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Original Article

Efficacy and safety of Wuling capsule for insomnia disorder: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objectives: Wuling capsule has been used in treatment of insomnia disorder in China for decades, but the reported treatment efficacy of different studies was not consistent. This study intended to evaluate the efficacy and safety of Wuling capsule for insomnia disorder, so as to provide evidence for clinical application.

Methods: Eight databases (MEDLINE, EMBASE, Ovid, Cochrane Library, Chinese National Knowledge Infrastructure, VIP information database, Chinese Biomedical Database and Wanfang) were searched from inception to September 14, 2021. Randomized controlled trials (RCTs) comparing Wuling capsule with controls in adults with insomnia disorder were eligible. The primary outcome was sleep quality assessed by Pittsburgh Sleep Quality Index (PSQI), and the secondary outcomes were severity of insomnia disorder measured by Sleep Dysfunction Rating Scale (SDRS) and adverse events. This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.

Results: Nineteen RCTs with a total of 1850 participants were included. In terms of sleep quality assessed by PSQI, Wuling capsule significantly lowered PSQI score (MD: −1.92, 95% CI: [−2.34, −1.50], $P < 0.00001$, $I^2 = 95\%$) compared to controls, and the effect of Wuling capsule was significantly better than control no matter when Wuling capsule as monotherapy (MD: −1.71, 95% CI: [−2.33, −1.09], $P < 0.00001$, $I^2 = 97\%$) or as adjunctive therapy (MD: −2.10, 95% CI: [−2.66, −1.55], $P < 0.00001$, $I^2 = 90\%$). Wuling capsule was more effective for the treatment duration lasted 8 weeks (MD: −2.57, 95% CI: [−3.52, −1.62], $P < 0.00001$, $I^2 = 93\%$) than 4 weeks (MD: −1.68, 95% CI: [−2.13, −1.22], $P < 0.00001$, $I^2 = 95\%$). In terms of severity of insomnia disorder measured by SDRS, Wuling capsule significantly reduced SDRS score (MD: −4.21, 95% CI: [−4.95, −3.46], $P < 0.00001$, $I^2 = 0\%$) compared to benzodiazepines. Wuling capsule significantly reduced adverse events compared to controls (RR: 0.47, 95% CI: [0.34, 0.65], $P < 0.00001$, $I^2 = 43\%$).

Conclusion: Wuling capsule can safely and effectively improve sleep quality in patients with insomnia disorder. However, these findings require careful recommendation due to the high heterogeneity and high risk of bias in the included trials. Clinical trials with higher quality designs are needed.

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Abbreviations

BZDs	Benzodiazepines
CCMD-3	Chinese Classification and Diagnostic Criteria of Mental Disorders-third edition
CI	Confidence Intervals
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-fifth edition
GABA	Gamma-aminobutyric Acid
GAD	Glutamate Decarboxylase
Glu	Glutamic Acid
ICD-10	International Statistical Classification of Diseases and Related Health Problems-tenth edition
ICSD-3	International Classification of Sleep Disorders-third edition
ITT	Intention to Treat
MD	Mean differences
non-BZDs	non-Benzodiazepines
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
RCTs	Randomized Controlled Trials
RR	risk ratio
SDRS	Sleep Dysfunction Rating Scale

1. Introduction

According to the diagnostic criteria for insomnia disorder in the International Classification of Sleep Disorders-third edition (ICSD-3), insomnia that occurs at least three times a week and lasts for at least three months is defined as chronic insomnia disorder, and insomnia that meets the criteria for symptoms but lasts less than three months is called short-term insomnia disorder [1]. Insomnia disorder has become a serious public health problem [2]. Studies have shown that the incidence of short-term insomnia disorder was 30–50 percent [3–5] and the incidence of chronic insomnia disorder was at least 5–15 percent [6–9] in general population, and it is higher in women and the elderly [10–12]. Insomnia disorder brings many adverse effects on health. Several studies have found that insomnia disorder was an important risk factor for the development of psychiatric disorders [13], especially mood disorders [14], and could increase the risk of recurrent depression [15] and alcoholism [16]. At the same time, insomnia disorder might increase the risk of diabetes [17], metabolic syndrome [18], cardiovascular disease [19,20] and hypertension [21,22]. The current drug therapy for insomnia disorder mainly includes benzodiazepines, benzodiazepines receptor agonists, sedative antidepressants, antipsychotics, melatonin, melatonin agonists, antihistamines, and orexin receptor antagonists [23–26]. However, these conventional drug therapy may bring many problems such as hangover effect, drug resistance, insomnia disorder recurrence and addiction [27,28]. Therefore, more and more people begin to seek complementary and alternative therapies including traditional Chinese medicine [29–31].

Wuling capsule as a leading Chinese patent medicine for insomnia disorder in China [32] was approved by China Food and Drug Administration (approval number: Guoyao Zhunzi Z19990048) [33]. The main ingredient of Wuling capsule is a pure Chinese medicine preparation isolated and refined from the rare medicinal fungus called Wuling, and studies showed that it could increase the amount of glutamate and gamma-aminobutyric acid (GABA) in the brain and promote the activity of glutamate dehydrogenase, the synthesis of inhibitory neurotransmitter GABA as well as the binding activity of GABA receptor in cerebral cortex, so as to enhance central sedation and regulate central nervous function [34]. Wuling capsule has been applied in clinical treatment of insomnia disorder for decades, but the results of therapeutic efficacy in different studies were not consistent. There has not been sufficient systematic evaluation of the efficacy and safety of Wuling capsule for insomnia disorder. This paper, based on literature research, adopted Cochrane systematic evaluation method to evaluate the efficacy and safety of Wuling capsule in the treatment of insomnia disorder, in order to provide evidence for clinical application.

2. Methods

This systematic review was registered at PROSPERO (No: CRD42019126385, https://www.crd.york.ac.uk/prospero/). This study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 [35] and was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [36].

2.1. Eligibility criteria

Inclusion criteria: 1) Types of studies: randomized controlled trials (RCTs) which evaluated the efficacy and safety of Wuling capsule for insomnia disorder were included in this review, in spite of blinding, publication status or language. 2) Participants: adult patients with insomnia disorder. Insomnia disorder needed to be defined by established diagnostic criteria such as the International Classification of Sleep Disorders-third edition (ICSD-3) [1], Diagnostic and Statistical Manual of Mental Disorders-fifth edition (DSM-5) [37], Chinese Classification and Diagnostic Criteria of Mental Disorders-third edition (CCMD-3) [38], International Statistical Classification of Diseases and Related Health Problems-tenth edition (ICD-10) [39], Chinese Guideline on Diagnosis and Treatment for Adult Insomnia Disorder [40]. 3) Interventions: Interventions were defined as Wuling capsule regardless of dosage, frequency, and treatment duration. Studies that evaluated Wuling capsule combined with conventional therapies were also eligible. 4) Comparators: the comparators comprised placebo, blank control and conventional therapy which included benzodiazepine drugs (BZDs), non-benzodiazepine drugs (non-BZDs) and psychotherapy (eg, cognitive behavioral therapy, sleep hygiene education). When another treatment was combined with Wuling capsule, the adjunct therapy needed to be the same as the control. 5) Outcomes: the main outcomes included sleep quality and severity of insomnia disorder measured by sleep questionnaires such as Pittsburgh Sleep Quality Index (PSQI) [41], Sleep Dysfunction Rating Scale (SDRS) [42] and so on; the evaluation proceeded at the end of the treatment course.

Exclusion criteria: 1) quasi-randomized trials allocated by date of birth, date of admission, medical record number, or registration order; 2) use of other herbal medicine either in intervention or control group.

2.2. Search strategy

The literature was searched in the following eight databases: MEDLINE, EMBASE, Ovid, Cochrane Library, Chinese National Knowledge Infrastructure Database, VIP information database, Chinese Biomedical Database and Wanfang Data Information Site. Publication time was set from inception to September 14, 2021. We used the following MeSH terms in conjunction with free-text terms to perform search: wuling capsule, wuling powder, sleep disorder, sleep disturbance, sleepless, wakeful, insomnia, agrypnia,

dyssomnia, somnambul, sleep initiation and maintenance disorders, sleep initiation, sleep maintenance, sleep deprivation, bibliographies of retrieved papers were searched for potential eligible studies. We returned to search just before the final analyses and further studies retrieved for inclusion. Details of search strategies were shown in Supplementary materials 1.

