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Review Article

Updated clinical evidence of Chinese herbal medicine for insomnia: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

This systematic review is to evaluate the efficacy and safety of Chinese herbal medicine (CHM) for people with insomnia. Randomized controlled trials (RCTs) investigating oral CHM alone or in combination with conventional therapies for primary insomnia were identified by searching English and Chinese publications and databases of clinical trial registration. Risk of bias was assessed according to the Cochrane Handbook 5.1. Meta-analysis was conducted using RevMan 5.2.4. Seventy-nine trials (7886 participants) were finally included in the review, and 76 were included in the meta-analysis. Twenty-seven trials reported the methods of random sequence generation, and five of them used the allocation concealment. Blinding of participants and personnel were used in 10 studies. The main meta-analysis showed that CHM alone was more effective than placebo by reducing scores of Pittsburgh Sleep Quality Index (mean difference, MD: –3.06, 95% confidence interval, CI: –5.14 to –0.98, $I^2 = 97\%$) and benzodiazepine drugs (BZDs) (MD: –1.94, 95% CI: –2.45 to –1.43, $I^2 = 96\%$). The effect was also seen when CHM was combined with BZDs compared with placebo plus BZDs (MD: –1.88, 95% CI: –2.78 to –0.97, $I^2 = 0\%$) or cognitive and behavioral therapy (MD: –3.80, 95% CI: –4.91 to –2.68, $I^2 = 68\%$) alone. There was no significant difference between CHM and placebo regarding the frequency of adverse events (relative risk, RR: 1.65, 95% CI: 0.67–4.10, $I^2 = 0$). Overall, oral CHM used as a monotherapy or as an adjunct to conventional therapies appears safe, and it may improve subjective sleep in people with insomnia. However, the typical effect of CHM for insomnia cannot be determined due to heterogeneity. Further study focusing on individual CHM formula for insomnia is needed. The development of a comparable placebo is also needed to improve the successful blinding in RCTs.

Abbreviations: AIS, Athens Insomnia Scale; BZDs, benzodiazepine drugs; BZRAs, benzodiazepine receptor agonists; CBT-i, cognitive behavior therapy for insomnia; CCMD, Chinese Classification and Diagnosis of Mental Disease; CGI, Clinical Global Impression; CGI-I, Clinical Global Impression-Improvement scale; CGI-S, Clinical Global Impression-Severity scale; CHM, Chinese herbal medicine; CI, confidence interval; CROs, Clinician-reported outcomes; DSM, Diagnostic and Statistical Manual of Mental Disorders; GABA, gamma-aminobutyric acid; GABAergic, gamma-aminobutyric acidergic; ICD, International Classification of Diseases; ISCD, International Classification of Sleep Disorders; ISI, Insomnia Severity Index; MCID, minimal clinical important difference; MD, mean difference; Non-BZDs, non-benzodiazepine drugs; PROs, patient-reported outcomes; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; RCTs, randomized controlled trials; RR, relative risk.

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1. Introduction

Insomnia is a common sleep disorder. Around one-third of adults experience the symptoms of insomnia, and approximately 6% meet the diagnosis of insomnia worldwide [1]. Insomnia can result in functional impairment as well as increase the risk of severe conditions such as depression and cardiovascular disease in the long term [2,3]. Growing evidence suggests that cognitive behavioral therapy for insomnia (CBT-i) is effective in improving subjective sleep outcomes [4]. However, it is underutilized in clinical practice because of difficulties in successful patient compliance [5] and high requirements of well-trained psychotherapists [6]. Pharmacotherapy such as benzodiazepine receptor agonists (BZRAs) is considered beneficial in improving sleep as well [7]. However, it is not without risks including tolerance and addiction from long-term use [8,9]. Therefore,

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new treatments with low risk to benefit ratio are needed for insomnia.

Chinese herbal medicine (CHM), originating from ancient China, has been used to treat insomnia for >2000 years in China [10]. In modern China, both traditional herbal formulae and patent herbal products coexist in the treatment of insomnia [11]. Furthermore, conventional medicine and CHM are coadministered frequently in clinical practice for sleep disorders [12–16]. In recent years, CHM has been increasingly used as a form of complementary and alternative medicine (CAM) in the Western world such as in America, Europe, and Australia [17]. Although the mechanism by which CHM improves sleep is not fully elucidated, preclinical studies have shown that some Chinese herbal formulae or single herbal ingredients have sedative–hypnotic functions, which is mediated by the gamma-aminobutyric acid-ergic (GABAergic) system [18]. For example, sour jujube seed (scientific name: *Ziziphus spinosa Hu*; pharmaceutical name: Semen Zizyphi Spinosae; and Chinese pinyin: suan zao ren) has been shown to enhance the activity of GABA, an inhibitory neurotransmitter, as a single herb [19] or as a main ingredient in a multi-herb formulation (known as sour jujube seed decoction), which modulates specific sedative effects by selective binding to the GABA(A) receptors [20].

The public perception of the benefit of CHM in improving overall sleep and the potential hypnotic effects in animal studies need to be supported through critical evaluation of the clinical evidence. Two previous systematic reviews concluded that there was insufficient evidence to support the efficacy of CHM for insomnia [21,22]. However, the latest Chinese evidence-based guideline for insomnia acknowledges the importance of CHM [11] without specific data on the role of CHM in clinical management for insomnia. Considering the growing number of clinical trials for CHM in recent years, it is important to update the search and evaluation to provide the best available evidence for insomnia. This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to answer four clinical questions for insomnia: (1) whether CHM is more effective than placebo; (2) whether CHM is more effective than conventional therapies such as BZRAs and psychotherapies; (3) whether the adjunct use of CHM provides better outcomes than conventional medicine alone; and (4) whether CHM is safe when used alone or in combination with conventional therapies.

2. Methods

2.1. Eligibility

2.1.1. Inclusion criteria

2.1.1.1. Study designs. The RCTs were eligible.

2.1.1.2. Participants. Participants of any age, gender, or ethnic background with the main complaint of insomnia were included. Insomnia needed to be defined by standard diagnostic instruments including International Classification of Sleep Disorders (ISCD) [23,24], Diagnostic and Statistical Manual of Mental Disorders (DSM) [25], Chinese Classification and Diagnosis of Mental Disease (CCMD) [26], International Classification of Diseases (ICD) [27], and other current guidelines [12,13,28–30].

2.1.1.3. Interventions and controls. Intervention included oral CHM treatment prepared in any form such as decoction, granule, capsule, and tablet. Studies that evaluated CHM combined with conventional therapies were also eligible. The comparators included placebo, pharmacotherapy routinely used such as benzodiazepine drugs (BZDs) and non-benzodiazepine drugs (non-BZDs), and psychotherapy such as CBT-i and sleep hygiene education. When another treatment was combined with CHM, the adjunct needed to be the same as the control.

2.1.1.4. Outcomes. The primary outcome was overall sleep quality measured by the Pittsburgh Sleep Quality Index (PSQI). PSQI is a well-validated and commonly used instrument for sleep quality assessment. The global scores (value range: 0–21 points) were calculated by its seven domains reported by patients, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction [31]. Higher scores indicated poorer sleep quality. It was translated into 56 additional languages including Mandarin Chinese [32]. In the Chinese population, its minimal clinically important difference (MCID) for Chinese medicine therapy was estimated to be 1.75 points by the standard error of measurement method or 1.54 by the distribution-based method [33]. Therefore, it was used as the threshold to assess the generalization of results to clinical practice.

Secondary outcomes included the following: (1) the total scores of the Athens Insomnia Scale (AIS) [34]; (2) the total scores of the Insomnia Severity Index (ISI) [35]; (3) the patient-rated sleep parameters such as sleep-onset latency, total sleep duration, sleep efficiency (ratio of time asleep to time on bed), and frequency of early awakenings; (4) objective sleep parameters measured by polysomnography (PSG), such as sleep-onset latency, total sleep duration, sleep efficiency, and times or duration of awakening after sleep onset; (5) clinical global impression (CGI) including the Clinical Global Impression-Severity scale (CGI-S) and Clinical Global Impression-Improvement scale (CGI-I) [36]; and (6) frequency and nature of adverse events.

2.1.2. Exclusion criteria

- Quasi-randomized controlled trials
- Insomnia defined as a symptom or a complaint only
- Insomnia induced by substances such as alcohol and drugs
- Participants with other sleep disorders, such as breathing-related sleep disorders, restless leg syndrome, narcolepsy, delayed sleep phase type of circadian rhythm sleep–wake disorders, and parasomnias
- Participants diagnosed with other mental disease and physical conditions
- Nonstandardized, but individualized, CHM and control for all participants
- Another form of Chinese medicine therapy such as acupuncture as control
- Pharmacotherapies not routinely recommended for insomnia, such as antihistamine drugs, as control
- No relevant outcomes

2.2. Database search and study selection

Five English databases (Cochrane Library, PubMed, EMBASE, CINAHL, and AMED), four Chinese databases (CBM, CNKI, CQVIP, and Wanfang), and five clinical trial registration databases (ClinicalTrials.gov, ICTRP, ChiCTR, EU-CTR, and ANZCTR) were comprehensively searched in May 2014. The search terms are specified in the Appendix A.

