$] and HLWDD combined with western medicine group [RR = 0.36, 95% CI (0.24, 0.53), $P < 0.05$].

**Conclusion** HLWDD alone or combined with western medicine is an effective treatment for insomnia caused by phlegm-heat internal disturbance, which has a high effective rate, significantly reduced PSQI score and TCM syndrome score, and favorable safety. The best course of treatment is 4 weeks.

## 1 Introduction

Insomnia means that when you have a suitable sleep environment and timing, you will still have insufficient sleep time (the total sleep time is less than six hours) and poor sleep quality (the number of awakenings during sleep is not less than two times), feel dizziness, fatigue, and exhaustion, and even have other discomfort symptoms after waking up [1]. Epidemiology shows that more than 10% in the general population suffers from physical and mental pain caused by insomnia with a growing trend [2-5]. The comprehensive prevalence rate of insomnia in China is over 15% [6]. Studies prove that insomnia may lead to anxiety [7], dementia [8], lung cancer [9], etc. The etiology and pathophysiology of insomnia are still unclear. However, there are effective clinical treatments, including drug therapy and cognitive behavioral therapy [10-12], among which benzodiazepine sedative hypnotics are widely used in the treatment of insomnia. It can shorten the time of falling asleep and increase the time of sleeping. However, long-term use of benzodiazepine sedative hypnotics will lead to adverse reactions such as drug resistance, dependence, and even serious side effects [13, 14]. Non-drug treatment of insomnia also has certain limitations [15, 16].

Traditional Chinese medicine (TCM) classic prescription for insomnia has a long history of reliable curative effect, with unique advantages and abundant clinical evidence. Huanglian Wendan Decoction (黄连温胆汤, HLWDD) has the effects of eliminating phlegm, clearing heat, and calming nerves, and it can be used to treat insomnia caused by internal disturbance of phlegm-heat. Clinical trial has proved that HLWDD is effective in treating insomnia caused by phlegm-heat internal disturbance, which can improve the sleep quality of patients [17]. Modern pharmacological studies have found that HLWDD is sedative, hypnotic, and anti-anxiety, and regulates brain excitation and inhibition [18]. Therefore, this study focused on the progress of HLWDD in improving phlegm-heat-related insomnia in clinical application, and used meta-analysis to integrate and analyze the large sample data of HLWDD in treating phlegm-heat internal disturbance insomnia patients, to provide a basis for clinical application.

## 2 Data and methods

### 2.1 Searching strategy

The study was conducted according to the Cochrane System Intervention Review Manual version 5.3.0. Eight databases including China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database, China BioMedical Literature Database (CBM), PubMed, Web of Science, Embase, and Cochrane Library were selected. In order to analyze contemporary researches, we focused on the reports in recent 10 years. The retrieval time was from January 1, 2012 to April 1, 2022. The keywords were “insomnia” “sleepless” “sleep disorder syndrome” “phlegm-heat internal disturbance” “HLWDD” “modified HLWDD” “effective rate” “Pittsburgh Sleep Quality Index (PSQI) score” “TCM syndrome score” and “adverse reactions”. Taking CNKI database as an example, the retrieval formula is: [(insomnia) OR (sleepless) OR (sleep disorder syndrome)] AND [(phlegm-heat internal disturbance) OR (phlegm-heat disturbing the heart)] AND [(HLWDD) OR (modified HLWDD)] AND [(effective rate) OR (PSQI score) OR (TCM syndrome score) OR (adverse reactions)].

### 2.2 Literature selection

**2.2.1 Inclusion criteria** (i) Clinical randomized controlled trial (RCT) includes blind and non-blind methods.

(ii) The diagnosis of insomnia conforms to authoritative standards such as *Guidelines for Diagnosis and Treatment of Insomnia in China* [19] or *Chinese Classification and Diagnostic Criteria of Mental Disorders* [20], and secondary insomnia is excluded. (iii) TCM syndrome differentiation conforms to the syndrome of phlegm-heat internal disturbance or phlegm-heat disturbing the heart. Dialectical points include main syndrome (insomnia, false sleep, dreaminess, and even pernoctation), and secondary syndromes (upset, stuffy chest and abdomen, excessive phlegm, dizziness, bitter taste, yellow and greasy tongue coating, and slippery pulse). Studies that can meet one or more items of both the main syndromes and secondary syndromes were selected. (iv) The control group was treated with conventional western medicine, and the treatment group was treated with HLWDD alone or HLWDD combined with the treatment of the control group (the dosage form, dosage, and usage were not limited). (v) The evaluation indexes of curative effect include effective rate, PSQI score, TCM syndrome score, and adverse reaction rate.

**2.2.2 Exclusion criteria** (i) In the treatment group, besides HLWDD, other Chinese medicine treatments were combined, such as acupuncture, massage, auricular points, and acupoint application. (ii) Letters, conference abstracts, case reports, animal experiments, reviews, and critical papers. (iii) Non-Chinese or English randomized controlled trials. (iv) Repeated published literature. (v) The mean or variance results before and after the experiment were not completely recorded. (vi) There is no literature that mentions clear diagnostic criteria of TCM and western medicine.

### 2.3 Data extraction and literature quality evaluation

Data extraction was completed by two researchers (LIANG Zhuang and YANG Zhao) independently according to the inclusion criteria and exclusion criteria, using standardized templates to extract detailed information from each included study. The information should include the first author, the year of publication, the age of the treatment group and the control group, the course of the disease, the sample size, the study design, the intervention measures, the course of treatment, and the outcome indicators of the treatment group and the control group. The authors used the criteria outlined in the Cochrane Handbook (Higgins and Altman 2008) to independently assess the research quality and risk of bias for each eligible literature. Six criteria were considered for bias evaluation: (i) random sequence distribution generation, (ii) distribution hiding, (iii) blind method, (iv) result data, (v) selective reporting, (vi) other bias. These items were identified as low bias risk, high bias risk, and unclear. Any differences are resolved through discussion. If no consensus can be reached, seek the opinions of the third independent researcher (YANG Lei).

### 2.4 Statistical analysis

Excel software was used to make statistics on the collected documents, and Stata v16.0 software provided by Cochrane Collaboration Network was used for statistical analysis. The data of binary variables were expressed by odds ratio (OR), the data of continuous variables were expressed by weighted mean difference (MD), and each effect was expressed by 95% confidence interval (CI). $I^2$ test was used to analyze the heterogeneity of the included studies. When the heterogeneity among the studies was low ($I^2 \leqslant 50\%$ and $P > 0.1$), the fixed effect model was used. When the heterogeneity was high ($I^2 > 50\%$ and $P \leqslant 0.05$), the random effect model was adopted. If the number of studies was greater than or equal to 10, funnel diagram was used to analyze the publication bias.