2.3. Study selection and data extraction

Two researchers (Zhou HF, Lin Q) independently screened the titles and abstracts to select potential literature according to the inclusion and exclusion criteria. The studies were discussed or judged by a third researcher (Zhao Y) when the first two researchers disagreed with each other. After preliminary screening, these researchers further read the full text of the potential literature to determine whether it was included. Two researchers (Zhou HF, Lin Q) used a standardized data extraction template to extract the basic data which included authors, titles of study, year of publication, sample size, types of studies, participants, age, course of disease, interventions, comparators, outcomes, adverse events, and treatment durations. We defined PSQI score as the primary outcome and SDRS score as secondary outcome. Adverse events were defined as a composite of events including headache, dizziness, gastrointestinal reaction, liver function damage, allergy, renal function damage and bleeding.

2.4. Risk of bias in individual studies

Two researchers (Zhou HF, Lin Q) independently accessed the risk of bias for each included study based on the Cochrane Handbook for Systematic Reviewers of Interventions version 5.1.0 [35]. The items included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and baseline data comparability (other bias). Each item was categorized as low/unclear/high risk of bias. We used the modified Jadad Scale [43] to evaluate the quality of included studies. We assigned quality categories based on the scores of each study. The categories were as followed: high quality (score 4–7), and low quality (score less than 4) [44]. When the judgment of bias evaluation was in disagreement, discussion with the third review author (Zhao Y) was conducted.

2.5. Data analysis

Where trials were sufficiently alike in terms of population and comparison interventions, their results were combined. Mean differences (MD) and 95% confidence intervals (95% CI) were reported for continuous outcomes, and risk ratio (RR) and 95% CI were reported for dichotomous variables. Heterogeneity among trials was assessed by Cochrane's Q test and I-squared statistic. According to Cochrane Handbook for Systematic Reviews of Interventions, the scale of I^2 had a range of 0–100% and values on the order of 0–25%, 25%–50%, 50%–75% and 75–100% were considered might not be important, may represent moderate heterogeneity, may represent substantial heterogeneity and considerable heterogeneity, respectively [35]. If P was less than 0.1, we assumed definite heterogeneity. For heterogeneous studies, we adopted use a random-effects model to estimate the overall effect instead of a fixed-effect model, because random-effects models assess the outcomes of the study according to within-trial as well as between-trial variance [45,46], thus providing more conservative results. Furthermore, meta-regression analysis was used to explore the sources of heterogeneity. The sensitivity analysis was also performed by removing each study one at a time to evaluate the stability of the results. Subgroup analysis was performed according to various types of interventions and different treatment durations. The publication bias was detected by the funnel plot, the Begger's test and the Egger's test [47,48].

3. Results

3.1. Description of included studies

In this review, we included 637 records in total from the primary search. After removal of duplicates, 273 records remained. After going through the titles and abstracts in detail, 203 records were excluded and 70 articles remained to be screened. By further reading the full texts of the remaining 70 articles, 51 articles were excluded for not meeting our eligibility criteria: 1 used mistaken data; the adjunct therapy was not same as the control in 6; 5 were not RCTs; 5 were quasi-randomized trials; the primary outcome was not insomnia disorder in 25; 3 used other herbal medicine or food supplements in control group; 6 did not describe the diagnostic criteria. Finally, 19 trials [49–67] were judged to be eligible and were included in meta-analysis. The study selection is summarized in a PRISMA 2009 flow diagram (Fig. 1).

3.2. Characteristics of included studies

The 19 included trials were all conducted in China. One [52] adopted multicenter design and the others adopted single center design. All trials were published between 2008 and 2021. One [52] was published in English and the others were in Chinese. The 19 trials involved 1850 participants (930 in the intervention group and 920 in the control group) with insomnia disorder. Insomnia disorder was diagnosed by ICSD-3 in one trial [63], ICD-10 in one trial [52], DSM-5 in one trial [56], CCMD-3 in 11 trials [50,51,53–55,57,58,60–62,65], and Chinese Guideline on Diagnosis and Treatment for Adult Insomnia disorder in 5 trials [49,59,64,66,67]. Eight trials compared Wuling capsule with benzodiazepines [49–51,53–55,65,66]; Four trials compared Wuling capsule plus benzodiazepines with benzodiazepines [58–60,67]; Five trials compared Wuling capsule plus sedating antidepressant with sedating antidepressant [56,57,61,62,64]; one trial compared Wuling capsule plus cognitive behavior therapy with cognitive behavior therapy [63]; one trial compared Wuling capsule with placebo [52]. The dosage of Wuling capsule in all trials was 0.99 g for each time, three times a day. Treatment duration lasted from 4 weeks to 12 weeks. The total score of PSQI was reported in 18 trials [49–64,66,67]. Five trials provided data on subscales of PSQI which included sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance and daytime dysfunction [49,59,62,65,66]. The SDRS was reported in 4 trials [51,53–55]. The complete characteristics of the included studies are shown in Table 1.

3.3. Risk of bias analysis

All included studies adopted RCT design, but only ten studies described the method of random sequence generation which included random number table [56,57,59,60,63–67] and stratified blocked randomization [52]. In terms of the remaining 9 trials, we did not find sufficient information to judge whether randomization was conducted properly. Allocation concealment and blind method were reported only in one trial [52]. Three trials [52,53,57] described dropout or withdrawal, nevertheless only one [52] of these trials adopted intention to treat (ITT) analysis. All trials except

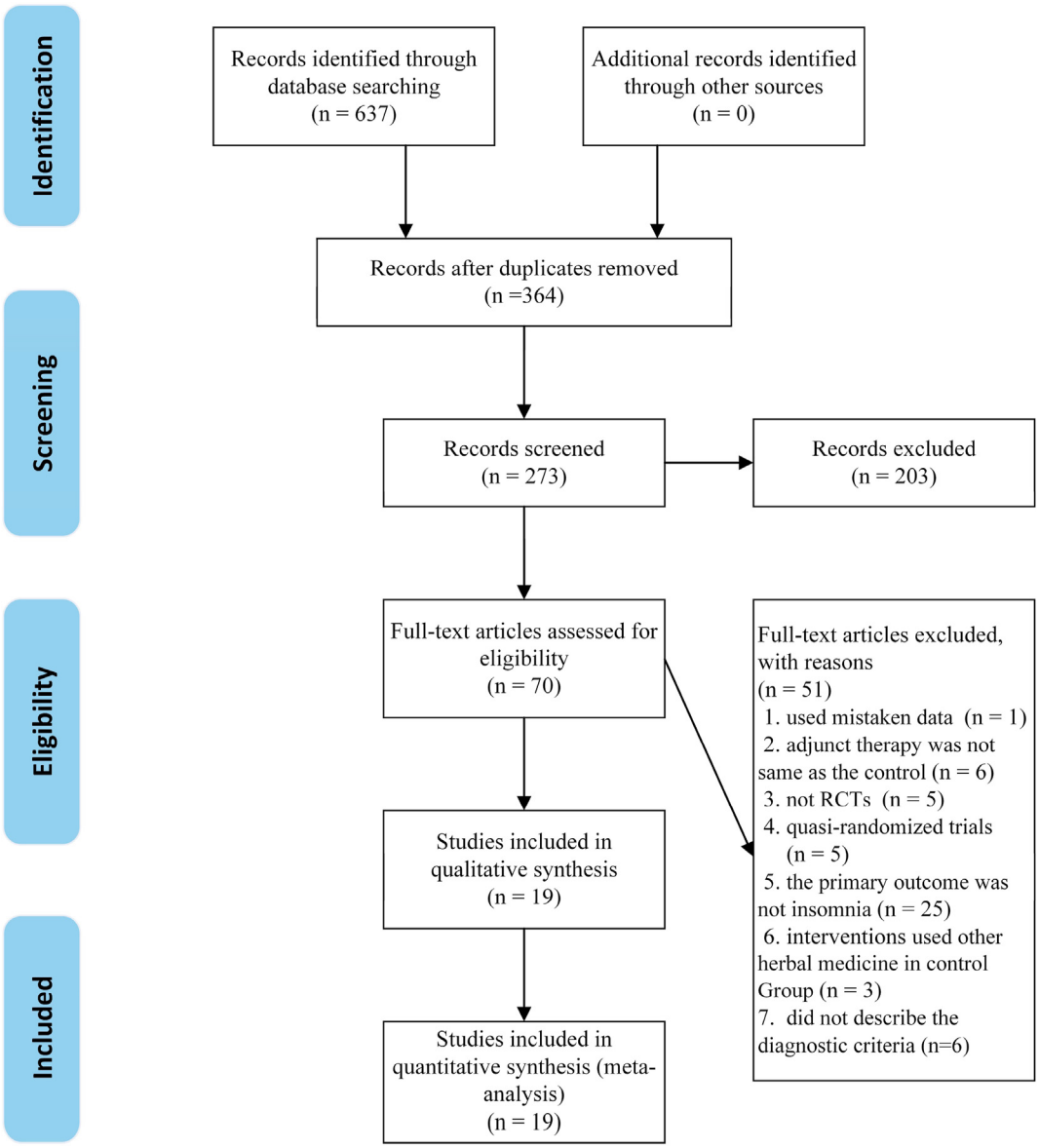

Fig. 1. PRISMA 2009 flow diagram for study selection process.

nine [51,54,55,58,62,63,65–67] described adverse events. Details of risk of bias assessment are shown in Fig. 2.