Two researchers (XN and JS) searched and screened the studies by finding duplications, excluding irrelevant titles and abstracts, and then selecting eligible studies by reviewing full texts.

2.3. Data extraction and management

Two researchers (XN and FL) extracted data in the manner of double entry and checking using EpiData Software, version 3.1 (EpiData Association, Odense, Denmark). Basic characteristics and outcome data were extracted, including authors, year of publication, diagnostic instrument, disease duration, stage, sample size, age, gender, details of intervention and control, information of

follow-up, outcomes, and adverse events. The data were exported from EpidData to Microsoft Excel 2010 to facilitate sorting. E-mails were sent to the authors for clarification if important data were unavailable, duplication was suspected, or when more than one article reported the same trial. Another researcher (JS) validated the final dataset and the translation into English.

2.4. Assessment of risk of bias in included studies

The risk of bias was appraised by two independent reviewers (XN and LZ) according to the Cochrane Collaboration's tool for assessing the risk of bias [37]. Seven domains were evaluated, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The assessment for blinding was made based on patient-reported outcomes (PROs) and clinician-reported outcomes (CROs). The objective sleep parameters rated by PSG were grouped as CROs because results can be affected by the assessors and assessment environments. Study protocols or registration information were used to help assess the risk of bias for selective reporting. The risk of other bias was judged by assessing baseline balance and funding source. Judgments were categorized as "low risk of bias," "high risk of biases," or "unclear risk of bias." Disagreement was resolved by discussion and consultation with a senior researcher (XG) when necessary.

2.5. Measures of treatment effect

Continuous outcomes were presented as mean difference (MD) with 95% confidence interval (CI) between two groups, whereas dichotomous data were presented as relative risk (RR) with 95% CI. RevMan software (Version 5.2.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used for data analysis.

For trials with more than one CHM intervention group such as CHM formula A versus CHM formula B versus pharmacotherapy, all relevant CHM groups were combined; for trials with more than one type of control such as CHM versus pharmacotherapy versus placebo, pair-wise comparison results were reported based on different class of comparators. When different outcomes for the same trial were reported in separate publications, the data were merged into one trial.

The predefined main comparisons in the meta-analysis were as follows: (1) CHM versus placebo, (2) CHM versus BZDs, (3) CHM versus non-BZDs, (4) CHM versus psychotherapy, (5) CHM plus BZDs versus placebo plus BZDs, (6) CHM plus non-BZDs versus placebo plus non-BZDs, (7) CHM plus psychotherapy versus placebo plus psychotherapy, (8) CHM plus BZDs versus BZDs, (9) CHM plus non-BZDs versus non-BZDs, and (10) CHM plus psychotherapy versus psychotherapy.

2.5.1. Subgroup analysis and solutions to heterogeneity

Clinical heterogeneity between trials for the primary outcome was addressed by further subgroup analysis noting important factors including treatment duration (≤4 weeks and >4 weeks), history of insomnia (<1 year and ≥1 year), and different preparations of CHM (decoction and non-decoction). Statistical heterogeneity was detected using a chi-squared test. The fixed-effect model was used to estimate the typical effect for studies with low heterogeneity ($I^2 < 50\%$), whereas the random-effects model was used to estimate the average distribution for studies with substantial unexplained heterogeneity ($I^2 \geq 50\%$).

2.5.2. Sensitivity analysis

Blinding of participants and allocation concealment are important for the PRO results. The primary outcome (PSQI) was a PRO, and sensitivity analysis was performed by only including trials with low risk of bias for blinding of participants and allocation concealment.

In studies comparing CHM with pharmacotherapies, the sensitivity analysis of PSQI scores was performed by including studies that removed the sixth domain (use of medication) because participants in the pharmacotherapy group would score higher on this domain.

Imbalance baseline can suggest failure of randomization [38]. Another sensitivity analysis was conducted by excluding the studies with the imbalance baseline of PSQI scores.

2.6. Publication bias

Publication bias was assessed when the subgroup included >10 studies.

3. Results

3.1. Description of included studies

3.1.1. Search results

The primary search identified 47,391 articles in literature databases and seven records in registries. Seventy-nine RCTs with 7886 participants published in 81 articles were finally included in the systematic review [39–119]. A total of 76 were also included in the meta-analyses [39–115,118]. The screening process is shown in Fig. 1.

3.1.2. Basic characteristics of the included studies

All included studies were randomized, parallel-group, controlled trials conducted in China between 2003 and 2014. Seven were multiarm studies [48,56,77,78,83,92,110], and the rest were two-arm studies. The treatment duration ranged from one week to three months (mean: 29 days, median: 29 days, mode: 28 days). Thirteen conducted follow-up ranging from one week to six months after the end of the treatment [43,45,63,65,80,81,87,89,100,101,103,108,116,117]. Participants ranged in age from 15 to 84 years, and insomnia was diagnosed by CCMD-3 in 64 studies [39,40,42–48,50–56,58–71,73,74,77–80,82,84,85,87,89–92,94–96,98–100,102,104–110,112–117,119], ICSD-2 in six studies [41,76,93,97,103,111], ICD-10 in seven studies [49,57,72,75,81,83,101,118], DSM-4 in one study [88], and Chinese national guideline in one study [86]. The duration of insomnia history ranged from one month to 30 years. The PSQI was reported in 59 studies [39–43,46–51,53–55,57,58,60–65,67,68,72–84,86–88,90–96,98–104,106,108,109,111,114,119], the AIS in eight studies [52,56,59,66,85,97,110,115], patient-rated sleep parameters in 13 studies [41,44,45,50,68,69,71,80,95,103,105,112], PSG-reported sleep parameters in two studies [76,94], and the CGI-S in four studies [70,89,107,113]. The ISI and the CGI-I were not reported in any study. Twenty-six studies used Chinese patent herbal products [41,48,54,58,60,64,67,71,74,75,80–83,91,93–96,99–101,103,104,108,111,119], and other studies used decoctions, the traditional form, and combination method. Sixty-six herbal formulae were investigated in the included studies. The most frequent formulae were *Xue Fu Zhu YuTang* (traditional decoction) and *Zao Ren An Shen Capsule* (patent product). The herb most commonly used was sour jujube seed. The complete characteristics of the included studies are shown in Tables 1 and 2.

3.2. Risk of bias in the included studies

Only one study registered the protocol in ChiCTR [76]. The risk of bias for other studies was assessed based on their publications. Twenty-seven studies (34.18%) reported adequate methods of random sequence generation, including computer