## 3 Results

### 3.1 Literature retrieval results

A total of 497 articles were screened out independently by the two researchers, and 374 articles (165 basic research articles, 41 theoretical researches, 75 reviews, 24 conference papers, and 69 duplicated literatures) were excluded by reading literature abstracts and titles. The remaining 123 articles were read through, 96 articles were excluded, and finally 27 articles were included, all of which were in Chinese (Figure 1). The basic information of the 27 articles [21-47] was shown in Table 1.

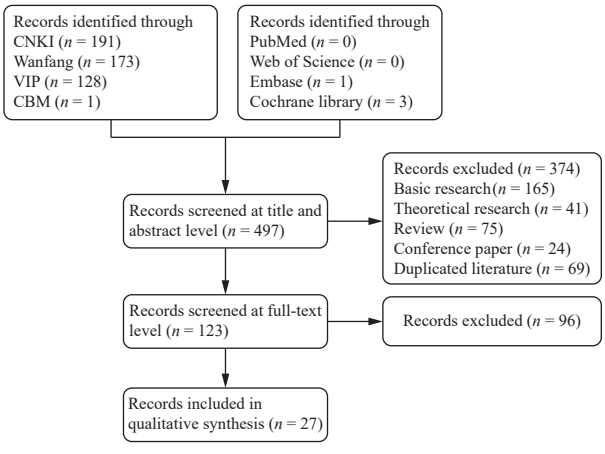


**Figure 1** Flow chart of literature screening

### 3.2 Bias risk assessment of the included studies

The bias risk assessment tool provided by Cochrane Collaboration Network was used. The 11 studies [21-23, 25, 28, 33, 35, 37, 42, 46, 47] which used random number table method were considered as low risk, while the rest studies which did not mention random grouping and scheme hiding, and blind method were considered as high risk (Figure 2).

**Table 1** Basic information and characteristic analysis of included studies

| First author | Year | Course of disease (T/C) | Age (T/C, years) | Case (T/C) | Intervention | | Duration | Outcome |
|---|---|---|---|---|---|---|---|---|
| | | | | | T | C | | |
| ZHANG Miao [21] | 2021 | / | (46.8 ± 7.0)/(45.5 ± 6.8) | 40/40 | HLWDD | Sweet dream oral liquid | 2 weeks | ②③ |
| YUAN Leping [22] | 2017 | (16.8 ± 4.3)/(17.1 ± 4.2) (months) | (47.9 ± 5.1)/(48.3 ± 4.9) | 110/113 | HLWDD + control group | Clonazepam tablets | 3 months | ①②④ |
| OUYANG Wenhui [23] | 2021 | (3.2 ± 0.5)/(3.1 ± 0.5) (years) | (55.1 ± 4.2)/(55.2 ± 4.2) | 32/32 | HLWDD + control group | Estazolam | 1 months | ①②③④ |
| ZHAO Dacheng [24] | 2022 | / | (44.5 ± 8.5)/(42.6 ± 8.2) | 45/45 | HLWDD + control group | Alprazolam tablets | 4 weeks | ①②④ |
| YE Shoujiao [25] | 2015 | (3.3 ± 2.1)/(4.0 ± 2.0) (years) | (40.6 ± 10.9)/(41.5 ± 9.7) | 60/60 | HLWDD | Estazolam | 20 days | ①②④ |
| WANG Wanjie [26] | 2013 | 36.2/39.8 (months) | 42.6/38.5 | 31/34 | HLWDD | Estazolam | 45 days | ①④ |
| PEI Guoxian [27] | 2013 | (24.3 ± 9.9)/(20.1 ± 11.7) (months) | (38.4 ± 9.5)/(41.7 ± 10.5) | 34/34 | HLWDD + control group | Estazolam | 4 weeks | ① |
| CHEN Xuemei [28] | 2019 | (19.9 ± 3.6)/(19.6 ± 3.4) (months) | (38.8 ± 4.6)/(38.6 ± 4.3) | 40/40 | HLWDD | Diazepam tablets | 20 days | ①④ |
| WANG Wei [29] | 2015 | (3.2 ± 1.6)/(2.9 ± 1.8) (years) | (44.2 ± 9.9)/(46.3 ± 9.3) | 26/23 | HLWDD | Estazolam | 30 days | ① |
| HAN Yanhui [30] | 2012 | (17.9 ± 11.7)/(17.2 ± 12.1) (months) | (37.0 ± 11.2)/(37.6 ± 12.1) | 58/55 | HLWDD | Diazepam tablets | 2 weeks | ①④ |
| LIN Bin [31] | 2014 | / | / | 60/60 | HLWDD | Diazepam tablets | 2 weeks | ①④ |
| ZHAO Yanhong [32] | 2014 | (15.3 ± 10.5)/(15.8 ± 11.2) (months) | (35.2 ± 11.2)/(35.7 ± 11.8) | 20/20 | HLWDD | Diazepam tablets | 2 weeks | ①④ |
| HUANG Qiaojie [33] | 2020 | (7.8 ± 4.1)/(7.8 ± 4.0) (months) | (40.4 ± 9.7)/(40.6 ± 10.4) | 30/30 | HLWDD | Zopiclone | 4 weeks | ①②③ |
| CHEN Xiaoyan [34] | 2020 | / | / | 30/30 | HLWDD | Estazolam | 4 weeks | ① |
| LIN Guoping [35] | 2021 | (16.8 ± 4.3)/(16.9 ± 4.3) (months) | (47.9 ± 5.1)/(47.9 ± 5.2) | 35/35 | HLWDD + control group | Clonazepam tablets | 3 months | ①②④ |
| SHENG Xiaoming [36] | 2019 | (3.1 ± 1.1)/(3.0 ± 1.1) (years) | (44.5 ± 6.2)/(44.5 ± 6.1) | 43/43 | HLWDD | Estazolam | 2 weeks | ①②④ |
| ZHU Qingxia [37] | 2019 | (2.3 ± 0.5)/(2.6 ± 0.4) (years) | / | 32/32 | HLWDD + control group | Estazolam | 6 weeks | ①②④ |
| ZHU Wei [38] | 2016 | / | (57.9 ± 11.7)/(58.1 ± 9.7) | 31/31 | HLWDD + control group | Estazolam | 4 weeks | ①②④ |
| LI Hongxing [39] | 2019 | (3.6 ± 2.6)/(3.5 ± 2.5) (weeks) | (49.1 ± 19.0)/(49.1 ± 19.1) | 36/36 | HLWDD + control group | Diazepam | 4 weeks | ①②④ |
| YANG Lianxiang [40] | 2018 | (4.1 ± 0.1)/(4.1 ± 0.1) (weeks) | (53.1 ± 1.1)/(53.15 ± 1.1) | 31/31 | HLWDD + control group | Estazolam | 4 weeks | ② |
| HU Min [41] | 2020 | / | (42.4 ± 10.2)/(46.6 ± 10.9) | 30/30 | HLWDD + control group | Estazolam | 4 weeks | ①②③ |
| CHAO Zhuang [42] | 2013 | / | (33.1 ± 9.2)/(35.6 ± 8.1) | 35/15 | HLWDD | Alprazolam tablets | 2 weeks | ①④ |
| RUAN Yiheng [43] | 2014 | (4.8 ± 2.3)/(4.6 ± 2.0) (weeks) | (37.9 ± 8.9)/(38.3 ± 9.2) | 112/96 | HLWDD | Estazolam | 4 weeks | ①④ |
| SU Hongmei [44] | 2013 | / | (45.9 ± 4.6)/(46.1 ± 6.3) | 70/70 | HLWDD | Estazolam | 4 weeks | ① |
| TIAN Yuqing [45] | 2014 | / | (41.1 ± 2.2)/(46.5 ± 3.9) | 36/36 | HLWDD | Estazolam | 4 weeks | ① |
| XUAN Shaomin [46] | 2018 | / | (46.2 ± 3.8)/(46.2 ± 3.8) | 46/46 | HLWDD | Estazolam | 3 weeks | ①②④ |
| HOU Yuanyuan [47] | 2012 | / | (43.5 ± 14.0)/(40.3 ± 16.0) | 33/32 | HLWDD + control group | Dexzopiclone | 2 weeks | ①④ |