3.4. Effect estimates of outcomes

3.4.1. Sleep quality measured by PSQI

In terms of the sleep quality assessed by PSQI, pooled results of the 18 trials [49–64,66,67] revealed that Wuling capsule significantly reduced PSQI score (MD: −1.92, 95% CI: [−2.34, −1.50], P<0.00001, I^2 = 95%). Subgroup analysis revealed that Wuling capsule significantly lowered PSQI score when using Wuling capsule compared to benzodiazepines (MD: −1.90,95% CI: [−2.55, −1.26], P < 0.00001, I^2 = 97%), or using Wuling capsule in combination with benzodiazepines compared to benzodiazepines (MD: −1.81, 95% CI: [−2.84, −0.78], P=0.0006, I^2 = 89%), or using Wuling capsule in combination with sedating antidepressants compared to sedating antidepressants (MD: −2.25, 95% CI: [−3.02, −1.48], P<0.00001, I^2 = 93%), or using Wuling capsule in combination with cognitive behavior therapy compared to cognitive behavior therapy (MD: −2.76, 95% CI: [−4.25, −1.27], P=0.0003). However, one trial revealed that Wuling capsule was not superior to control when using Wuling capsule compared to placebo (MD: −0.07, 95% CI: [−0.98, 0.84], P=0.88). These results are shown in Fig. 3.

In terms of Wuling Capsule as monotherapy [49–55,66] or as adjunctive therapy [56–64,67] compared to control, subgroup analysis showed that the effect of Wuling capsule was significantly better than control when Wuling capsule as monotherapy (MD: −1.71, 95% CI: [−2.33, −1.09], P<0.00001, I^2 = 97%), and Wuling capsule in combination with conventional drug was more effective than conventional drug alone (MD: −2.10, 95% CI: [−2.66, −1.55], P<0.00001, I^2 = 90%) too. At the same time, the effect of Wuling capsule as adjunctive therapy maybe superior to that as monotherapy which was assessed by MD value. These results are shown in Fig. 4.

The treatment duration lasted 4 weeks in 12 trials [49–53,55,59–61,64,66,67] and 8 weeks in 5 trials [54,56,57,62,63]. In case of treatment duration, subgroup analysis showed that Wuling capsule significantly lowered PSQI score no matter the

Table 1
Basic characteristic of the included studies.

Include studies	Participants	Sample size (T/C)	Gender (M/F)		Age: Mean ± SD, years		Intervention		Therapeutic course	Outcomes	Diagnostic criteria	JADAD score
			T	C	T	C	T	C				
Lin Y 2013	Insomnia disorder	94/92	NS	NS	32 ± 19	30 ± 17	Wuling capsule 0.99 g tid	Placebo 0.99 g tid	4 weeks	PSQI	ICD-10	7
Liu XY 2018	Insomnia disorder	36/35	10/26	7/28	57.33 ± 9.76	59.45 ± 12.88	Wuling capsule 0.99 g tid	Estazolam 1 mg qn	4 weeks	PSQI	CGDTAI	1
Chen JY 2014	Insomnia disorder	35/33	16/19	15/18	34.2 ± 9.46	36.8 ± 10.78	Wuling capsule 0.99 g tid	Estazolam 2 mg qn	4 weeks	PSQI	CCMD-3	1
Huang XY 2011	Insomnia disorder	50/50	21/29	19/31	44.58 ± 10.25	44.2 ± 7.83	Wuling capsule 0.99 g tid	Diazepam 5 mg qn	4 weeks	PSQI + SDRS	CCMD-3	1
Zhu HF 2010	Insomnia disorder	32/30	14/18	15/15	46.2 ± 6.5	45.1 ± 6.2	Wuling capsule 0.99 g tid	Estazolam 2 mg qn	4 weeks	PSQI + SDRS	CCMD-3	2
Feng XD 2008	Insomnia disorder	25/23	NS	NS	NS	NS	Wuling capsule 0.99 g tid	Alprazolam 0.4 mg qn	8 weeks	PSQI + SDRS	CCMD-3	1
Liu YX 2014	Insomnia disorder	24/24	10/14	12/12	41.29 ± 11.61	42.58 ± 10.89	Wuling capsule 0.99 g tid + paroxetine 20 mg qn	Paroxetine 20 mg qn	8 weeks	PSQI	CCMD-3	4
Xing XR 2016	Insomnia disorder	63/63	38/25	37/26	46.3 ± 7.43	45.3 ± 7.34	Wuling capsule 0.99 g tid + paroxetine 20 mg qn	Paroxetine 20 mg qn	8 weeks	PSQI	DSM-5	3
Wang J 2021	Insomnia disorder	49/49	30/19	27/22	49.85 ± 7.90	50.48 ± 7.51	Wuling capsule 0.99 g tid	Estazolam 1 mg qn	4 weeks	PSQI	CGDTAI	3
Zeng ZC 2013	Insomnia disorder	50/50	30/20	28/22	44.7 ± 4.2	41.2 ± 3.8	Wuling capsule 0.99 g tid	Diazepam 5 mg qn	4 weeks	PSQI + SDRS	CCMD-3	1
Chen YH 2021	Insomnia disorder	30/29	9/21	10/19	45.06 ± 12.41	45.12 ± 12.87	Wuling capsule 0.99 g tid + Dexzopiclone 3 mg qn	Dexzopiclone 3 mg qn	4 weeks	PSQI	CGDTAI	3
Liu YY 2020	Insomnia disorder	47/48	19/28	21/27	41.03 ± 11.95	40.57 ± 11.3	Wuling capsule 0.99 g tid + Estazolam 2 mg qn	Estazolam 2 mg qn	4 weeks	PSQI	CCMD-3	3
Xu YH 2020	Insomnia disorder	50/50	21/29	19/31	46.59 ± 9.15	47.26 ± 8.15	Wuling capsule 0.99 g tid + Estazolam 1 mg qn	Estazolam 1 mg qn	12 weeks	PSQI	CCMD-3	1
Zhan FF2020	Insomnia disorder	50/49	21/29	18/31	51.19 ± 8.54	52.61 ± 8.35	Wuling capsule 0.99 g tid + Alprazolam 0.4 mg qn	Alprazolam 0.4 mg qn	4 weeks	PSQI	CGDTAI	3
Liu WH 2019	Insomnia disorder	37/37	17/20	19/18	46.78 ± 6.28	47.14 ± 6.39	Wuling capsule 0.99 g tid + Mirtazapine 15 mg qd	Mirtazapine 15 mg qd	8 weeks	PSQI	CCMD-3	1
Wang HK 2021	Insomnia disorder	100/100	61/39	59/41	50.63 ± 6.75	50.15 ± 7.86	Wuling capsule 0.99 g tid + Trazodone Hydrochloride 50 mg qd	Trazodone Hydrochloride 50 mg qd	4 weeks	PSQI	CGDTAI	3
Zeng YB 2019	Insomnia disorder	51/51	20/31	22/29	41.38 ± 4.52	42.25 ± 3.28	Wuling capsule 0.99 g tid + Paroxetine Hydrochloride 20 mg qd	Paroxetine Hydrochloride 20 mg qd	4 weeks	PSQI	CCMD-3	1
Li YF 2021	Insomnia disorder	55/55	26/29	28/27	87.25 ± 3.79	88.15 ± 3.81	Wuling capsule 0.99 g tid + Cognitive behavior therapy	Cognitive behavior therapy	8 weeks	PSQI	ICSD-3	3
Liu LB 2021	Insomnia disorder	52/52	35/17	32/20	55.94 ± 3.26	56.23 ± 3.47	Wuling capsule 0.99 g tid + Dexzopiclone 3 mg qn	Dexzopiclone 3 mg qn	8 weeks	PSQI subscales	CCMD-3	3

Abbreviations: T: treatment; C: control; CCMD-3, Chinese Classification and Diagnostic Criteria of Mental Disorders-third edition; CGDTAI: Chinese Guideline on Diagnosis and Treatment for Adult Insomnia Disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-fifth edition; F: female; M: male; ICD-10, International Statistical Classification of Diseases and Related Health Problems-tenth edition; ICSD-3, International Classification of Sleep Disorders-third edition; NS: not stated; PSQI: Pittsburgh Sleep Quality Index; SDRS, Sleep Dysfunction Scale.