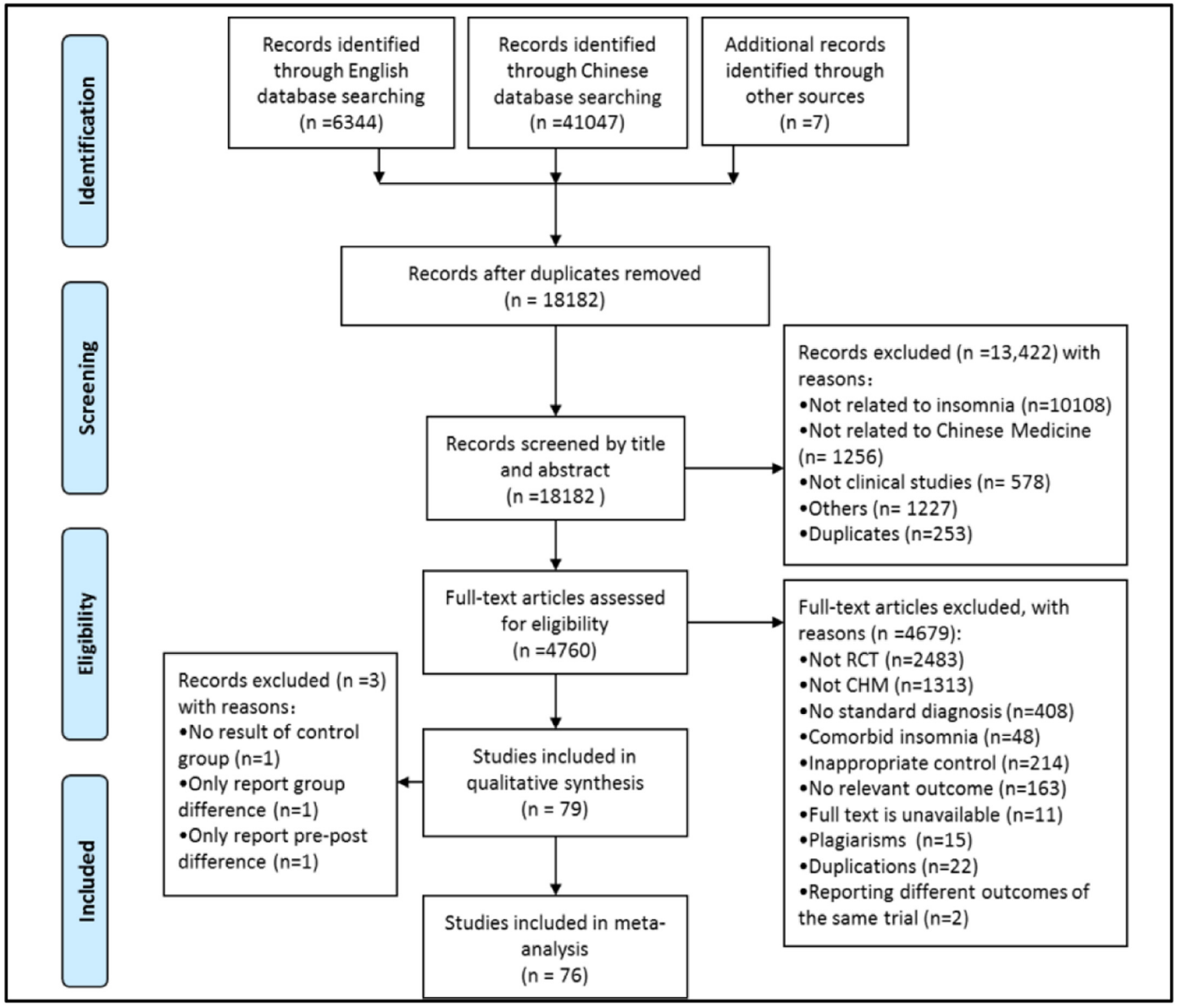

Fig. 1. Flowchart of study screening.

software [68,76,80,81,95,101,104], random number table [40,43,48,50,53,54,57,65,69,73,77,78,82–84,87,88,90,93,106,108], and drawing of lots [111]. Sequence allocation was concealed in five studies (6.33%) [68,75,80,81,95,101]. Blinding of participants and personnel were performed in 10 studies (12.66%) [41,63,68,76,80,81,94,95,101,104,108]. Only one study (1.27%) used an independent outcome assessor [76]. Two studies (2.53%) had high dropout rate with unreported reasons, and they did not appropriately treat missing data [76,87]. One study (1.27%) did not report its predefined primary outcome (PSQI scores) with unreported reason [112]. Three studies showed imbalance baseline (3.80%) [50,82,109]. Sixteen studies (20.25%) were supported by nonprofit institutions, such as by national scientific funding [75,76,95] or local scientific grant [43,46–48,64,73,77,78,84,85,87,93,111,115], and the rest did not declare the presence or absence of a conflict of interest and the funding sources. The risk of bias is summarized in Fig. 2.

3.3. Estimated effect of CHM on insomnia

3.3.1. Pittsburgh Sleep Quality Index

3.3.1.1. CHM alone versus control. In terms of sleep quality assessed by PSQI, CHM was more effective than placebo (MD: –3.06, 95% CI: –5.14 to –0.98, $I^2 = 97\%$; n = eight RCTs, 853 participants) [63,68,80,83,94–96,101] and BZDs (MD: –1.94, 95% CI: –2.45 to –1.43, $I^2 = 96\%$; $n = 35$ RCTs, 3361 participants) [40,42,43,46–51,53–55,57,60–62,64,67,72–75,82,83,86,87,90,93,98–100,102,103,106,114]. However, CHM was not superior to non-BZDs (MD: –0.16, 95% CI: –0.65–0.33, $I^2 = 57\%$; n = three RCTs, 323 participants) [39,65,84] or psychotherapy (MD: –1.23, 95% CI: –2.48–0.01, n = one RCT, 120 participants) [92]. A four-arm, double-blind, double-dummy RCT (33 participants) reported that CHM plus placebo of BZDs was not superior to BZDs plus placebo of CHM (MD: –2.10, 95% CI: –6.00–1.80) or placebo of BZDs plus placebo of CHM (MD: –1.60, 95% CI: –4.45–1.25) [76]. The results are shown in Fig. 3.

Table 1
Basic characteristic of the included studies.

Study	Arm	Randomized sample size: I/C	Age: mean (SD) years, I/C	Gender: M/F	Diagnostic instrument	Duration of insomnia history: mean (SD), I/C	Outcomes	Follow-up
Niu ZZ 2014 [87]	2	48/48	41.32 (7.46) /40.12 (8.66)	38/58	CCMD-3	28.36 (11.51) m/26.89 (13.65) m	PSQI	10 d
Li ZJ 2014 [79]	2	50/50	43.32 (11.31)/42.13 (12.41)	47/54	CCMD-3	28.36 (8.38) m/27.62 (7.68) m	PSQI	No
Cai TR 2013 [43]	2	98/49	46.2 (6.5)/47 (6.2)	56/91	CCMD-3	5.6 (1.2) y/5.9 (1) y	PSQI	3 m
Hou N 2013 [60]	2	54/54	42.3 (5.3)/43.5 (4.3)	NS	CCMD-3	NS	PSQI	No
Wang SM 2013 [94]	2	48/48	45.12 (11.51)/44.58 (12.17)	34/62	CCMD-3	27.16 (35.05) m/25.99 (32.17) m	PSQI and PSG	No
A M 2013 [39]	2	41/41	44.45 (8.33)/45.12 (7.76)	55/27	CCMD-3	6.32 (2.43) y/6.76 (2.01) y	PSQI	No
Gan JG 2013 [54]	2	60/60	67.2 (5)/66.5 (9.2)	46/74	CCMD-3	19.4 (6.1) m/20.6 (8.7) m	PSQI	No
Zhang XZ 2013 [112]	2	110/55	40.5 (8.6)/41.3 (9.2)	65/100	CCMD-3	16.5 (2.7) m/15.5 (2.8) m	Patient-rated sleep parameters	No
Huang HB 2013 [63]	2	33/33	28 (2.14)/30 (2.21)	32/34	CCMD-3	1.6 (0.61) y/1.4 (0.47) y	PSQI	30 d
Huang WM 2013 [97]	2	39/35	41.7 (10.5)/40.8 (9.8)	31/43	ICSD-2	19.2 (5.5) m/17.7 (4.7) m	AIS	No
Li GX 2013 [75]	2	35/35	49.93 (11.54)/52.7 (10.54)	27/34	WHO ICD-10	10.13 (13.42) y/11.94 (10.31) y	PSQI	No
Sun XA 2013 [91]	2	50/50	40.34 (12.6)/41.15 (12.7)	51/49	CCMD-3	2.64 (5.11) y/2.15 (4.18) y	PSQI	No
Yuan CX 2013 [108]	2	30/30	39.57 (12.38)/34.53 (11.73)	11/49	CCMD-3	2.18 (2.08) y/2.18 (1.98) y	PSQI	7 d
Lin YY 2013 [82]	2	30/30	70.85 (3.06)/71.14 (3.24)	27/33	CCMD-3	6.43 (3.88) y/6.55 (3.12) y	PSQI	No
Han YC 2013 [57]	2	32/32	45.2 (19.3)/40.7 (16)	26/38	WHO ICD-10	7.8 (3.4) m/8.3 (3.9) m	PSQI	No
Pan BX 2013 [88]	2	40/40	40.25 (11.71)/41.25 (15.3)	36/44	DSM-4	3.30 (5.29) y/3.22 (4.14) y	PSQI	No
Qian C 2012 [41]	2	158/52	44.97 (13.55)/42.75 (13.81)	74/136	ICSD-2	108.32 (44.12) d/111.79 (44.96) d	PSQI and patient-rated sleep parameters	No
Chen WM 2012b [46]	2	60/30	39.8 (12.77)/37.3 (12.39)	53/37	CCMD-3	28.2 (11.9) m/24.9 (12.3) m	PSQI	No
Zhang CL 2012 [51]	2	48/30	50/49	49/29	CCMD-3	1.9 y/1.8 y	PSQI	No
Sheng CJ 2012 [50]	2	25/21	56.1 (6.5)/57.3 (7.1)	18/28	CCMD-3	NS	PSQI and patient-rated sleep parameters	No
Yang YL 2012 [117]	2	60/60	73.15 (10.19)/73.18 (10.15)	81/39	CCMD-3	4.97 (2.11) y/4.95 (2.15) y	PSQI	6 m
Yang XC 2012 [99]	2	30/30	41 (12)/43 (13)	28/32	CCMD-3	7 m–1 y/6 m–21 y	PSQI	No
Chen WM 2012a [47]	2	50/30	38.95 (10.57)/38.35 (11.58)	43/37	CCMD-3	26.5 (10.8) m/25.9 (11.2) m	PSQI	No
Wang LH 2012 [93]	2	38/38	61 (12.4)/61 (12.8)	34/36	ICSD-2	NS	PSQI	No
Lou YY 2012 [109]	2	30/30	72.83 (6.18)/74.1 (7.33)	31/29	CCMD-3	4.13 (2.11) y/5.34 (4.2) y	PSQI	No
Li Y 2012 & Li Y 2013 [77,78]	3	30/30/30	NS	NS	CCMD-3	NS	PSQI	No
Li GR 2012 [74]	2	30/30	37.8/37.4	28/32	CCMD-3	NS	PSQI	No
Zhang HM 2012 [59]	2	32/34	34.32 (1.45)/32.34 (1.67)	27/39	CCMD-3	7.34 (0.65) m/9.13 (0.15) m	AIS	No
Li XL 2012 [102]	2	96/90	43 (2)/43.5 (1)	73/113	CCMD-3	1.5 (0.5) y/1.8 (0.2) y	PSQI	No
Miao WH 2012 [96]	2	30/29	44.46 (12.34)/43.51 (12.81)	18/41	CCMD-3	24.70 (29.74) m/17.48 (15.63) m	PSQI	No
Kuang JG 2012 [69]	2	40/40	73.8/74.1	43/37	CCMD-3	3.7 y/4.1 y	Patient-rated sleep parameters	No
Li DY 2012 [73]	2	52/52	45.9 (11.3)/44.54 (10.6)	41/63	CCMD-3	9.3 (4.7) m/10.7 (5.3) m	PSQI	No
Luo HO 2012 [84]	2	60/59	NS	46/71	CCMD-3	NS	PSQI	No
Zhu GQ 2012 [114]	2	34/34	NS	32/36	CCMD-3	NS	PSQI	No
Cai Y 2011 [44]	2	21/21	40.17 (11.26)/41.36 (11.48)	19/23	CCMD-3	15.92 (11.55) m/16.39 (12.21) m	Patient-rated sleep parameters	No
Qi GF 2011 [55]	2	40/40	51.2 (10.3)/53.5 (12.42)	36/44	CCMD-3	5.62 (2.35) y/6.30 (3.12) y	PSQI	No
Sun P 2011 [90]	2	40/40	66.7 (5.8)/67.1 (6.2)	25/55	CCMD-3	12.8 (6.4) m/13.28 (6.9) m	PSQI	No
Zhu WH 2011 [115]	2	31/30	NS	20/40	CCMD-3	NS	AIS	No
Huang XY 2011 [64]	2	50/50	44.58 (10.25)/44.2 (7.83)	40/60	CCMD-3	5.3 (1.5) y/5.1 (1.8) y	PSQI	No
Jia B 2011 [40]	2	39/39	50.63 (10.56)/47.76 (10.58)	37/41	CCMD-3	18 m/16 m	PSQI	No
Wang C 2011 [42]	2	60/60	39.3/37.6	54/66	CCMD-3	2.9 y/3.1 y	PSQI	No
Yang XH 2011 [105]	2	50/50	46.1/45	50/50	CCMD-3	9.78 m/9.44 m	Patient-rated sleep parameters	No
Jing XW 2011 [104]	2	21/27	41.82 (12.88)/42.37 (11.64)	12/35	CCMD-3	7.9 (3.84) y/5.7 (2.53) y	PSQI	No