T represents treatment group; C represents control group. ① Effective rate, ② PSQI score, ③ TCM syndrome score, ④ Adverse reaction.

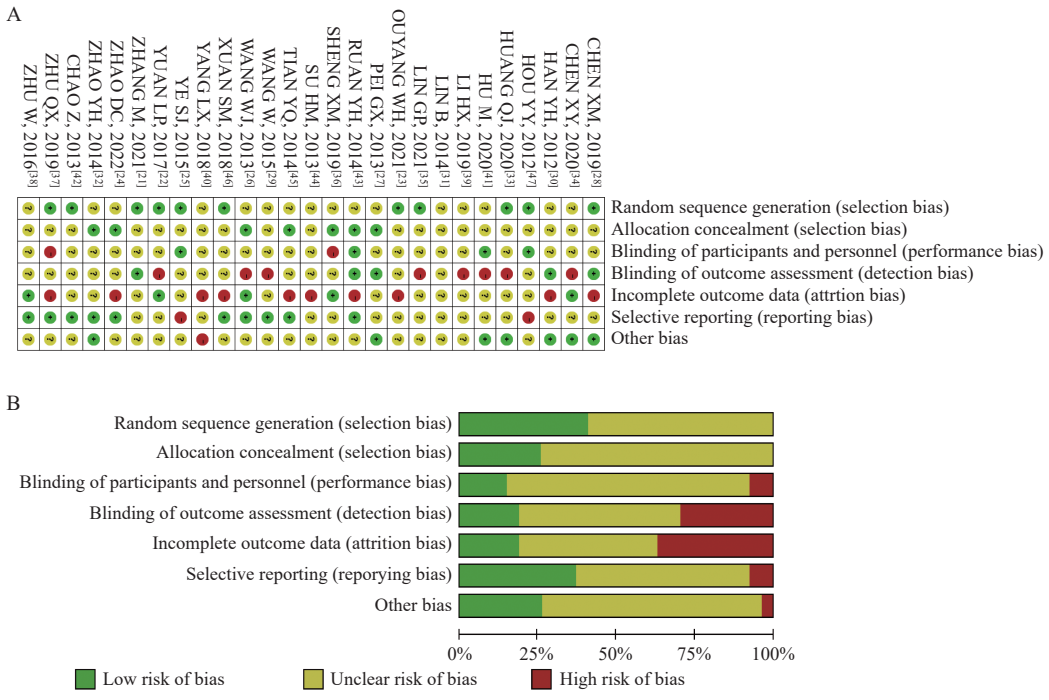


**Figure 2** Evaluation of literature quality risk bias

A, detailed description of methodological quality assessment. B, risk bias of the included studies.

### 3.3 Meta-analysis of effective rate, PSQI score, TCM syndrome score, and incidence of adverse reactions

**3.3.1 Effective rate** A total of 25 studies [22-39, 41-47] used clinical effective rate as the outcome index, among which 1 109 patients in the HLWDD treatment group and 1 070 patients in the control group were included. Meta-analysis was carried out on the 25 RCTs, and the heterogeneity test was $P = 1.000$, $I^2 = 0\%$, with low heterogeneity. A fixed effect model was adopted. Meta-analysis results [RR = 1.14, 95% CI (1.06, 1.22), $P = 0.000$] showed that the curative effect of the treatment group was significantly higher than that of the control group (Figure 3).

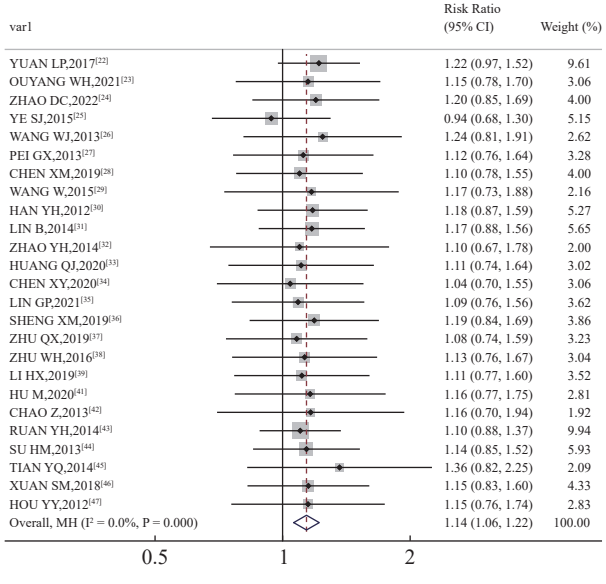


**Figure 3** Forest plot for effective rate

The funnel diagram analysis results of clinical total effective rate are shown in Figure 4. The funnel diagram of 25 included studies is drawn with OR as abscissa and standard error logOR as ordinate. The scattered points of the graph are roughly distributed around the vertical line, and the scattered points of the graph are symmetrical, suggesting that the results are relatively stable. Considering each author has greater subjective initiative when observing the funnel diagrams, it is necessary to objectively evaluate the size of publication bias, sensitivity analysis, and the begg and egger of publication bias. The heterogeneity analysis chart indicated that the effective rate of the YE Shoujiao's control group was higher than that of the treatment group, with no significant difference. The results showed that begg $P = 0.624$ ($P > 0.05$) and egger $P = 0.897$ ($P > 0.05$), there was no significant publication bias. And through sensitivity analysis, it is found that no study may affect the summary results or the total effective rate (Figure 5).