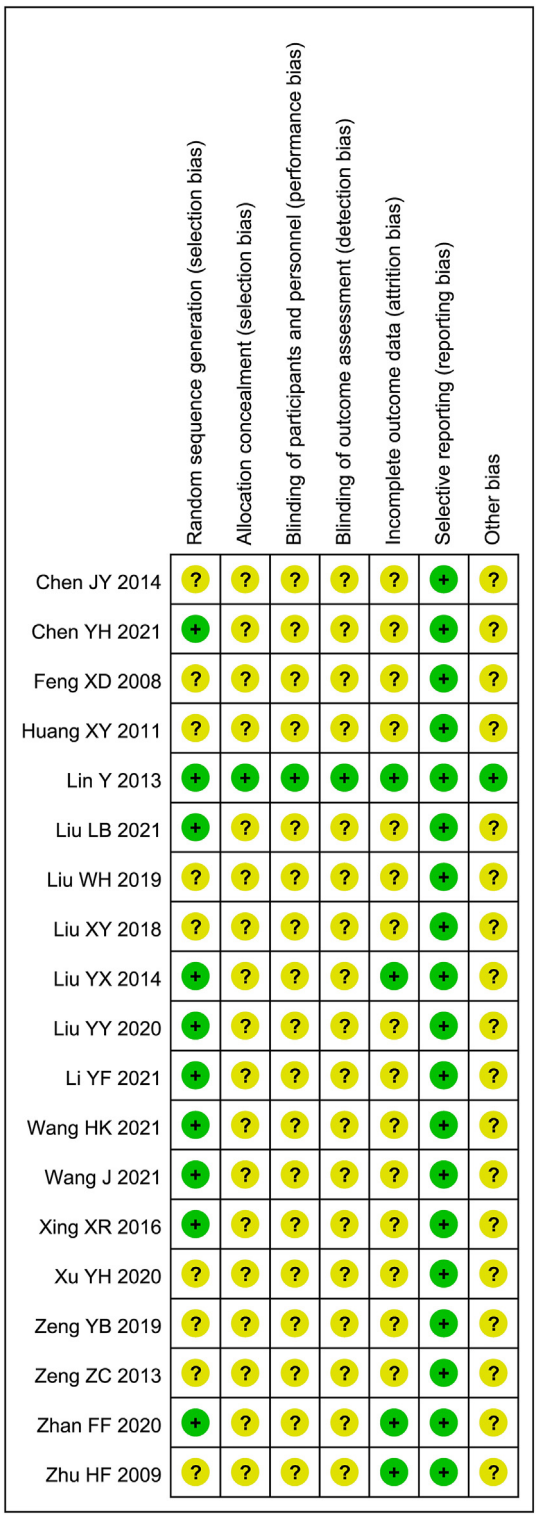

Fig. 2. Risk of bias in the included studies.

treatment duration lasted 4 weeks (MD: −1.68, 95% CI: [−2.13, −1.22], P<0.00001, I^2 = 95%) or 8 weeks (MD: −2.57, 95% CI: [−3.52, −1.62], P<0.00001, I^2 = 93%). Meanwhile Wuling capsule was more effective in treating insomnia disorder for 8 weeks than the duration of 4 weeks. From this point we could find a trend that longer the therapeutic course last, maybe better the treatment effect is. These results are shown in Fig. 5.

Insomnia disorder was diagnosed by ICSD-3 in one trial [63], ICD-10 in one trial [52], DSM-5 in one trial [56], CCMD-3 in 11 trials [50,51,53–55,57,58,60–62,65], and CGDTAI in 5 trials [49,59,64,66,67]. In case of various diagnostic criteria for insomnia disorder, subgroup analysis showed that Wuling capsule significantly lowered PSQI score no matter the diagnostic criteria were CCMD-3 (MD: −1.81, 95% CI: [−2.31, −1.32], P<0.00001, I^2 = 95%), or CGDTAI (MD: −2.01, 95% CI: [−2.83, −1.20], P<0.00001, I^2 = 91%), or DSM-5 (MD: −3.44, 95% CI: [−3.82, −3.06], P<0.00001), or ICSD-3 (MD: −2.76, 95% CI: [−4.25, −1.27], P=0.0003). However, one trial revealed that Wuling capsule was not superior to control when the diagnostic criteria was ICD-10 (MD: −0.07, 95% CI: [−0.98, 0.84], P=0.88). These results are shown in Fig. 6.

Five trials [49,59,62,65,66] provided data on subscales of PSQI which included sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance and daytime dysfunction. Pooled results of the 5 trials demonstrated that Wuling capsule lowered the scores of sleep quality (MD: −0.42, 95% CI: [−0.46, −0.39], P<0.00001, I^2 = 68%), sleep latency (MD: −0.32, 95% CI: [−0.57, −0.07], P = 0.01, I^2 = 97%), sleep duration (MD: −0.30, 95% CI: [−0.33, −0.26], P<0.00001, I^2 = 96%), habitual sleep efficiency (MD: −0.31, 95% CI: [−0.46, −0.15], P = 0.0002, I^2 = 92%), sleep disturbance (MD: −0.26, 95% CI: [−0.30, −0.22], P<0.00001, I^2 = 91%) and daytime dysfunction (MD: −0.38, 95% CI: [−0.49, −0.27], P<0.00001, I^2 = 87%) when compared to benzodiazepines or sedating antidepressants (Supplementary materials 2, Figs. S1–S6).

3.4.2. Severity of insomnia disorder measured by SDRS

Four trials [51,53–55] presented severity data of insomnia disorder assessed by Sleep Dysfunction Rating Scale (SDRS). As shown in Fig. 7, pooled results of the 4 trials demonstrated that Wuling capsule significantly reduced SDRS score (MD: −4.21, 95% CI: [−4.95, −3.46], P<0.00001, I^2 = 0%) compared to BZDs.

3.4.3. Adverse events

Among the 19 trials, 9 trials [51,54,55,58,62,63,65–67] did not report any information about adverse events, and 141 adverse events were reported in the remaining 10 trials, and Wuling capsule significantly reduced adverse events when compared to control (RR: 0.47, 95% CI: [0.34, 0.65], P<0.00001, I^2 = 43%). Subgroup analysis showed that Wuling capsule significantly lowered adverse events when using Wuling capsule compared to benzodiazepines (RR: 0.27, 95% CI: [0.11, 0.67], P=0.005, I^2 = 32%), or using Wuling capsule in combination with sedating antidepressants compared to sedating antidepressants (RR: 0.39, 95% CI: [0.24, 0.62], P<0.00001, I^2 = 22%), but no statistic difference was found whether using Wuling capsule in combination with benzodiazepines compared to benzodiazepines (RR: 0.57, 95% CI: [0.26, 1.22], P=0.15, I^2 = 67%), or compared to placebo (RR: 1.40, 95% CI: [0.56, 3.52], P=0.48). Results above are shown in Fig. 8.