(*continued on next page*)

Table 1 (*continued*)

Study	Arm	Randomized sample size: I/C	Age: mean (SD) years, I/C	Gender: M/F	Diagnostic instrument	Duration of insomnia history: mean (SD), I/C	Outcomes	Follow-up
Chen YY 2011 [49]	2	32/20	46.6 (1.5)/59.2 (0.9)	20/32	WHO ICD-10	3.2 (0.3) y/3.3 (0.4) y	PSQI	No
Xiao LG 2010 [72]	2	33/32	68.2 (18.3)/67.5 (19)	38/27	WHO ICD-10	38 (18.5) m/45 (16.2) m	PSQI	No
Jiang HQ 2010 [61]	2	183/183	71.9/70.8	176/188	CCMD-3	33.1(5.7) m/31.4 (7.1) m	PSQI	No
Wang ZT 2010 [95]	2	41/39	NS	NS	CCMD-3	NS	Patient-rated sleep parameters	No
Liao RD 2010 [116]	2	22/18	48.95 (1.468)/50.6 (1.911)	31/9	CCMD-3	NS	PSQI	3m
Huang D 2010 [62]	2	42/38	50.2 (9.2)/53.6 (8.7)	47/33	CCMD-3	9.56 (5.42) y/10.37 (6.63) y	PSQI	No
Wang F 2010 [53]	2	59/60	40.23 (10.79)/39.92 (11.47)	36/83	CCMD-3	37.49 (7.36) m/35.81 (9.92) m	PSQI	No
Tian J 2010 [66]	2	30/30	70 (7)/67 (5)	26/34	CCMD-3	NS	AIS	No
Huang Y 2010 [65]	2	62/62	47 (9)/48 (10)	60/64	CCMD-3	4.8 (1.2) y/4.16 (1.6) y	PSQI	4w
Song XH 2010 [81,101]	2	106/106	NS	54/147	WHO ICD-10	NS	CGI-S	2w
Lian FM 2009 [80]	2	71/36	43.14 (13.91)/44.73 (13.92)	39/68	CCMD-3	19.83 (27.13) m/20.92 (45.12) m	Patient-rated sleep parameters	1w
Xia CY 2009 [52]	2	60/60	42.18 (9.82)/42.75 (10.72)	33/87	CCMD-3	11.09 (14.27) m/11.84 (14.29) m	AIS	No
Zhang XP 2009 [111]	2	82/80	71.14 (3.24)/70.85 (3.07)	89/73	ICSD-2	6.51 (3.27) y/6.02 (3.45) y	PSQI	No
Xu HK 2009 [58]	2	42/40	56 (7)/58 (7)	36/46	CCMD-3	56 (7) m/92 (8) m	PSQI	No
Nie ZH 2009 [86]	2	50/45	37.81(10.42)/41.24 (9.14)	39/53	Chinese guideline	NS	PSQI	No
She YQ 2009 [106]	2	60/59	36.68 (8.53)/35.32 (9.13)	0/119	CCMD-3	3.22 (3.37) y/3.51 (3.67) y	PSQI	No
Li X 2008 [98]	2	68/52	36.64 (4.51)/37.26 (4.79)	60/60	CCMD-3	9 (4.85) m/8.89 (4.52) m	PSQI	No
Jiang LP 2008 [70]	2	34/34	44.8 (14.1)/39.26 (12.38)	31/37	CCMD-3	6.27 (4.18) m/5.91 (4.31) m	CGI-S	No
Feng XD 2008 [100]	2	25/23	NS	20/28	CCMD-3	NS	PSQI	Unclear
Zhang XM 2008 [103]	2	43/41	NS	38/46	ICSD-2	NS	PSQI and patient-rated sleep parameters	3m
Zhang JP 2008 [71]	2	30/30	41.26 (10.25)/40.3 (13.62)	36/24	CCMD-3	2.35 (5.22) y/2.25 (4.27) y	PSQI and patient-rated sleep parameters	No
Sun Y 2008 [118]	2	52/50	3836	44/58	WHO ICD-10	1.56 (1.04) y/1.61 (1.03) y	PSQI	No
Ren YJ 2007 [89]	2	50/50	NS	48/62	CCMD-3	NS	CGI-S	7d
Chang C 2006 [119]	2	19/18	18-65	12/25	CCMD-3	51.32 (73.32) m/60.14 (92.3) m	PSQI	No
Chen JF 2006 [67]	2	30/30	NS	28/32	CCMD-3	NS	PSQI	No
Zheng SY 2006 [113]	2	34/34	38.67 (15.42)/39.26 (12.38)	28/40	CCMD-3	6.27 (4.18) m/5.92 (4.33) m	CGI-S	No
Luo LC 2006 [85]	2	52/30	51.2/50.5	32/50	CCMD-3	2.6 y/2.5 y	AIS	No
Chen FQ 2005 [45]	2	180/90	42 (15.4)/41 (14.9)	100/170	CCMD-3	NS	Patient-rated sleep parameters	3m
Yu HT 2005 [107]	2	48/45	32.6 (8.9)/30.6 (8.4)	45/48	CCMD-3	2.2 (0.6) y/2.8 (4.6) y	CGI-S	No
Zhang JF 2003 [68]	2	113/114	44.09 (13.29)/44.97 (13.11)	68/159	CCMD-3	79.64 (102.66) m/71.89 (93.5) m	PSQI and patient-rated sleep parameters	No
Zhu T 2013 [92]	3	60/60/60	NS	71/109	CCMD-3	NS	PSQI	No
Chen H 2012 [56]	3	30/30/30	NS	75/15	CCMD-3	NS	AIS	No
Liu Y 2009 [83]	3	30/30/30	36.9 (11.48)/37.2 (11.36)/ 37.8 (11.38)	38/52	WHO ICD-10	8.9 (2.89) m/9.3 (2.18) m/9.8 (2.28) m	PSQI	No
Chen WQ 2008 [48]	3	68/72/76	62.19 (6.09)/64.32 (6.71)/ 66.19 (5.81)	108/108	CCMD-3	NS	PSQI	No
Zhan SQ 2008 [110]	3	39/21/40	43.8 (12.8)/47.1 (10.8)/44.6 (14.4)	35/65	CCMD-3	NS	AIS	No
Li Y 2009 [76]	4	NS	32.7 (9.2)/37.6 (10.3)/38.4 (13.8)/30 (9.7)	8/25	ICSD-2	56.1 (36.4) d/39 (37.7) d/51.1 (32.9) d/ 47.7 (33.2) d	PSQI and PSG	No

Abbreviations: AIS: Athens Insomnia Scale; BZDs: benzodiazepine drugs; C: control; CBT-i: Cognitive and behavioral therapy for insomnia; CHM: Chinese herbal medicine; CGI-S: Clinician Global Impression-Severity; CCMD-3: Chinese Classification and Diagnosis of Mental Disease, Third Edition; CGDTAI: Chinese Guideline on Diagnosis and Treatment for Adult Insomnia; DSM-4: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; d: day/days; F: female; M: male; m: month/months; I: intervention; ISCD-2: International Classification of Sleep Disorders, Second Edition; NS: not stated; PSQI: Pittsburgh Sleep Quality Index; PSG: polysomnography; WHO ICD-10: World Health Organization International Classification of Diseases, 10th Version; w: week/weeks; y: year/years.