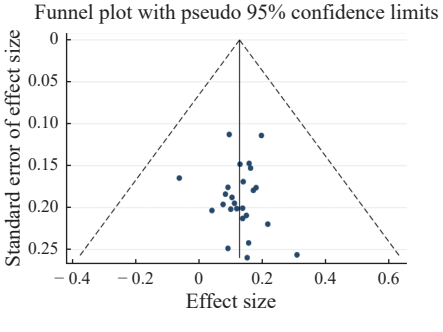


**Figure 4** Funnel plot for total clinical effective rate

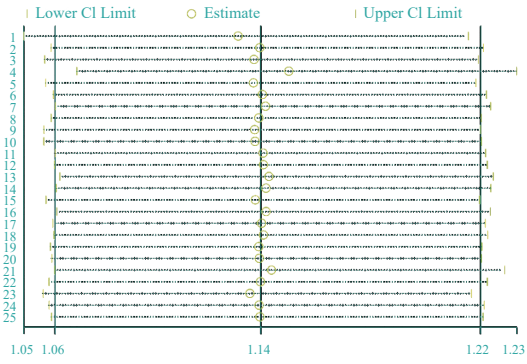


**Figure 5** Sensitivity analysis

**3.3.2 PSQI score** A total of 14 studies [21-25, 33, 35-41, 46] adopted the PSQI scoring index, and among them, 601 patients were included in the HLWDD treatment group, and 604 patients were included in the control group. The 14 RCTs were analyzed by meta-analysis, and the heterogeneity test was $P = 0.001$, $I^2 = 63\%$, with high heterogeneity. A random effect model was adopted. Meta-analysis results [SMD = – 0.31, 95% CI (– 0.42, – 0.20), $P = 0.000$] showed that PSQI scores significantly decreased in the treatment group compared with the control group (Figure 6), indicating that HLWDD improved insomnia symptoms effectively.

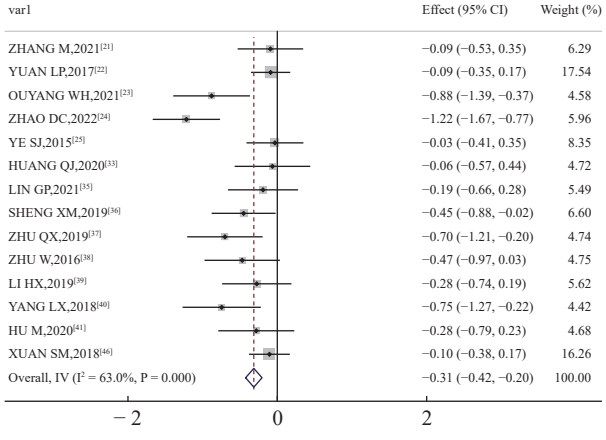


**Figure 6** Forest plot for PSQI score

**3.3.3 TCM syndrome score** A total of four studies [21, 23, 33, 41] used TCM syndrome score as an index, including 132 patients in the HLWDD treatment group and 132 patients in the control group. Meta-analysis was carried out on the four RCTs, and the heterogeneity test was $P = 0.000$, $I^2 = 97.2\%$, with high heterogeneity. A random effect model was adopted. Meta-analysis results [SMD = – 0.40, 95% CI (– 0.67, – 0.12), $P = 0.005$] showed that TCM syndrome score in the treatment group was significantly lower than that in the control group (Figure 7).

**3.3.4 Incidence of adverse reactions** A total of 18 studies [22-26, 28, 30-32, 35-39, 42, 43, 46, 47] reported the incidence of adverse reactions, and among them, 856 patients were included in the HLWDD group, and 817 patients were in the control group. A meta-analysis of the above 18 RCTs

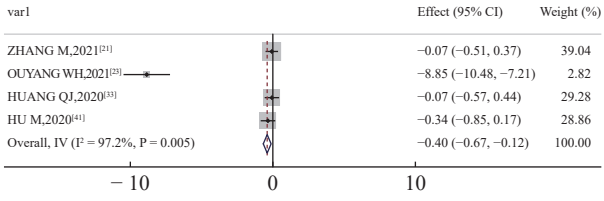


**Figure 7** Forest plot for TCM syndrome score

was performed, and the heterogeneity test was $P = 0.037$, $I^2 = 40.8\%$, with low heterogeneity. The fixed effect model was adopted. The meta-analysis results [RR = 0.21, 95% CI (0.15, 0.29), $P = 0.000$] showed that the incidence of adverse reactions in the HLWDD treatment group was significantly lower than that in the control group (Figure 8).

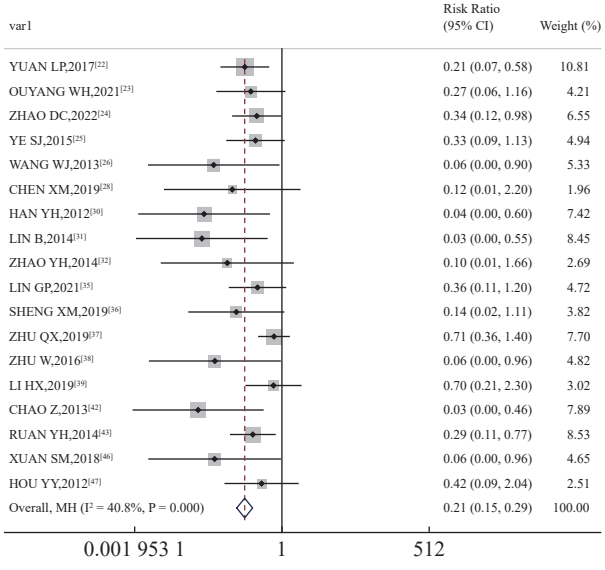


**Figure 8** Forest plot for adverse reaction rate

Adverse reactions were reported in eight studies in the treatment group, including five cases of lethargy, five cases of dizziness, and five cases of gastrointestinal symptoms (loss of appetite, nausea, increased saliva, and diarrhea). The main adverse reactions were nervous system symptoms, as well as dry mouth, bitter taste, rash, and fatigue, etc. Adverse reactions in the control group were mainly dizziness, lethargy, limb weakness, and memory decline. Among them, YUAN [22] also reported one case of abnormal liver function in the treatment group. ZHU [37] reported that there were four cases of ataxia in the treatment group and three cases in the control group, which were considered as vestibular ataxia, mainly showing the aggravation of dizziness.

### 3.4 Subgroup analysis

Because $I^2$ of PSQI score and TCM syndrome score was more than 50%, and the heterogeneity was high, we made a subgroup analysis from two aspects: different treatment courses, and the use of HLWDD alone and HLWDD combined with western medicine to seek the source of high heterogeneity.