3.5. Meta-regression

The results of meta-analysis showed that there was considerable heterogeneity (75%–100%) among 18 studies. We conducted a meta-regression analysis in which numbers of subjects, treatment duration, interventions, control drugs, JADAD scores and diagnostic criteria were taken as covariables, and the results showed that the heterogeneity in the included studies had no significant correlation with the above covariables (Supplementary materials 2, Table S1). Considering that subjects included in different studies differ in age and course of disease, it may be the main source of heterogeneity. However, several articles [54,56,57] included in the meta-analysis

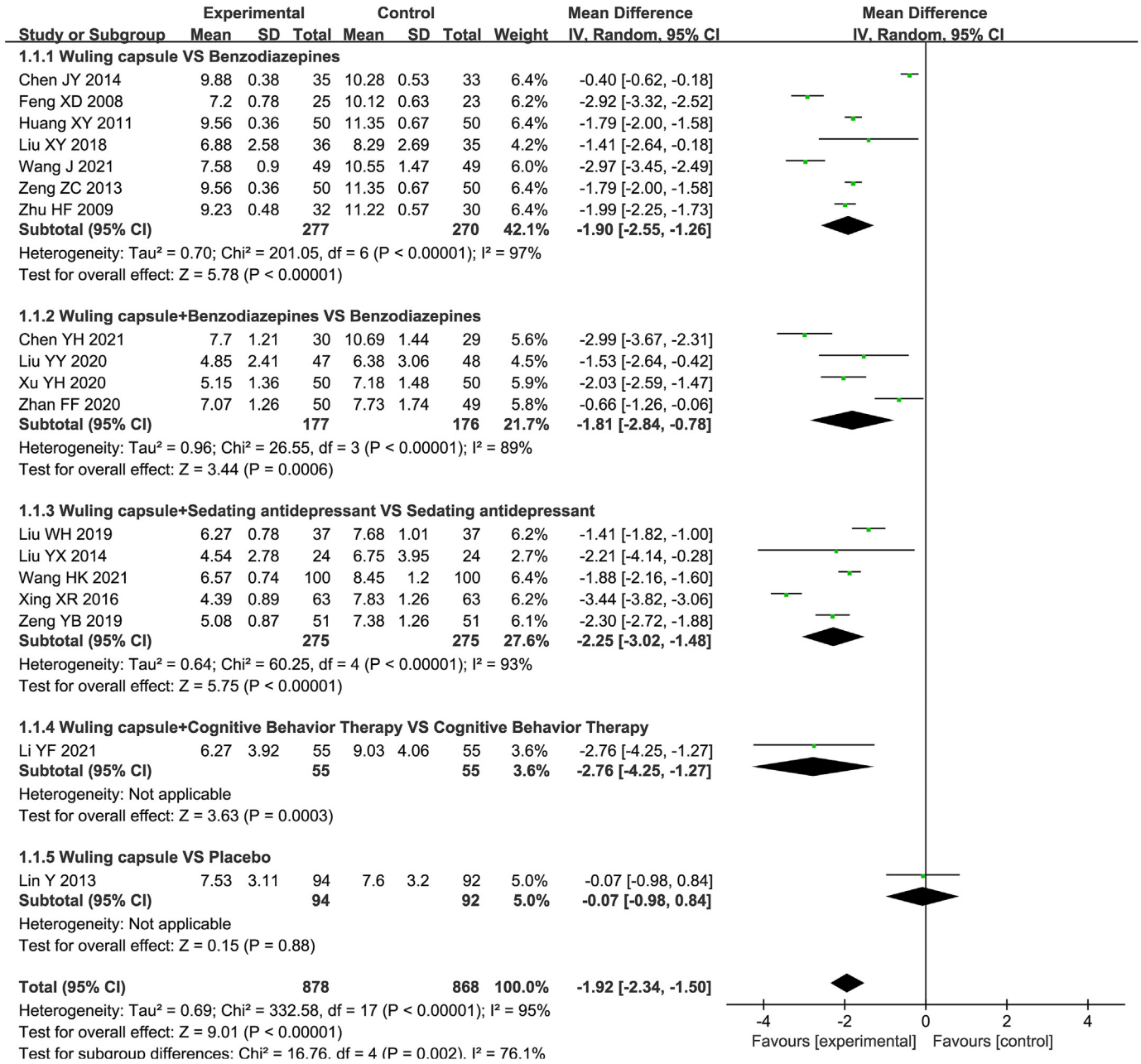

Fig. 3. Comparison of the sleep quality measured with PSQI between the Wuling capsule and controls.

did not describe the age and disease course of the subjects, so age and disease course of subjects could not be included as covariables in the meta-regression and further analysis. Therefore, the source of heterogeneity in this meta-analysis is still uncertain, and the results should be interpreted carefully.

3.6. Sensitivity analysis

Only one study (186 participants) had low risk of bias relating to allocation concealment and blinding of participants [52]. This trial showed that Wuling capsule was not superior to placebo assessed by PSQI. Result of the placebo-controlled RCT was not consistent with the pooled result of all included studies, so we cannot rule out the possibility that efficacy concluded might come from placebo effect rather than from Wuling capsule itself.

To assess if any study had a dominant effect on the meta-analysis result, the main summary estimate was evaluated after excluding each study separately. The results showed that the pooled effects of Wuling capsule for insomnia disorder did not change substantially if a single studies were omitted (Supplementary materials 2, Fig. S7).

3.7. Publication bias

Fig. 9 is a funnel diagram of the impact of Wuling capsule on PSQI in patients with insomnia disorder, showing asymmetry, indicating possible publication bias. Begge's test and egger's test respectively obtained $z = 0.27$ ($P = 0.791$) and $t = -0.84$ ($P = 0.411$), indicating that there was no publication bias in statistics. Although the probability of publication bias was statistically small, we still

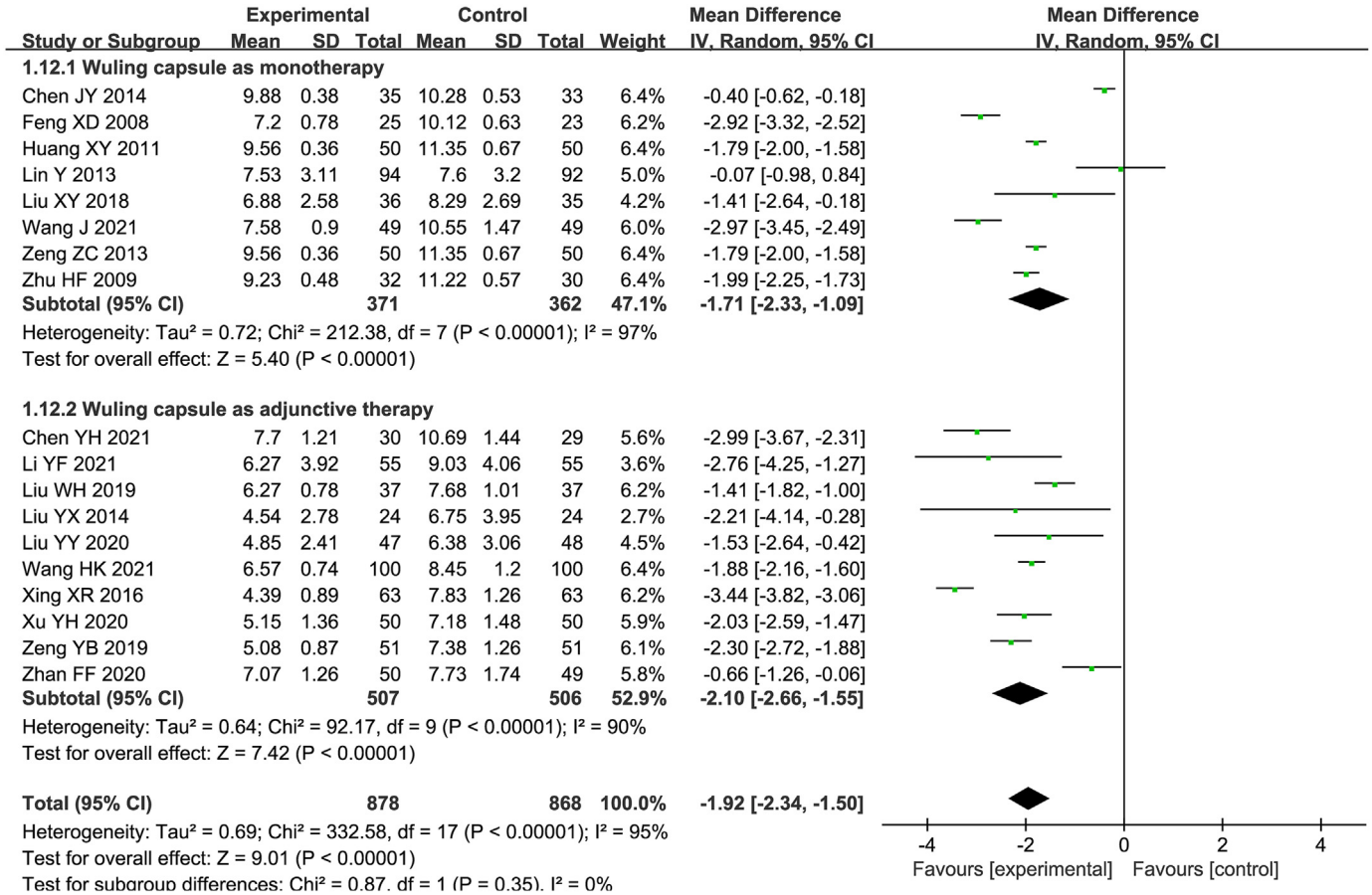

Fig. 4. PSQI of Wuling capsule as monotherapy or as adjunctive therapy vs control.

believed that there was a greater possibility of publication bias, because the published studies were all Chinese literature, and the positive results were easier to publish.