Table 2
Details of the treatment in the included studies.

Study	Formula	[d]Herbal ingredients	[c]IM	Preparation	Dosage	Frequency	Comparator	Treatment duration
Niu ZZ 2014 [87]	Bu Shen Shu Gan Tang	*shu di, gou qi zi,sheng di, xuan shen, mai dong, dang gui, chuan xiong, chai hu, zhi ke, huang qin, huang lian, gan cao, ye jiao teng, bai he, zhen zhu mu*	N	decoction	1 pack decocted twice	bid	clonazepam tablet, 2–4 mg, qn	30 d
Li ZJ 2014 [79]	Jia Wei Chang Pu Yu Jin Tang	*shi chang pu, yu jin, huang lian, rou gui, yun fu shen, yuan zhi,bai zi ren*	Y	decoction	1 pack decocted 3 times	tid	estazolam tablet, 2 mg, qn	30 d
Cai TR 2013 [43]	Tiao Zhong Hua Tan An Shen He Ji	*suan zao ren, fu ling, chai hu, huang qin, zhi mu, fa ban xia, chuan xiong, chen pi, zhu ru, shou wu teng, zhen zhu mu, zhi shi,zhi gan cao*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1–2 mg qn	2 w
Hou N 2013 [60]	Mian An Ning Ke Li	*dan shen, shu di huang, shou wu teng, bai zhu, chen pi, yuan zhi,da zao*	N	granule	1 bag	bid	alprazolam tablet ,0.4 mg qn	3 w
Wang SM 2013 [94]	Zao Ren An Shen Pian	*he shou wu, suan zao ren, sang shen,he huan hua, bai zi ren, dang gui, shu di huang, yuan zhi,chai hu*	N	tablet	4 tablets	tid	Placebo	4 w
A M 2013 [39]	Zi Ni Yang Xin An Shen Tang	*sheng di huang ,mai men dong, dang gui, dan shen, ren shen, fu shen, bai zi ren, suan zao ren,ye jiao teng,zhi gan cao*	N	decoction	1 pack decocted 3 times	tid	zolpidem tablet, 5 mg, qn	4 w
Gan JG 2013 [54]	Zao Ren An Shen Jiao Nang	*suan zao ren, dan shen,wu wei zi*	N	capsule	5 tablets	qn	alprazolam tablet ,0.8 mg, qn	4 w
Zhang XZ 2013 [112]	Yang Yin An Shen Jiao Nang	*suan zao ren, wu wei zi, ye jiao teng, zhi mu, fu shen, he huan hua, dan shen, hu po,ling ci shi*	N	capsule	3 mg	bid	alprazolam tablet, 0.4–0.8 mg, qn	4 w
Huang HB 2013 [63]	Xie Cao	*xie cao*	N	powder	3 g	tid	Placebo	150d
Huang WM 2013 [97]	Wen Dan Tang plus Xue Fu Zhu Yu Tang Jia Jian	*fa ban xia, chen pi, zhu ru, zhi shi, fu ling, tao ren, hong hua, chi shao, chuan xiong, niu xi, sheng di huang,dang gui, ,jie geng,gan cao*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 2 mg, qn	30 d
Li GX 2013 [75]	Wen Dan Ning Xin Ke Li	*suan zao ren, dang shen, ban xia, chen pi, zhu ru, zhi shi, fu ling,shi chang pu, yuan zhi, shu di huang, long gu, mu li,zhi gan cao*	N	granule	6 g	tid	estazolam tablet, 1–2 mg, qn	4 w
Sun XA 2013 [91]	Shui Mian Ling	*ren shen, huang qi, wu wei zi, bai he, zhi yu cao,chao suan zao ren, ye jiao teng, dan shen, yuan zhi,fu ling, sheng di,nv zhen zi, chai hu, yu jin, he huan pi, shen qu, shan zha, you dong, bai zhu, zhi ke,ban xia*	Y	pill	10 g	tid	zopiclone tablet, 3.75 mg qn	4 w
Yuan CX 2013 [108]	Mei An Ke Li	*suan zao ren ,ren shen ,ci wu jia ,fu ling ,dang gui ,chuan xiong*	Y	granule	4.0 g	qn	placebo + estazolam, 1 mg, qn	2 w
Lin YY 2013 [82]	Jian Nao Ning Shen Ke Li	*suan zao ren ,bai zi ren ,huang lian ,zhi zi ,bai shao ,mai dong ,dan shen ,long gu ,zhen zhu mu ,yuan zhi ,bai he ,shou wu teng*	N	granule	1 bag	bid	estazolam tablet, 1 mg, qn	4 w
Han YC 2013 [57]	Tian Wang Bu Xin Dan	*bai shao ,dan shen ,chao zao ren ,bai zi ren ,bai he ,shou wu teng ,chao bai zhu ,fu ling ,sha ren ,ji nei jin ,zhen zhu mu ,duan long chi ,rou gui ,bai dou kou ,zhi gan cao ,zhi zi*	N	decoction	1 pack decocted 4 times	qid	alprazolam tablet ,0.4–0.8 mg,qn	4 w
Pan BX 2013 [88]	Jian Pi Shu Gan Tang plus Fu Fang Zao Ren Jiao Nang	*tang ji :dang shen ,fu chao bai zhu ,fu ling ,chen pi ,fa ban xia ,chao chai hu ,bai shao ,dang gui ,bo he ,yi yi ren ,shan yao ,zhi yuan zhi ,shou wu ,shen qu ,sha ren ,chao gu ya ,gan cao*	Y	Decoction + capsule	1 bag decocted twice;0.4g	bid; qn	estazolam tablet, 0.5–1 mg, qn	2 w
Qian C 2012 [41]	Nan Wu Wei Zi Jiao Nang	*nan wu wei zi*	Y	capsule	2 capsules	qn	Placebo	4 w
Chen WM 2012b [46]	Tian Wang Bu Xin Dan	*suan zao ren ,bai zi ren ,dang gui ,tian men dong ,mai men dong ,sheng di huang ,dang shen ,dan shen ,xuan shen ,fu ling ,wu wei zi ,yuan zhi ,ju geng*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1 mg qn	8 w
Zhang CL 2012 [51]	Zi Ni Yi Shen An Mei Tang	*shu di huang ,yin yang huo ,huang jing ,nv zhen zi ,wu wei zi ,bai shao ,suan zao ren ,sheng long gu,sheng mu li ,fo shou ,gan song*	N	decoction	1 pack decocted twice	bid	diazepam tablet, 5 mg qn	1 m

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Table 2 (*continued*)