**3.4.1 Meta-analysis of different treatment courses** (i) Effects of different treatment courses on effective rate. In order to verify the effect of different treatment courses on the effective rate, 25 studies were divided into three groups. There were nine studies in 2 – 3 weeks of treatment [25, 28, 30-32, 36, 42, 46, 47], 12 studies in 4 weeks [23, 24, 27, 29, 33, 34, 38, 39, 41, 43-45], and four studies in more than 4 weeks [22, 26, 35, 37]. The results showed that there was no significant difference between the 2 – 3 weeks treatment group and the control group [RR = 1.12, 95% CI (1.00, 1.26), $P > 0.05$]. The effective rate of the 4 weeks treatment group was significantly higher than that of the control group [RR = 1.14, 95% CI (1.03, 1.26), $P < 0.05$]. There was no significant difference between the treatment group with more than 4 weeks treatment and the control group [RR = 1.17, 95% CI (1.00, 1.37), $P > 0.05$]. In general, the total effective rate of the treatment group was significantly higher than that of the control group [RR = 1.14, 95% CI (1.06, 1.22), $P = 0.002$] (Figure 9), and the optimal treatment course is 4 weeks.

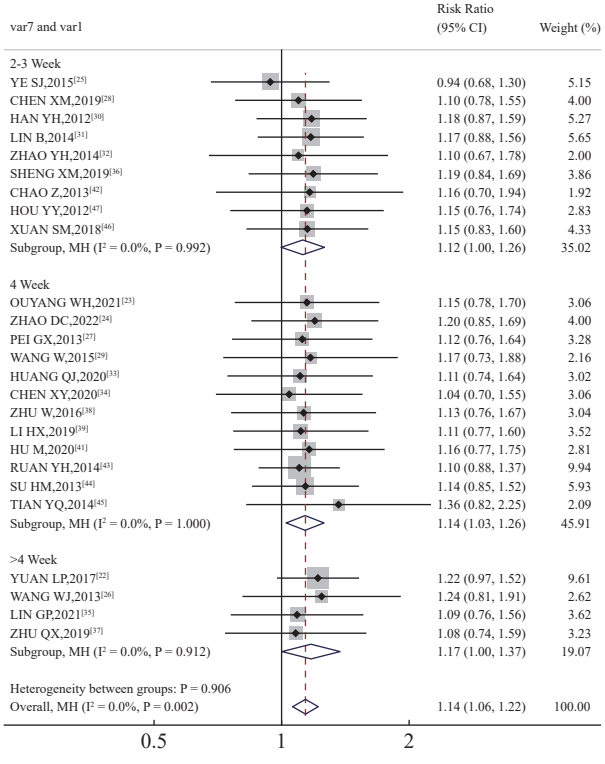


**Figure 9** Forest plot for effective rate based on different treatment courses

(ii) Effects of different treatment courses on PSQI score. To verify the relationship between PSQI score and treatment course, 14 studies were divided into three groups, including five studies [21, 25, 36, 40, 46] in 2 – 3 weeks of treatment, six studies [23, 24, 33, 38, 39, 41] in 4 weeks, and three studies [22, 35, 37] in more than 4 weeks. The results showed that there were significant differences between the treatment group and the control group after 2 – 3 weeks [SMD = – 0.21, 95% CI (– 0.38, – 0.04), $P < 0.05$], 4 weeks [SMD = – 0.55, 95% CI (– 0.75, – 0.35), $P < 0.05$], and more than 4 weeks of treatment [SMD = – 0.21, 95% CI (– 0.42, – 0.01), $P < 0.05$]. In general, the PSQI score of the treatment group was significantly lower than that of the control group [SMD = – 0.31, 95% CI (– 0.42, – 0.20), $P = 0.000$] (Figure 10).

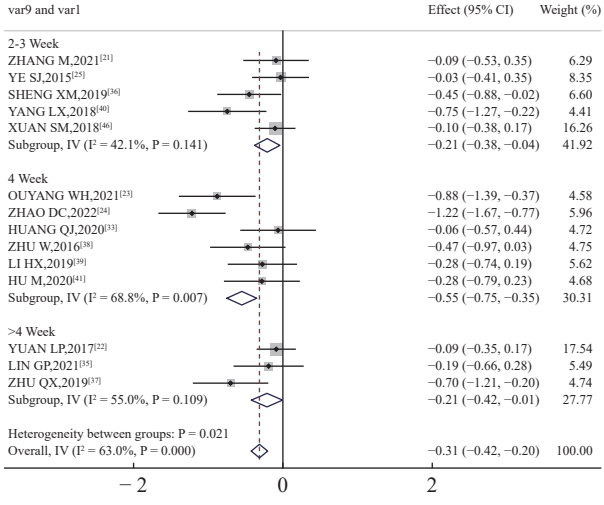


**Figure 10** Forest plot for PSQI score based on different treatment courses

(iii) Effects of different treatment courses on TCM syndrome score. In order to verify the relationship between TCM syndrome score and treatment course, four studies were divided into two groups, including one study [21] in the 2 – 3 weeks treatment course and three studies [23, 33, 41] in the 4 weeks treatment course. The results showed that there was no significant difference between the treatment group and the control group after 2 – 3 weeks of treatment [SMD = – 0.07, 95% CI (– 0.51, 0.37), $P > 0.05$]. There was a significant difference between the 4 weeks treatment group and the control group [SMD = – 0.60, 95% CI (– 0.96, – 0.25), $P < 0.05$]. The result showed that there was no significant difference between the 2 – 3 weeks treatment group and the control group. It may not be representative, because there was only one study of 2 – 3 weeks of treatment, and this may lead to errors. In general, the TCM syndrome score of the treatment group was significantly lower than that of the control group [SMD = – 0.40, 95% CI (– 0.67, – 0.12), $P = 0.005$] (Figure 11). The TCM syndrome score of the 4 weeks treatment group is much lower than that of the control group, suggesting that the 4 weeks treatment course may be the best choice.

(iv) Effects of different treatment courses on adverse reactions. In order to verify the relationship between adverse reactions and the treatment course, 18 studies were divided into three groups, including nine studies [25, 28, 30-32, 36, 42, 46, 47] in 2 – 3 weeks of treatment, five studies [23, 24, 38, 39, 43] in 4 weeks, and four studies [22, 26, 35, 37] in more than 4 weeks. The results showed that there were significant

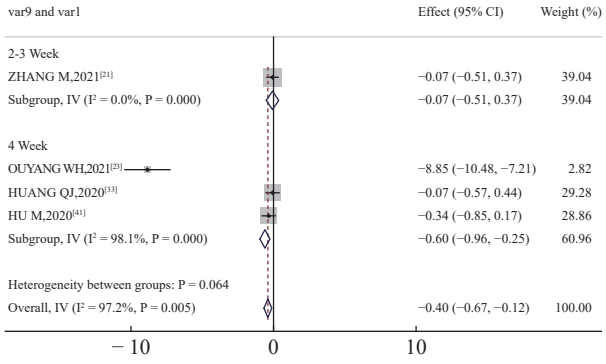


**Figure 11** Forest plot for TCM syndrome score based on different treatment courses

differences between the treatment group and the control group after 2 – 3 weeks [RR = 0.07, 95% CI (0.03, 0.17), $P < 0.05$], 4 weeks [RR = 0.29, 95% CI (0.17, 0.51), $P < 0.05$], and more than 4 weeks of treatment [RR = 0.33, 95% CI (0.20, 0.55), $P < 0.05$]. In general, the incidence of adverse reactions in the treatment group was significantly lower than that in the control group [RR = 0.21, 95% CI (0.15, 0.29), $P = 0.000$]. The study found that there was no significant difference among the groups of different treatment courses on the adverse reactions, but due to the low quality of the study, a further study is recommended (Figure 12).