4. Discussion

This study is a systematic review to estimate the efficacy and safety of Wuling capsule for insomnia disorder. At the same time, we investigated the impact of different treatment strategies, different therapeutic course on the therapeutic effect, which brought more clinical significance to our results. Nineteen RCTs with a total of 1850 participants were eligible and were included. Pooled results revealed that Wuling capsule significantly improved sleep quality and reduced the severity of insomnia disorder. Through the subgroup analysis we found that the effect of Wuling capsule was significantly better than control no matter when Wuling capsule as monotherapy or as adjunctive therapy. At the same time, the effect of Wuling capsule as adjunctive therapy maybe superior to that as monotherapy, hence Wuling Capsule has add-on effect when used in combination with conventional drugs. As for the treatment duration we found that Wuling capsule significantly lowered PSQI score no matter the treatment duration lasted 4 weeks or 8 weeks, and we could find a trend that the longer the treatment duration last, maybe the better the treatment effect is. However, evaluated by Jadad score, the overall quality of the included studies was poor, and the sample size was rather small. Although most studies showed superior effect for Wuling capsule, however, one well-designed placebo-controlled clinical trial indicated that Wuling capsule was not superior to placebo. As placebo effect might play an important role in the treatment of insomnia disorder and mood disorders [68], placebo-controlled trials would be more convincing. Considering the previous fact, it could be concluded that Wuling Capsule maybe effective in treating insomnia disorder, but the clinical evidence is not sufficient. In terms of the safety assessment, fewer adverse events were reported in Wuling capsule group when compared to controls. This finding suggested that Wuling capsule may be safe for managing insomnia disorder.

The biological name of Wuling is Xylaria nigripe, which belongs to the Xylariaceae family of fungi, and its major component is Wuling mycelia [69]. Wuling mycelia is rich in amino acids, vitamins, glycosides, adenosine, microminerals and micronutrients. Among them, glutamic acid (Glu) accounts for the highest proportion of amino acids [70]. It is not only a key compound for energy metabolism and protein synthesis [34], but also an important neurotransmitter that plays a key role in long-term potentiation and plays an important role in learning and memory [71]. Under the catalysis of glutamate decarboxylase (GAD), glutamate can also produce inhibitory GABA in GABA-ergic neurons [34]. Pharmacological studies have shown that Wuling mycelium can increase the permeability of the excitatory neurotransmitter Glu and vitamin B6 in the brain tissue so as to enhance the activity of GAD, increase the synthesis of GABA, and increase the activity of its receptors, thus exerting a sedation and sleep-promoting properties [72]. Animal studies have also shown that Wuling mycelia may have the ability to increase the amount of glutamate and GABA in the brain and promote the activity of glutamate dehydrogenase, the synthesis of inhibitory neurotransmitter GABA as well as the binding activity of

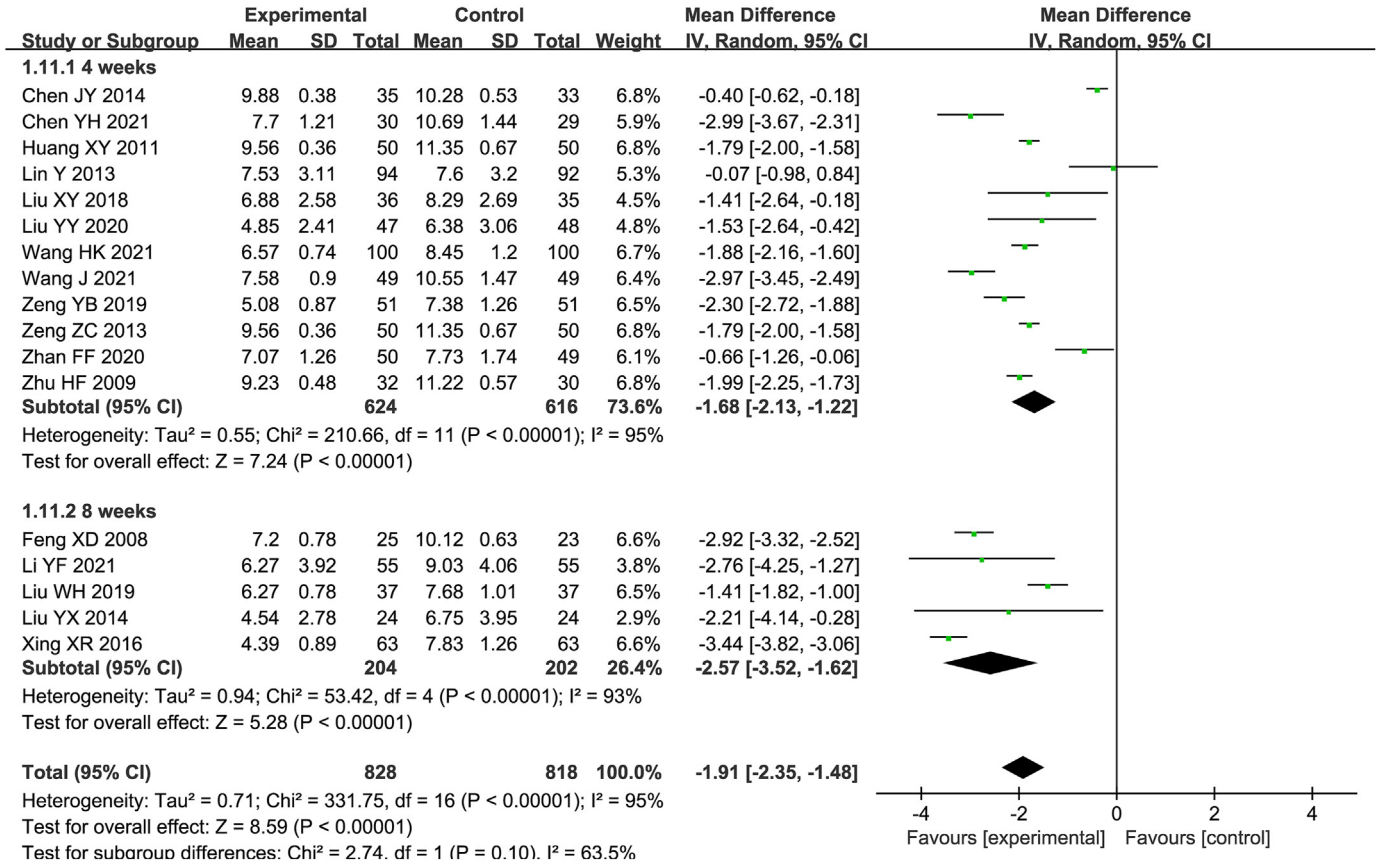

Fig. 5. Effects of different treatment duration of wuling capsule on the total score of PSQI.

GABA receptor in cerebral cortex, so as to mediate the function of the central nervous system [73].

On the other hand, Oxidative stress and inflammatory response play an important role in the pathogenesis of insomnia disorder [74]. Studies have found that the levels of inflammatory factor (TNF-α and IL-6) and oxidative stress indicators (SOD and MDA) were significantly decreased after the treatment with Wuling capsule [69]. Therefore, inhibiting oxidative stress and inflammation may be another potential mechanism for Wuling Capsules to improve insomnia disorder.

However, significant heterogeneity was found in this study, suggesting that effect estimates between studies may more variable than expected due to chance alone. The factors that may affect the clinical usage of Wuling capsule were analyzed. In particular, subgroup analysis showed that for PSQI scores after treatment, treatment duration was correlated with MD, suggesting that longer treatment duration was associated with larger effect size. Meta-regression results did not found the main sources of heterogeneity. Overall, the causes of the observed heterogeneity may be multimodal, and the interpretation of subgroup analysis and meta-regression are limited by their observational nature and inherent flaws, such as confounding and aggregation bias.