Study	Formula	[d]Herbal ingredients	[c]IM	Preparation	Dosage	Frequency	Comparator	Treatment duration
Sheng CJ 2012 [50]	Jian Pi He Wei Zhong Yao	*yi yi ren ,huai shan yao ,fu ling ,ze xie ,zhu ling ,chen pi ,jiao san xian ,pu gong ying ,suan zao ren ,gan cao*	N	decoction	NS	NS	diazepam tablet, 5–10 mg, qn	10 d
Yang YL 2012 [117]	Suan Zao Ren Shui	*suan zao ren*	N	decoction	1 pack decocted once	qn	benzodiazepine drugs without details	1 w
Yang XC 2012 [99]	Jie Yu Wan	*zi shao ,chai hu ,dang gui ,fu ling ,gan cao ,xiao mai ,da zao ,yu jin ,he huan pi*	N	pill	4 g	bid	estazolam tablet, 1–2 mg, qn	4 w
Chen WM 2012a [47]	Gui Pi Tang	*huang qi ,dang shen ,bai zhu ,dang gui ,fu shen ,suan zao ren ,yuan zhi ,mu xiang ,gan cao ,long yan rou*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1 mg, qn	8 w
Wang LH 2012 [93]	Er Dong Yang Xin Kou Fu Ye	*di huang,tian dong,mai dong,huang qi,dang shen,bai zhu*	N	oral solution	20 ml	bid	estazolam tablet, 1 mg qn	4 w
Lou YY 2012 [109]	Wen Yang Huo Xue Ning Xin Fang	*dang gui ,zhi fu pian ,tao ren ,hong hua ,chuan xiong ,gua lou ke ,chi shao ,sheng di ,shi chang pu ,jiu yuan zhi ,suan zao ren ,ye jiao teng ,zhen zhu mu*	Y	decoction	1 pack decocted once	qd	estazolam tablet, 1 mg, qn	4 w
Li Y 2012 & Li Y 2013 [77,78]	1.Qing Zhen Tang; 2.Jia Wei Wen Dan Tang	*1. huang lian ,sha shen ,bai he ,dan shen ,yuan zhi ,niu xi ,shi ju pu ,gan cao ,rou gui ,fu ling ,zhu ru ,yan huang bai ,long gu ,mu li, zhu ye,ge gen ,yu jin; 2. chen pi ,fa ban xia ,fu ling ,zhi shi ,zhu ru ,shi chang pu ,dan nan xing ,zhi mu ,yuan zhi ,zhen zhu mu ,ye jiao teng ,chuan xiong ,bai he ,chao zao ren ,gan cao*	Y	decoction	1 pack decocted once	qd	CBT	8 w
Li GR 2012 [74]	Zao Ren An Shen Jiao Nang	*chao suan zao ren ,dan shen ,cu zhi wu wei zi*	N	capsule	5 capsules		estazolam tablet, 1 mg, qn	2 w
Zhang HM 2012 [59]	Xue Fu Zhu Yu Tang	*chai hu ,zhi ke ,chi shao ,tao ren ,chuan hong hua ,dang gui ,chuan xiong ,sheng di ,niu xi ,ju geng*	N	decoction	1 pack decocted 3 times	tid	estazolam tablet, 1 mg, qn	4 w
Li XL 2012 [102]	Xue Fu Zhu Yu Tang	*tao ren ,hong hua ,dang gui ,sheng di huang ,chuan xiong ,chi shao ,niu xi ,ju geng ,chai hu ,zhi ke ,gan cao*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1 mg, qn	4 w
Miao WH 2012 [96]	Xin Ren Shen An Jiao Nang	*sheng di huang,suan zao ren,lian zi xin,yuan zhi,chen pi,gan cao*	N	capsule	1.35 g	tid	Placebo	4 w
Kuang JG 2012 [69]	Tian Ma Gou Teng Yin	*tian ma ,gou teng ,shi jue ming ,du zhong ,niu xi ,shan zhi ,huang qin ,ye jiao teng ,fu shen*	N	decoction	1 pack decocted twice	bid	diazepam tablet, 2.5 mg, qn	4 w
Li DY 2012 [73]	He Wei An Shen Fang	*ban xia ,yi yi ren ,shi chang pu ,fu ling ,bai zhu ,he huan pi ,ye jiao teng ,chao zao ren ,*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1 mg, qn	4 w
Luo HO 2012 [84]	He Wei An Shen Fang	*ban xia ,sheng yi ren ,chen pi ,fu ling ,bai zhu ,chai hu ,chao huang qin ,ye jiao teng ,zhi gan cao*	N	decoction	1 pack decocted twice	bid	zolpidem tablet, 10 mg, qn	4 w
Zhu GQ 2012 [114]	Gan Cao Xie Xin Tang	*gan cao ,dang shen ,huang qin ,huang lian ,gan jiang ,ban xia ,da zao*	N	decoction	1 pack decocted twice	bid	alprazolam tablet ,0.4–0.8 mg, qn	12 w
Cai Y 2011 [44]	Zi Ni Shu Gan Qing Xin Tang	*chai hu ,yu jin ,fo shou ,zhi zi ,he huan pi ,ye jiao teng ,suan zao ren ,bai shao ,chuan lian zi ,fu shen ,an mu xiang ,zhi mu ,gan cao*	N	decoction	1 pack decocted twice	bid	diazepam tablet, 2.5–5.0 mg, qn	2 w
Qi GF 2011 [55]	Zi Ni Qing Hua Zi Yin Fang	*ban xia ,xia ku cao ,jiang can ,yu jin ,huang lian ,bai he ,zhi mu ,fu ling ,yuan zhi ,chao zao ren ,sheng di huang ,dang gui ,dan shen ,ye jiao teng ,sheng long chi*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1 mg, qn	28 d
Sun P 2011 [90]	Zi Ni Jie Yu Hua Tan An Shen Tang	*huang lian ,dan nan xing ,chai hu ,bai shao ,zhi ke ,xiang fu ,zhu ru ,ban xia ,chang pu ,yu jin ,fu ling ,ye jiao teng ,yuan zhi ,sheng gan cao*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 2 mg, qn	30 d
Zhu WH 2011 [115]	Wu Ling Jiao plus Nang Zao Ren An Shen Jiao Nang	*wu ling jun*	N	capsule	3capsules	tid, qn	estazolam tablet, 1 mg, qn	30 d
Huang XY 2011 [64]	Wu Ling Jiao Nang	*wu ling jun*	N	capsule	3 capsules	tid	diazepam tablet, 5 mg, qn	4 w

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Table 2 (*continued*)

Study	Formula	[d]Herbal ingredients	[c]IM	Preparation	Dosage	Frequency	Comparator	Treatment duration
Jia B 2011 [40]	Wen Bu Zhen She Fang	*zhi fu zi ,rou gui ,yin yang huo ,ling ci shi ,long chi ,zhen zhu mu ,wu wei zi ,chang pu ,yuan zhi ,zhi gan cao*	N	decoction	1 pack decocted twice	bid	diazepam tablet, 5 mg, qn	30 d
Wang C 2011 [42]	Qing Xin Ning Shen Fang	*lian zi xin ,jiu huang lian ,shui niu jiao ,lian qiao ,shan zhi ,zhu ye ,wu wei zi ,mai dong ,yuan zhi ,chang pu ,yu jin ,suan zao ren ,bai zi ren*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1 mg, qn	4 w
Yang XH 2011 [105]	Gui Pi Tang	*huang qi ,fu ling ,bai zhu ,dang shen ,suan zao ren ,mu xiang ,yuan zhi ,zhi gan cao ,long yan rou ,dang gui ,bai zi ren ,ye jiao teng ,he huan pi*	N	decoction	1 pack decocted 3 times	tid	estazolam tablet, 1 mg, qn	4 w
Jing XW 2011 [104]	Xin Shen Ning Pian	*suan zao ren ,fu ling ,shou wu teng ,shen qu ,wei zi*	Y	tablet	6 tablets	tid	placebo + estazolam tablet, 1 mg, qn	3 w
Chen YY 2011 [49]	Chai Hu Jia Long Mu Tang plus Ban Xia Xie Xin Tang	*chai hu ,huang qin ,huang lian ,ban xia ,dang shen ,gui zhi ,bai shao ,gan jiang ,sheng long gu ,sheng mu li ,ye jiao teng ,gan cao ,da zao*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 2 mg, qn	8 w
Xiao LG 2010 [72]	Bu Xin An Shen Hua Tan Fang	*shu di huang ,bai shao yao ,e jiao ,suan zao ren ,fu shen ,bai zi ren ,chen pi ,fa ban xia ,zhu ru ,he huan pi*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 1.3 mg, qn	6 w
Jiang HQ 2010 [61]	Fu Zha Zao Ren Tang	*fu ling ,shan zha ,suan zao ren*	N	decoction	1 pack decocted twice	bid	alprazolam tablet , 0.4–0.8 mg, qn	3 w
Wang ZT 2010 [95]	San Qi Ke Li	*suan zao ren ,ji xue teng ,san qi ,xiao ji*	N	granule	1 bag	qd	Placebo	4 w
Liao RD 2010 [116]	No Name Formula	*sang ye ,ju hua ,tian ma ,gou teng ,chai hu ,long gu ,mu li ,yu jin ,shi chang pu ,chi bai shao ,dan shen ,he huan pi*	N	decoction	1 pack decocted once	qd	estazolam tablet, 1–2 mg, qn	2 w
Huang D 2010 [62]	Xue Fu Zhu Yu Tang	*tao ren ,hong hua ,dang gui ,chuan xiong ,sheng di huang ,chi shao ,chai hu ,zhi ke ,niu xi ,ju geng ,gan cao*	N	decoction	1 pack decocted twice	bid	alprazolam tablet, 0.8 mg, qn	4 w
Wang F 2010 [53]	Jie Yu Ning Shen Fang	*chai hu ,yu jin ,bai zi ren ,dang shen ,bai zhu ,shan yao ,suan zao ren ,shan yu rou ,yuan zhi ,fu shen ,bai he ,sheng long mu ,zhen zhu mu ,hu po ,tao ren*	N	decoction	1 pack decocted twice	bid	diazepam tablet, 5 mg qn	28 d
Tian J 2010 [66]	Shen Qi Wu Wei Zi Pian	*wu wei zi ,dang shen ,huang qi ,suan zao ren*	N	tablet	3 tablets	tid	estazolam tablet, 1 mg, qn	8 w
Huang Y 2010 [65]	An Shen Gao	*lian zi ,qian shi ,fu ling ,hei zhi ma ,mi zao ren ,bai zi ren ,ye jiao teng ,yuan zhi ,e jiao*	N	soft extracts	15 ml	qn	zopiclone tablet, 7.5 mg, qn	6 w
Song XH 2010 [81,101]	Wu Ling Jiao Nang	*wu ling jun*	N	capsule	0.99 g	tid	Placebo	4 w
Lian FM 2009 [80]	Chan Ye An Shen Jiao Nang	*tian zhu huang ,can tui ,shou wu teng ,jiang can ,di long ,bai shao ,gou teng ,fa ban xia ,suan zao ren ,yuan zhi*	N	capsule	2 g	qd	Placebo	3 w
Xia CY 2009 [52]	Xia's No.1 Sleep Prescription	*huang qi, bai zhu, suan zao ren,ye jiao teng, he huang pi, dan shen, huai xiao mai, fu ling, zhi yuan zhi, long gu, e jiao*	N	decoction	1 pack decocted twice	bid	Estazolam, 1 mg, qn	6 w
Zhang XP 2009 [111]	Shen Song Yang Xin Jiao Nang	*ren shen ,mai dong ,wu wei zi ,sang ji sheng, shan zhu yu,suan zao ren ,dan shen ,chi shao ,tu bie chong ,gan song ,huang lian ,long gu*	Y	capsule	1.6g	qn to tid	CBT	12w
Xu HK 2009 [58]	Yin Dan Xin Nao Tong Ruan Jiao Nang	*yin xing ye ,deng zhan xi xin ,dan shen ,jiao gu lan ,san qi ,bing pian ,shan zha ,da suan*	Y	capsule	0.8g	bid	estazolam tablet, 2 mg, qn	4 w
Nie ZH 2009 [86]	Rou Gan Ning Shen Tang	*suan zao ren ,long chi ,bai shao ,ye jiao teng ,he huan pi ,yu jin ,dan pi ,chao zhi zi ,gua lou pi ,fu ling ,*	N	decoction	1 pack decocted twice	bid	alprazolam tablet, 0.4–0.8 mg, qn	2 w
She YQ 2009 [106]	No Name Formula	*suan zao ren ,chuan xiong ,fu ling ,zhi mu ,gan cao*	N	decoction	1 pack decocted twice	bid	diazepam tablet, 5 mg, qn	4 w
Li X 2008 [98]	Zhu Mian Tang	*ye jiao teng ,chao zao ren ,wu wei zi ,lian zi rou ,bai zi ren ,shi chang pu ,yuan zhi ,fu ling ,zhi mu ,zhu ru ,ban xia ,gan cao*	N	decoction	1 pack decocted twice	bid	alprazolam tablet , 0.4–0.8 mg, qn	20 d
Jiang LP 2008 [70]	Jie Yu Wan	*bai shao ,chai hu ,dang gui ,yu jin ,fu ling ,bai he ,he huan pi ,gan cao ,xiao mai ,da zao ,*	N	pill	12 g	tid	estazolam tablet, 2–12 mg, bid	6 w
Feng XD 2008 [100]	Wu Ling Jiao Nang	*wu ling jun*	N	capsule	3 capsules	tid	alprazolam tablet, 0.4–0.8 mg, qn	60 d