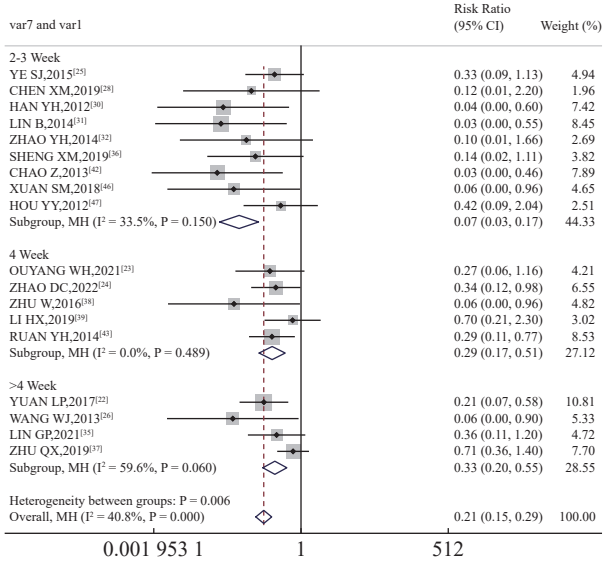


**Figure 12** Forest plot for the adverse reactions based on different treatment courses

**3.4.2 Meta-analysis of HLWDD alone and HLWDD combined with western medicine** (i) Effective rate of HLWDD alone and HLWDD combined with western medicine. In order to verify the effect of HLWDD alone and HLWDD combined with western medicine on the total effective rate, 25 studies were divided into two groups, among which 15 studies [25, 26, 28-34, 36, 42-46] used HLWDD alone, and 10 studies [22-24, 27, 35, 37-39, 41, 47] used HLWDD combined with western medicine. The results showed that the effective rate of the treatment group with HLWDD alone was higher than that of the control group [RR = 1.09, 95% CI (1.00, 1.20), $P < 0.05$]. The effective rate in the treatment group with HLWDD combined with western medicine was higher than that in the control group [RR = 1.15, 95% CI (1.03, 1.29), $P < 0.05$]. In general, the total effective rate of the treatment group was significantly higher than that of the control group, [RR = 1.12, 95% CI (1.04, 1.20), $P = 0.000$] (Figure 13). There was no significant difference in the total effective rate between HLWDD alone and HLWDD combined with western medicine.

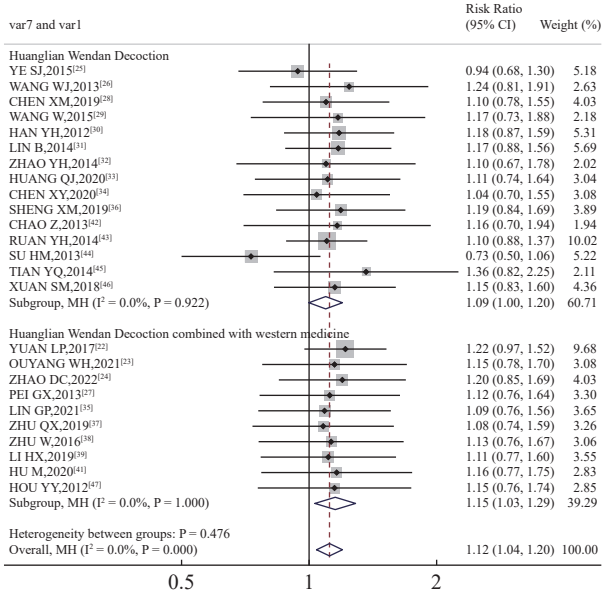


**Figure 13** Forest plot for effective rate of HLWDD alone and HLWDD combined with western medicine

(ii) PSQI score of HLWDD alone and HLWDD combined with western medicine. In order to verify the relationship between PSQI score and the use of HLWDD alone and HLWDD combined with western medicine, 14 studies were divided into two groups, among which five studies [21, 25, 33, 36, 46] were treated with HLWDD alone, and nine studies [22-24, 35, 37-41] were treated with HLWDD combined with western medicine. The results showed that there was no significant difference between the treatment group with HLWDD alone and the control group [SMD = – 0.16, 95% CI (– 0.35, 0.02), $P > 0.05$]. The PSQI score of the treatment group with HLWDD combined with western medicine was significantly lower than that of the control group [SMD = – 0.44, 95% CI (– 0.59, – 0.30), $P < 0.05$]. In general, the total PSQI score of the treatment group was significantly lower than that of the control group [SMD = – 0.34, 95% CI (– 0.46, – 0.23), $P = 0.000$] (Figure 14). Therefore, treatment of HLWDD combined with western medicine is recommended.

(iii) TCM syndrome score of HLWDD alone and HLWDD combined with western medicine. In order to verify the relationship between TCM syndrome score and the

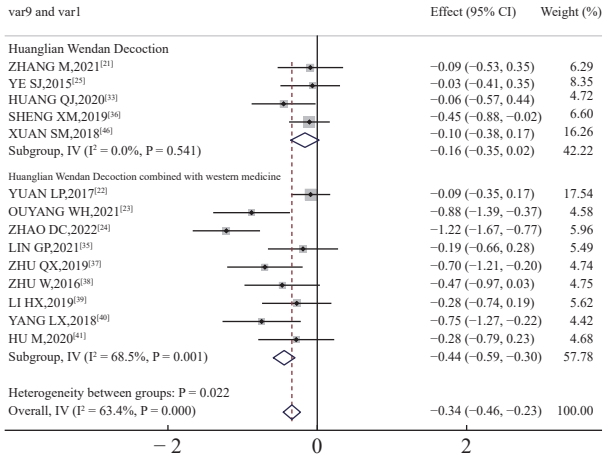


**Figure 14** Forest plot for PSQI score of HLWDD alone and HLWDD combined with western medicine

use of HLWDD alone and HLWDD combined with western medicine, four studies were divided into two groups, of which two studies [21, 33] were treated with HLWDD alone, and two studies [23, 41] were treated with HLWDD combined with western medicine. The results showed that there was no significant difference between the treatment group with HLWDD alone and the control group [SMD = – 0.07, 95% CI (– 0.40, – 0.26), $P > 0.05$]. There was significant difference between the treatment group with HLWDD combined with western medicine and the control group [SMD = – 1.10, 95% CI (– 1.59, – 0.61), $P < 0.05$]. In general, the TCM syndrome score of the treatment group was significantly lower than that of the control group, [SMD = – 0.40, 95% CI (– 0.67, – 0.12), $P = 0.005$] (Figure 15). HLWDD combined with the western medicine group can improve TCM syndrome score more obviously, so it is recommended.