In terms of the risk of bias, some problems in the process of randomization are mainly caused by the lack of allocation concealment. However, the main risk of bias lies in the measurement of results. Participants may aware of their assignment even if not told. Since results are self-reported and subjective, the absence of blinding may affect outcome evaluation by placebo and/or nocebo effects. In addition, although PSQI was widely used in insomnia disorder research, such self-assessment report cannot replace the role of objective measurement tools (such as polysomnography) in the evaluation of insomnia disorder. Lacking of objective evaluation evidence may lead to selection bias in the final results. Furthermore, the definition of insomnia disorder varied across trials. Through the subgroup analysis we found that the effect of Wuling capsule was significantly better than control no matter the diagnostic criteria were CCMD-3, or CGDTAI, or DSM-5, or ICSD-3. However, one trial revealed that Wuling capsule was not superior to control when the diagnostic criteria was ICD-10. Due to these differences, a sensitivity analysis by removing the studies corresponding to the same diagnostic criteria separately was also conducted, and the results were stable. Although sensitivity analysis showed stable results, considering the differences between different diagnostic criteria, it may lead to selection bias by improper selection of subjects making the study results deviate from the true picture.

4.1. Comparison with previous studies

Only one systematic review and meta-analysis on the efficacy and safety of Wuling capsule for insomnia disorder [75] was conducted before. Compared to this meta-analysis, our meta-analysis has some preponderance. First, we searched related studies from more databases and the search strategy was more comprehensive, thus reducing bias of results due to incomplete literature search. Second, some newly-published studies were included in our meta-analysis. Third, in the meta-analysis, we performed subgroup analysis of the heterogeneous results from different aspects to make the results more stable.

In our review, we found positive correlation between treatment effect and treatment duration, and Wuling Capsule has add-on

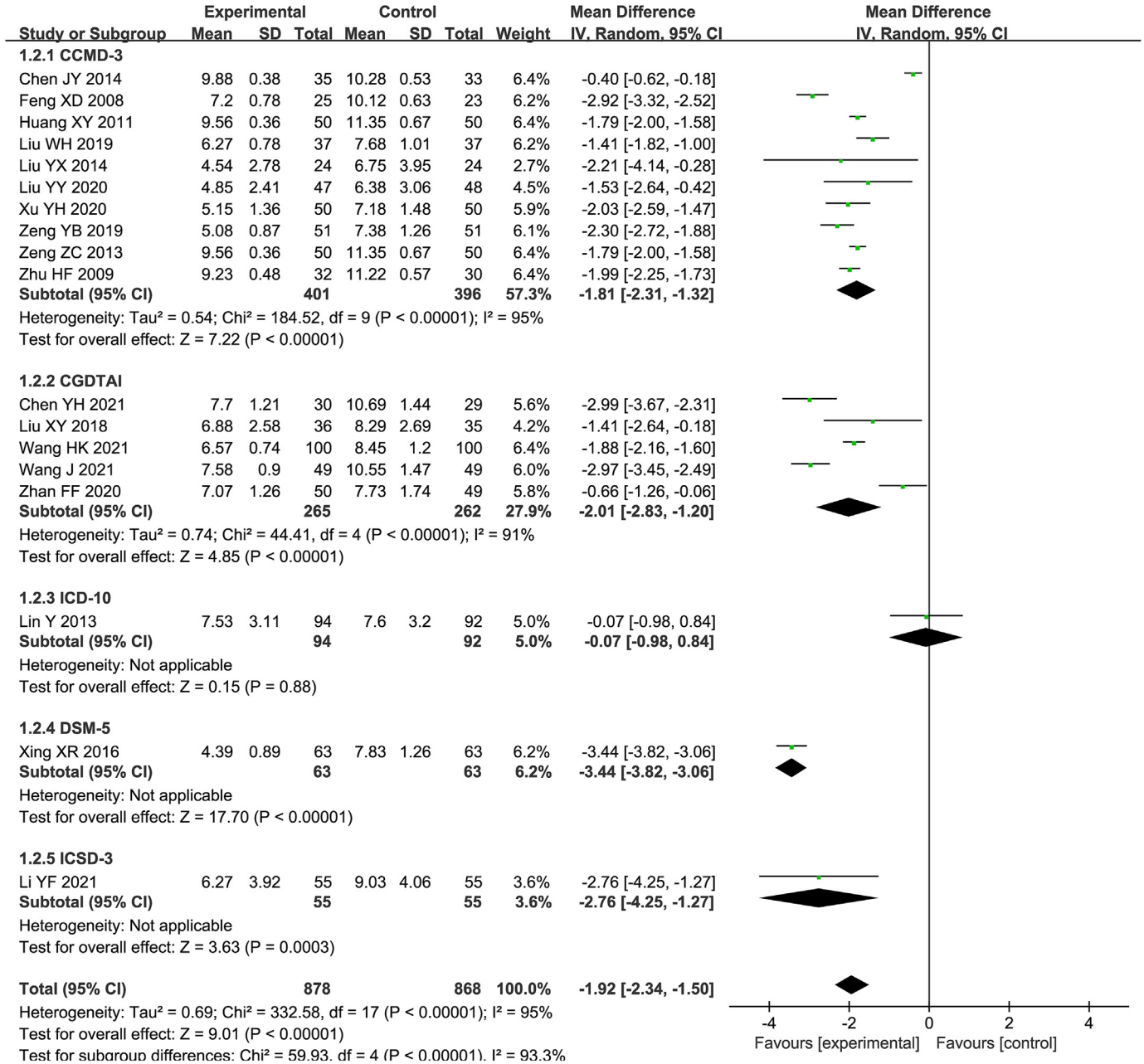

Fig. 6. Effect of Wuling capsules on the total PSQI score when different diagnostic criteria were used.

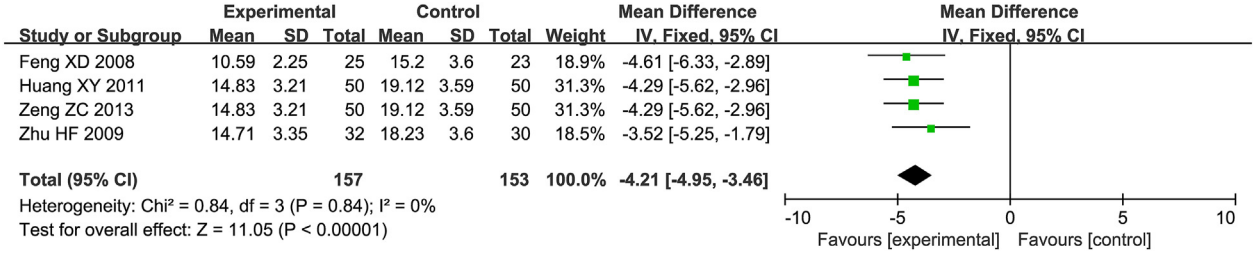

Fig. 7. Comparison of severity of insomnia disorder measured by SDRS between the Wuling capsule and controls.