(*continued on next page*)

Table 2 (*continued*)

Study	Formula	[d]Herbal ingredients	[c]IM	Preparation	Dosage	Frequency	Comparator	Treatment duration
Zhang XM 2008 [103]	An Shen Jiao Nang	*suan zao ren ,zhi mu ,dan shen ,fu ling ,chuan xiong ,mai dong ,zhi shou wu ,wu wei zi*	N	capsule	4 capsules	tid	alprazolam tablet, 0.4–0.8 mg, qn	8 w
Zhang JP 2008 [71]	Ye He Jian Nao Pian	*ye jiao xi ,he huan pi ,wu wei zi ,yuan zhi*	Y	tablet	5 capsules	tid	zopiclone tablet, 7.5 mg, qn	4 w
Sun Y 2008 [118]	Zi Ni Wu Hua Shu Gan Tang	*fo shou hua ,dai dai hua ,lv e mei ,chuan piao hua ,mei gui hua ,shou di ,dang gui ,bai shao ,chao bai zhu ,zhi gan cao*	N	decoction	1 pack decocted twice	bid	alprazolam tablet, 0.4–0.8 mg, qn	4 w
Ren YJ 2007 [89]	Zao Ren An Shen Jiao Nang	*suan zao ren ,dan shen ,wu wei zi*	N	capsule	5 capsules	qn	estazolam tablet, 1 mg, qn	16 d
Chang C 2006 [119]	Xin Ren Shen An Jiao Nang	*sheng di huang ,suan zao ren ,lian zi xin ,yuan zhi ,chen pi ,gan cao*	Y	capsule	3 capsules	tid	Placebo + sleep hygiene education	4 w
Chen JF 2006 [67]	Tian Meng Jiao Nang	*huang jing ,huang qi ,dang shen ,ci wu jia ,yin yang huo (zhi),shan yao ,ze xie ,fu ling ,gou qi zi ,shu di huang ,ma qian zi (zhi)*	N	capsule	3 capsules	bid	alprazolam tablet, 0.4–0.8 mg, qn	1 m
Zheng SY 2006 [113]	Bai Lian Tang	*bai he ,lian zi xin ,chao zao ren ,shan yu rou ,sheng mu li ,fu shen ,mai dong ,wu wei zi ,shi chang pu ,chuan bei mu ,he huan pi*	N	decoction	1 pack decocted twice	bid	estazolam tablet, 2–12 mg, bid	6 w
Luo LC 2006 [85]	Yi Shen Qiang Shen Yin	*rou cong rong ,huang jing ,huang qi ,shan zha ,jue ming zi*	N	granule	4.5g	qd	diazepam tablet, 5 mg, qn	1 m
Chen FQ 2005 [45]	An Shui Chong Ji	*chai hu ,dang gui ,xia ku cao ,gou teng ,dan shen ,sheng di ,long yan rou ,bai he ,zhen zhu mu ,ye jiao teng*	N	granule	9–18 g	tid	diazepam tablet, 2.5–5.0 mg, qn	1 m
Yu HT 2005 [107]	Jia Wei Suan Zao Ren Tang	*suan zao ren ,zhi mu ,chuan xiong ,fu ling ,long gu ,chi shao ,wu wei zi ,yuan zhi ,gan cao*	Y	decoction	1 pack decocted once	qd	lorazepam tablet, 0.5–1.5 mg, qn	4 w
Zhang JF 2003 [68]	Suan Zao Ren Gao	*suan zao ren ,zhi mu ,fu ling ,chuan xiong*	N	soft extracts	20 g	bid	Placebo	4 w
Zhu T 2013 [92]	Yang Xin An Shen Tang	*bai zi ren ,ye jiao teng ,he huan pi hua,fu shen ,chao zao ren ,dang gui ,bai shao ,hu po mo ,wu wei zi ,chen pi ,zhi ke*	N + Y	decoction	1 pack decocted twice	bid	CBT	4 w
Chen H 2012 [56]	Bai Le Mian Jiao Nang	*bai he ,ci wu jia ,shou wu teng ,suan zao ren ,he huan hua ,zhen zhu mu ,shi gao ,fu ling ,yuan zhi ,dang can ,sheng di huang ,mai dong ,wu wei zi ,deng xin cao ,dan can*	N + Y	capsule	4 capsules	bid	zolpidem, 10 mg, qn	8 w
Liu Y 2009 [83]	Zao Ren An Shen Jiao Nang	*zao ren ,dan can ,wu mei zi*	N	capsule	5 capsules	qn	[a]1: estazolam tablet, 1 mg, qn; 2: placebo, 5 capsule, bid	3 w
Chen WQ 2008 [48]	Nao Kang II	*zhi shou wu ,shou di ,san qi ,chang pu*	N + Y	oral solution	50 ml	bid	diazepam tablet, 2.5 mg, qn	4 w
Zhan SQ 2008 [110]	Huo Li Su Kou Fu Ye	*zhi shou nia ,gou qi zi ,zhi huang jing ,huang qi ,yin yang huo ,dan can*	N + Y	oral solution	10 ml	bid	zolpidem, 5–10 mg, qn	4 w
Li Y 2009 [76]	Jia Wei Xiao Yao San	*suan zao ren, fu shen, chai hu, dang gui,bai shao, bai shu, gan cao,bao he ,wei sheng jiang*	N + Y	decoction	1 pack decocted twice	bid	1. Estazolam 1 mg, qn + placebo of CHM; 2.placebo of CHM + placebo of estazolam[b]	6 w

Notes: Abbreviations: CBT-i: cognitive behavior therapy for insomnia; CHM: Chinese herbal medicine; IM: integrative medicine; N: no, stating Chinese herbal medicine is used alone; Y: yes, stating Chinese herbal medicine is used as an adjunct to conventional medicine; N + Y: stating there are two intervention groups, one for Chinese herbal medicine and the other for integrative medicine; d: day/days; m: month/months; w:week/weeks; y:year/years.