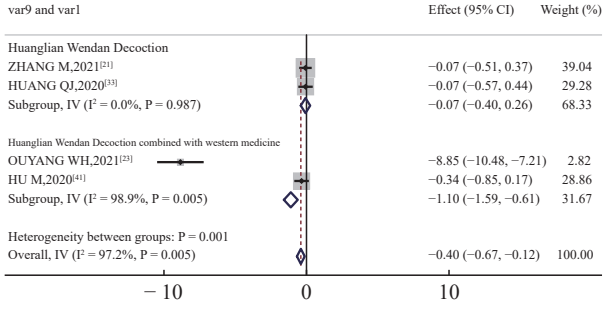


**Figure 15** Forest plot for TCM syndrome score of HLWDD alone and HLWDD combined with western medicine

(iv) Adverse reactions of HLWDD alone and HLWDD combined with western medicine. In order to explore the relationship between adverse reactions and the use of HLWDD alone or HLWDD combined with western medicine, 18 studies were divided into two groups. Among them, 10 studies [25, 26, 28, 30-32, 36, 42, 43, 46] were treated with HLWDD alone, and eight studies [22-24, 35, 37-39, 47] were treated with HLWDD combined with western medicine. The results showed that the incidence of adverse reactions in the treatment group with HLWDD alone was significantly lower than that in the control group [RR = 0.08, 95% CI (0.04, 0.17), $P < 0.05$]. The incidence of adverse reactions in the treatment group with HLWDD combined with western medicine was significantly lower than that in the control group [RR = 0.36, 95% CI (0.24, 0.53), $P < 0.05$]. In general, the incidence of adverse reactions in the treatment group was significantly lower than that in the control group [RR = 0.27, 95% CI (0.19, 0.39), $P = 0.000$] (Figure 16). There is no significant difference in adverse reactions between HLWDD alone and HLWDD combined with western medicine groups.

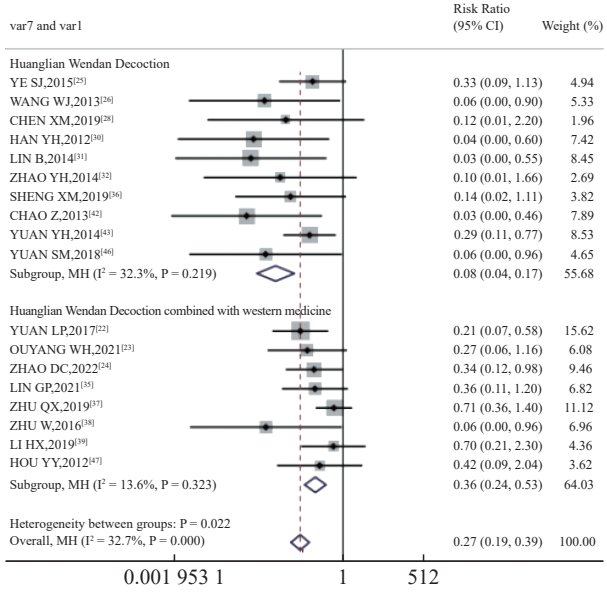


**Figure 16** Forest plot for adverse reaction rate of HLWDD alone and HLWDD combined with western medicine

## 4 Discussion

With the acceleration of the life pace and the increase of life pressure, insomnia has become a high incidence and refractory disease, which has brought a huge burden to patients' health and financials. Nowadays, more and more people tend to have unhealthy habits of greasy and sweet food, excessive tobacco and alcohol, staying up late, etc., which may lead to spleen deficiency, excessive phlegm, and blockage of meridians. When the meridians are blocked by the phlegm and dampness, Qi of the heart will be stagnated and cause insomnia in the end. It is recorded in *Jingyue's Complete Works* (*Jing Yue Quan Shu*,《景岳全书》) that "Sleep is based on Yin, vitality is in charge, stable vitality ensures sleep quality, and unstable vitality brings sleepless" [48]. It is recorded in the *Complete Collection of Ancient and Modern Medical Systems* (*Gu Jin Yi Tong Da Quan*, 《古今医统大全》): "There are many insomnia patients who are disturbed by

phlegm-heat, unsteadiness of vitality, excessive thinking, and stagnation phlegm" [49]. The author found that the insomnia patients with phlegm-heat internal disturbance using HLWDD achieved better curative effect when copying prescriptions with teachers in clinical practice.

HLWDD is derived from Wendan Decoction (温胆汤) in the *Three Cathodes and One Disease Prescription Theory* (*San Yin Ji Yi Bing Zheng Fang Lun*, 《三因极一病证方论》) written by CHEN Wuze in Song Dynasty [50]. It was first found in the *Six Causes and Articles Discrimination* (*Liu Yin Tiao Bian*, 《六因条辨》) compiled by LU Tingzhen in Qing Dynasty [51]. The prescription consists of eight herbs: Huanglian (Coptidis Rhizoma), Banxia (Pinelliae Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Fuling (Poria), Zhishi (Aurantii Fructus Immaturus), Zhuru (Bambusae Caulis in Taenias), Shengjiang (Zingiberis Rhizoma Recens), and Gancao (Glycyrrhizae Radix et Rhizoma). Among them, Huanglian (Coptidis Rhizoma) clears heat and purges the fire, eliminates dampness, and removes toxic materials. Chenpi (Citri Reticulatae Pericarpium) soothes the liver to regulate Qi flow and remove stagnation. Banxia (Pinelliae Rhizoma) dries dampness and resolves phlegm. Fuling (Poria) strains off dampness and regulates the stomach. Zhishi (Aurantii Fructus Immaturus) relieves stagnated Qi to remove retention and eliminate phlegm and accumulated food. Zhuru (Bambusae Caulis in Taenias) clears away heat and phlegm, stops vomiting, and relieves vexation. The combination of Shengjiang (Zingiberis Rhizoma Recens), and Gancao (Glycyrrhizae Radix et Rhizoma) reinforces the spleen, regulates the stomach, and removes dampness and phlegm [52]. According to the results of modern pharmacology research, Huanglian (Coptidis Rhizoma) can coordinate the process of brain excitation and inhibition, and play a hypnotic and sedative role; Banxia (Pinelliae Rhizoma) can play a hypnotic and sedative role by inhibiting peripheral and central nerves; triterpenoids, an effective component in Zhuru (Bammbusae Caulis in Taenias) can enhance immunity and improve sleep [15]. The results of this study showed that the total effective rate of modified HLWDD in treating insomnia was higher than that of the control group, and the TCM syndrome score and PSQI score were significantly lower than those of the control group. Previous studies pay little attention to the best treatment course for HLWDD in treating insomnia. This study comprehensively found that the period of 4 weeks is the best treatment course for treating insomnia. There is no significant difference in the effective rate and adverse reaction rate of HLWDD alone and HLWDD combined with western medicine, but the difference in reducing TCM syndrome score and PSQI score in the combined western medicine group is statistically significant. It is suggested that HLWDD combined with western medicine group is better in clinical practice.