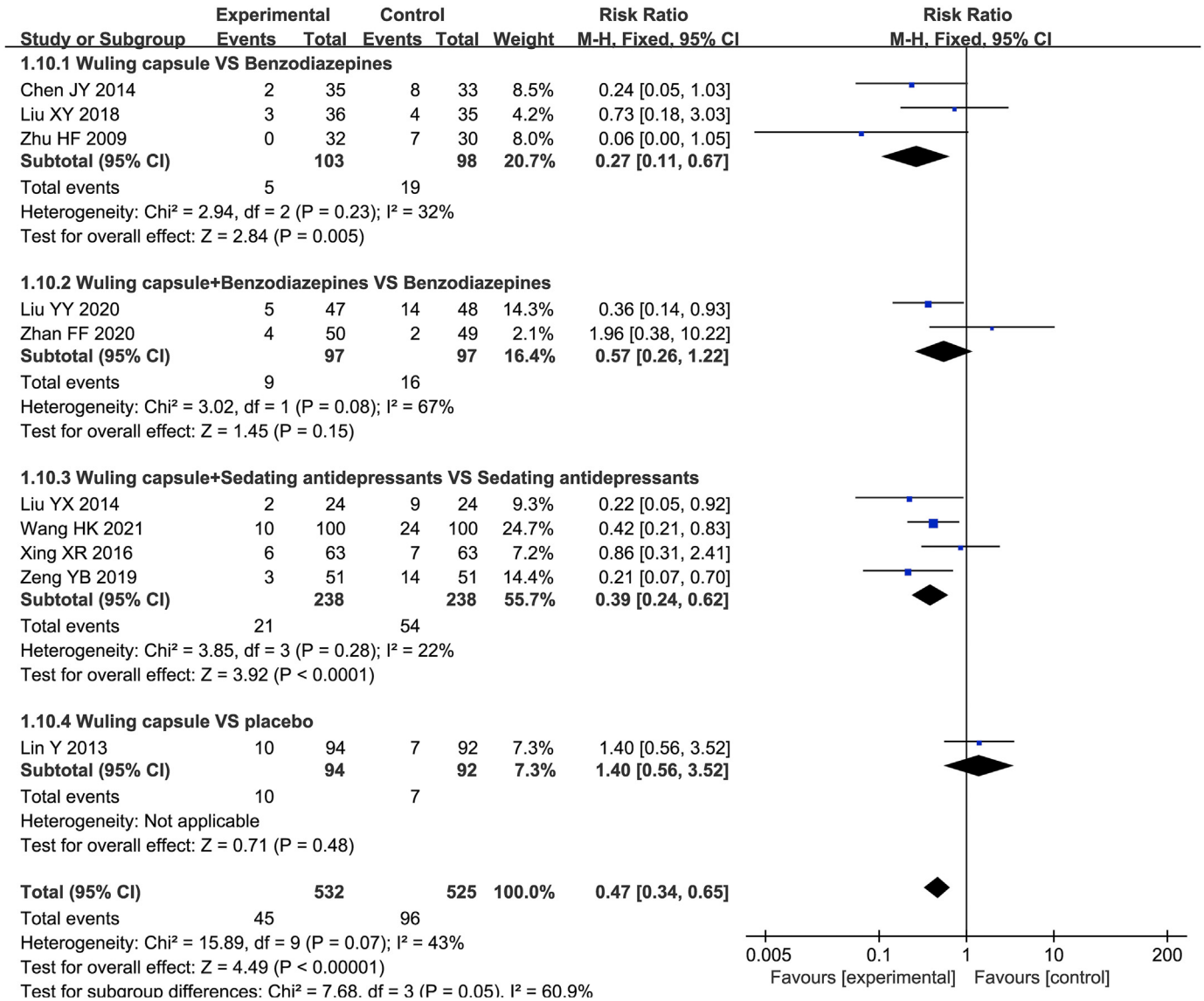

Fig. 8. Comparison of the number of adverse events between the Wuling capsule and controls.

effect when used in combination with conventional drugs, which was not noted in the previous meta-analysis. Our study carried out a more comprehensive, up-to-date, and PRISMA-compliant systematic review which provided more reliable clinical evidence.

4.2. Limitations

There are several limitations in this systematic review. First of all, most of the trials did not specify the specific details of random mode, allocation concealment and so on. This greatly weakens the credibility of the evidence. Second, only one trial was double-blind and placebo-controlled. Non-double-blind and non-placebo control may lead to performance bias and detection bias. Third, only 3 studies described loss of follow-up or withdraw, and only 1 of them carried out ITT analysis. Fourth, these trials did not describe the study plan or published the study protocol in advance, so there may be attrition bias and selective reporting bias in these studies. Fifth, insomnia disorder needs long-term treatment, but long-term follow-up was absent in these studies to evaluate the long-term efficacy of Wuling capsule. Sixth, all included studies in this meta-analysis used self-assessment scales such as the PSQI and SDRS as primary outcomes. It should be clearly noted that these indices are based on self-assessment, unlike physiological indices, and therefore may not be objective. As individuals have different understandings of the scales, responses to these scales would be influenced by the individual's overall bias toward more or less symptom reporting, which may result in benevolence bias, central tendency and common method bias, leading to inaccurate results [76]. Seventh, the definition of insomnia varies from trial to trial, and it may lead to selection bias due to different subject selection, skewing the study results from the true picture. Finally, the greater heterogeneity and publication bias of the results require us to interpret the final results carefully.

4.3. Implications for research

The findings of this study are not strong enough to support the use of wuling capsule as a treatment for insomnia disorder. For the future studies, first, we recommend that the design of RCTs and the reporting of clinical study results should be carried out in strict

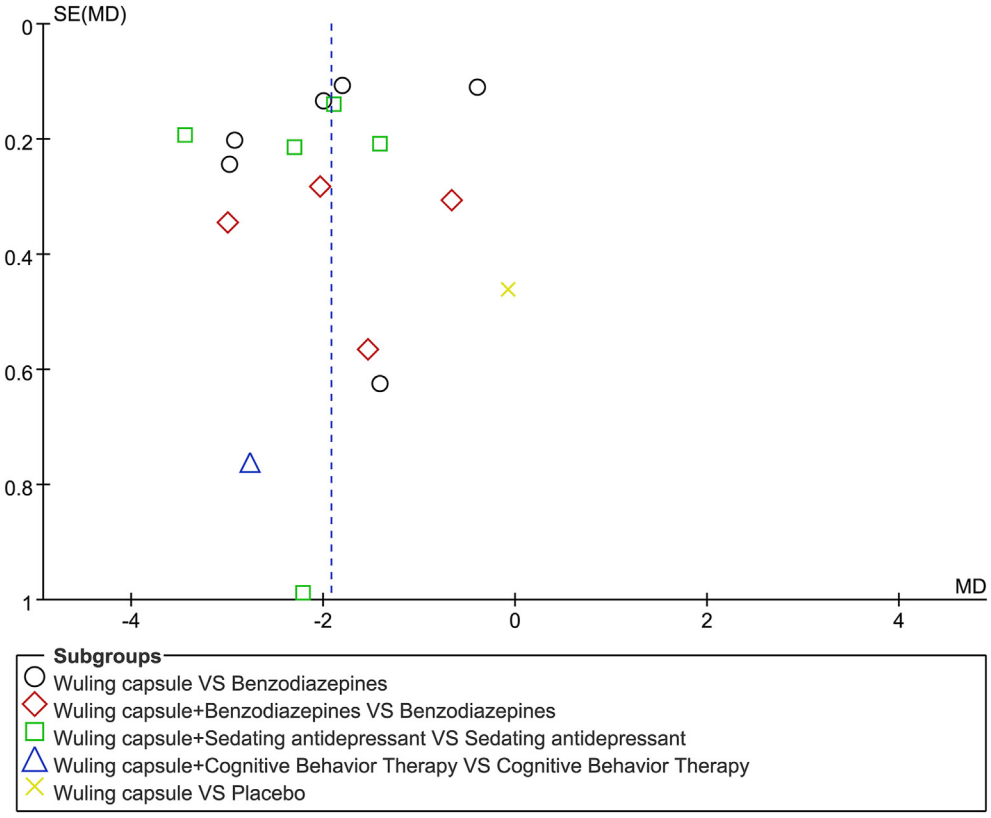

Fig. 9. Funnel plot of the included trials with PSQI data.

accordance with the requirements of the CONSORT 2010 statement to ensure the scientific quality and rigor of studies. Second, the outcome measures should contain not only subjective scales, but also validated objective examinations, such as polysomnography. Third, since insomnia disorder may fluctuate in a long course whether receiving treatment or not, continuous follow-up is important to determine the true efficacy and long-term effect of Wuling capsule. Fourth, now neuroimaging technology is widely used to investigate the neural correlates of insomnia disorder, so it is suggested to use neuroimaging technology to explore the possible mechanism of Wuling capsule for insomnia disorder.

5. Conclusions

Wuling capsule can safely and effectively improve sleep quality in patients with insomnia disorder. However, these findings require careful recommendation due to the high heterogeneity and high risk of bias in the included trials. Therefore, more randomized, double-blind, placebo-controlled trials that follow the CONSORT 2010 guideline are needed.

Authors' contributions

Lin Q, Zhou HF and Zhao Y conceived and drafted this systematic review and registered the protocol at PROSPERO. Zhou HF and Lin Q developed the search strategy and conducted the literature research, study selection, data extraction and risk of bias assessment. Han WB, Wang DY, Pan GZ, Peng WH, Wang ZC and Ren XX interpreted the evidence from methodological and clinical perspective. Zhou HF and Lin Q contributed to manuscript drafting. Wang X oversaw the conduct of the study. All authors have read, critically reviewed, and approved the final manuscript.

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2022.03.014.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.03.014.

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