This study mainly evaluated the safety of HLWDD in treating insomnia caused by phlegm-heat internal disturbance from the incidence of adverse reactions. Eighteen of the 27 studies reported the incidence of adverse reactions. Meta-analysis showed that the incidence of adverse reactions of HLWDD in treating insomnia with phlegm-heat internal disturbance was lower than that of the control group. It shows that HLWDD may be safer than western medicine in treating insomnia, but it still needs a large sample, strict standard randomized controlled trial, and long-term follow-up to evaluate the difference in the incidence of adverse reactions between groups. At the same time, eight studies reported the occurrence of adverse reactions after medication, and among them, four studies reported that there were no adverse reactions, and four studies reported that the treatment group or control group had adverse symptoms such as lethargy, dizziness, nausea, diarrhea, dry mouth and bitter taste, and fatigue of limbs. Most of the symptoms did not affect the treatment, and the patients could tolerate it or relieve themselves after stopping the drug, without serious adverse reactions. Benzodiazepines were used to treat insomnia in the control group, which has been proven to be accompanied by side effects such as dizziness, lethargy, drowsiness, and fatigue [15]. Due to the poor quality of the methodology included in the study, the safety conclusions need to be further clarified and verified. This study suggests that we should pay attention to the possible adverse reactions and risk avoidance when using HLWDD combined with western medicine.

Although the result of this study can be concluded that HLWDD is effective for insomnia caused by phlegm-heat internal disturbance, there are some defects in the methodology of this study. (i) In the treatment group, not all the studies use the original prescription. In the control group, different types of western medicines were used, which caused the diversification of treatment methods. (ii) There was no long-term follow-up in all trials, and there was no effective evaluation of late efficacy and safety. (iii) Blind method and allocation concealment method were not mentioned in 27 studies, which may lead to selective publication bias. (iv) The sample size is small and the quality is poor, which may affect the meta-analysis results. Therefore, more clinical randomized controlled trials of high-quality and large samples are needed to obtain more objective clinical evidence in the future. In general, meta-analysis shows that HLWDD can improve insomnia caused by phlegm-heat internal disturbance, and reduce TCM syndrome score and PSQI score, and HLWDD combined with western medicine has the best effect on insomnia with the 4 weeks treatment course.

## Fundings

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## Competing interests

The authors declare no conflict of interest.

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# 黄连温胆汤单独或联合西药治疗痰热内扰型失眠有效性及安全性的 Meta 分析

杨蕾[a], 何丽云[b*], 陈霄[c], 王凯悦[c], 方永军[d], 梁壮[a], 杨昭[a]

*a. 陕西中医药大学第一临床医学院, 陕西 咸阳 712046, 中国*
*b. 中国中医科学院中医临床基础医学研究所, 北京 100700, 中国*
*c. 陕西中医药大学附属西安中医脑病医院脑病九科, 陕西 西安 710038, 中国*
*d. 陕西中医药大学附属医院脑病三科, 陕西 咸阳 712000, 中国*

**【摘要】目的** 对近 10 年来报道的黄连温胆汤单独或联合西药治疗痰热内扰型失眠的有效性及安全性进行评估。**方法** 在中国知网、维普、万方、中国生物医学数据库、PubMed、Web of science、Embase 和 Cochrane Library 数据库中检索自 2012 年 1 月 1 日至 2022 年 4 月 1 日黄连温胆汤单独或联合西药治疗痰热内扰型失眠的随机对照试验。经筛选后对纳入文献进行分析，评估黄连温胆汤对痰热内扰型失眠的有效率、匹茨堡睡眠质量指数量表（PSQI）评分、中医证候积分及不良反应的影响。亚组分析黄连温胆汤治疗不同时间后的效果，比较单独使用黄连温胆汤与黄连温胆汤联合西药治疗的效果。**结果** 最终纳入 27 篇随机对照试验，共计 2 395 例患者。Meta 分析结果显示黄连温胆汤单独或联合西药组对比西药组疗效更好［RR = 1.14, 95% CI (1.06, 1.22), *P* = 0.000］，黄连温胆汤单独或联合西药组对比西药组 PSQI 评分［SMD = – 0.31, 95% CI (– 0.42, – 0.20), *P* = 0.000］、中医证候积分［SMD = – 0.40, 95% CI (– 0.67, – 0.12), *P* = 0.005］、不良反应率［RR = 0.21, 95% CI (0.15, 0.29), *P* = 0.000］显著降低。亚组分析显示黄连温胆汤单独或联合西药组对比西药组，治疗 4 周疗效更好［RR = 1.14, 95% CI (1.03, 1.26), *P* < 0.05］；黄连温胆汤单独或联合西药组对比西药组，疗程为 4 周时，中医症候积分降低更明显［SMD = – 0.60, 95% CI (– 0.96, – 0.25), *P* < 0.05］；黄连温胆汤单独或联合西药组对比西药组在治疗周期上与 PSQI 积分、不良反应率无明显相关性。单独使用黄连温胆汤组与西药组相比有效率［RR = 1.09, 95%CI (1.00, 1.23), *P* < 0.05］较于黄连温胆汤联合西药组对比西药组有效率［RR = 1.15, 95% CI (1.03, 1.29), *P* < 0.05）效果相同；黄连温胆汤联合西药组对比西药组 PSQI 积分［SMD =– 0.44, 95% CI (– 0.59, – 0.30), *P* < 0.05］、中医症候积分［SMD = – 1.10, 95% CI (– 1.59, – 0.61), *P* < 0.05］显著降低；单独使用黄连温胆汤不良反应发生率［RR = 0.08, 95% CI (0.04, 0.17), *P* < 0.05］与黄连温胆汤联合西药治疗不良反应发生率［RR = 0.36, 95% CI (0.24, 0.53), *P* < 0.05］无明显差异。**结论** 黄连温胆汤单独或联合西药治疗痰热内扰型失眠疗效是肯定的，有效率高、PSQI 评分及中医证候积分显著降低，并且有较好的安全性，最佳疗程是 4 周。

**【关键词】**黄连温胆汤；痰热内扰；西药；失眠；疗效；Meta 分析