[a] There are two groups of control: pharmacotherapy and placebo.

[b] This is a study including four groups: Chinese herbal medicine plus placebo of pharmacotherapy, Chinese herbal medicine plus pharmacotherapy, pharmacotherapy plus placebo of Chinese herbal medicine, and placebo of Chinese herbal medicine plus placebo of pharmacotherapy.

[c] When Chinese herbal medicine is used as an adjunct to conventional medicine, the control is the same as the conventional medicine in intervention group.

[d] The herbal ingredients are presented as Chinese pinyin. The correspondent scientific names are specified in the book "Dan Bensky, editor. Chinese Herbal Medicine: Materia Medica, Third Edition. Seattle, WA: Eastland Press, Inc; 2004."

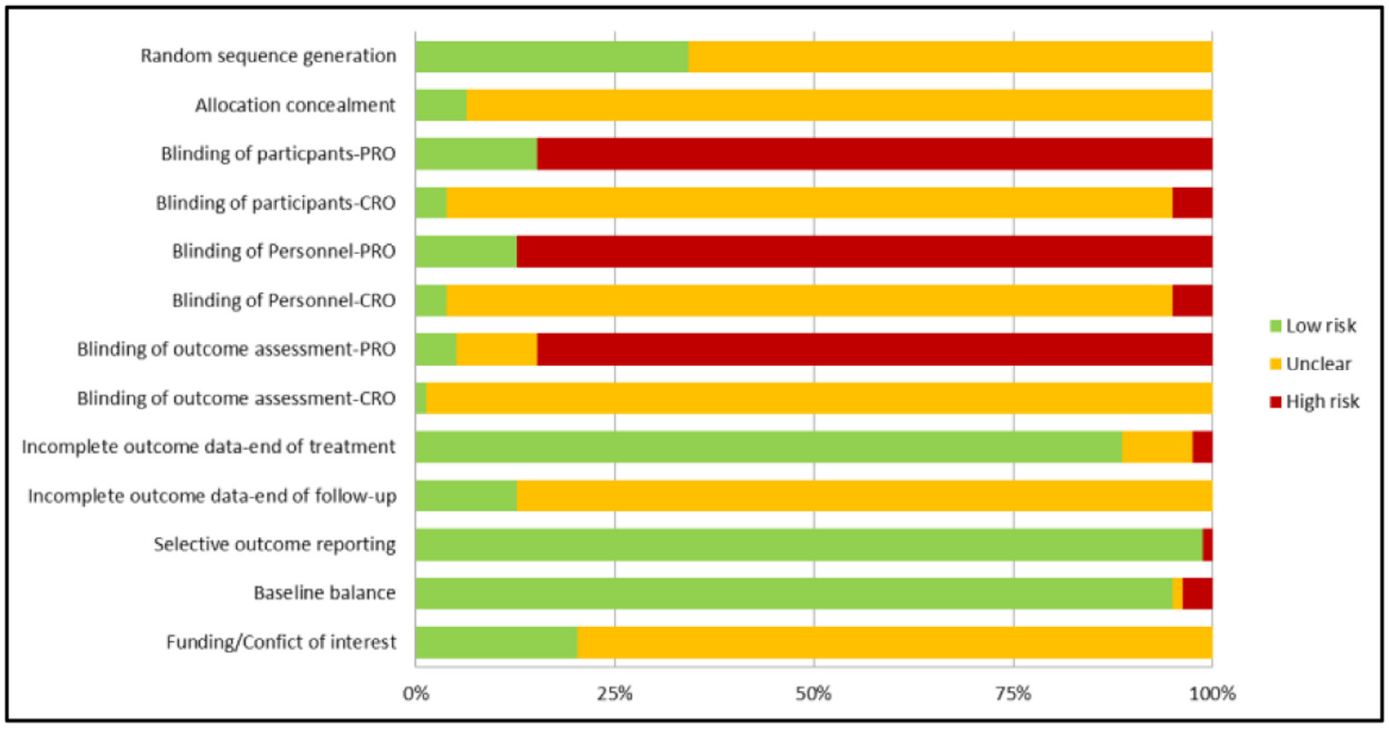

Fig. 2. Risk of bias in included studies. CRO: clinician-reported outcome; PRO: patient-reported outcome.

At the end of follow-up ranging from 1 week to 3 months, CHM group had a significantly better effect on the PSQI scores than placebo (MD: –6.30, 95% CI: –12.58 to –0.02, I^2 = 97%; n = two RCTs, 158 participants) [63,80],, BZDs (MD: –3.61, 95% CI: –5.81 to –1.40, I^2 = 97%; n = three RCTs, 228 participants) [87,100,103], and non-BZDs (MD: –2.70, 95% CI: –3.33 to –2.07; n = one RCT, 124 participants) [65]. The results are showed in Supplementary Fig. S1.

3.3.1.2. CHM plus conventional medicine versus control. In terms of sleep quality assessed by the PSQI scores, the effect of CHM plus BZDs was significantly better than that of placebo plus BZDs (MD: –1.88, 95% CI: –2.78 to –0.97, I^2 = 0; n = three RCTs, 121 participants) [76,104,108] and BZDs alone (MD: –3.19, 95% CI: –4.40 to –1.99, I^2 = 89%; n = five RCTs, 462 participants) [48,58,79,88,109]. CHM plus psychotherapy was more effective than psychotherapy alone (MD: –3.80, 95% CI: –4.91 to –2.68, I^2 = 68%; n = three RCTs, 372 participants) [77,78,92,111]. However, CHM plus non-BZDs was not superior to non-BZDs alone (MD: –1.15, 95% CI: –2.49–0.19; n = one RCT, 96 participants) [91]. One RCT (193 participants) reported that CHM plus sleep hygiene education was not superior to placebo plus sleep hygiene education (MD: –0.81, 95% CI: –2.26–0.64) [41]. The results are shown in Fig. 4.

At the end of a 7-day follow-up, the effect of CHM plus BZDs on PSQI scores was not superior to placebo plus BZDs (MD: –1.43, 95% CI: –3.04–0.18; n = one RCT, 60 participants) [108]. The results are shown in Supplementary Fig. S2.

3.3.2. Athens Insomnia Scale

3.3.2.1. CHM alone versus control. In terms of global sleep quality evaluated by the AIS, CHM was more effective than BZDs (MD: –1.42, 95% CI: –2.21 to –0.64, I^2 = 63%; n = six RCTs, 463 participants) [52,59,66,85,97,115], but not more effective than non-BZDs (MD: 0.14, 95% CI: –0.26–0.54, I^2 = 0%; n = two RCTs, 121 participants) [56,110]. The results are shown in Supplementary Fig. S3.

3.3.2.2. CHM plus conventional medication versus control. The effect of CHM plus non-BZDs on the AIS scores was similar to that of non-BZDs alone (MD: –0.57, 95% CI: –0.95 to –0.19, I^2 = 0%; n = two RCTs, 120 participants) [56,110]. The results are shown in Supplementary Fig. S4.

3.3.3. Patient-rated sleep parameters

3.3.3.1. Sleep-onset latency. In terms of sleep-onset latency reported by patients, CHM was more effective than placebo (MD: –19.87 min, 95% CI: –26.93 to –12.82 min, I^2 = 0%; n = three RCTs, 395 participants) [68,80,95], but not more effective than BZDs (MD: –13.81 min, 95% CI: –31.27–3.65 min, I^2 = 92%; n = three RCTs, 329 participants) [69,103,112]. There was no significant difference between the effect of CHM plus non-BZDs and non-BZDs alone (MD: –1.93 min, 95% CI: –11.30–7.44 min; n = one RCT, 60 participants) [71] or CHM plus sleep hygiene and BZDs plus sleep hygiene (MD: –2.81 min, 95% CI: –8.17–2.55 min; n = one RCT, 193 participants) [41]. The results are shown in Supplemental Figs. S5 and S6. At the end of a 3-month follow-up period, participants who received CHM reported shorter sleep-onset latency than those who received BZDs (MD: –32.00 min, 95% CI: –45.84 to –18.16 min; n = one RCT, 84 participants) [103].

3.3.3.2. Total sleep duration. In terms of total sleep duration reported by patients, CHM was more effective than placebo (MD: 0.78 h, 95% CI: 0.55–1.01 h, I^2 = 0%; n = three RCTs, 395 participants) [68,80,95] and BZDs (MD: 1.12 h, 95% CI: 0.36–1.87, I^2 = 95%; n = seven RCTs, 783 participants) [44,45,50,69,103,105,112]. The results are shown in Supplemental Fig. S7. At the end of a 3-month follow-up period, participants who received CHM reported longer total sleep duration than those who received BZDs (MD: 1.60 h, 95% CI: 1.08–2.12 h; n = one RCT, 84 participants) [103].

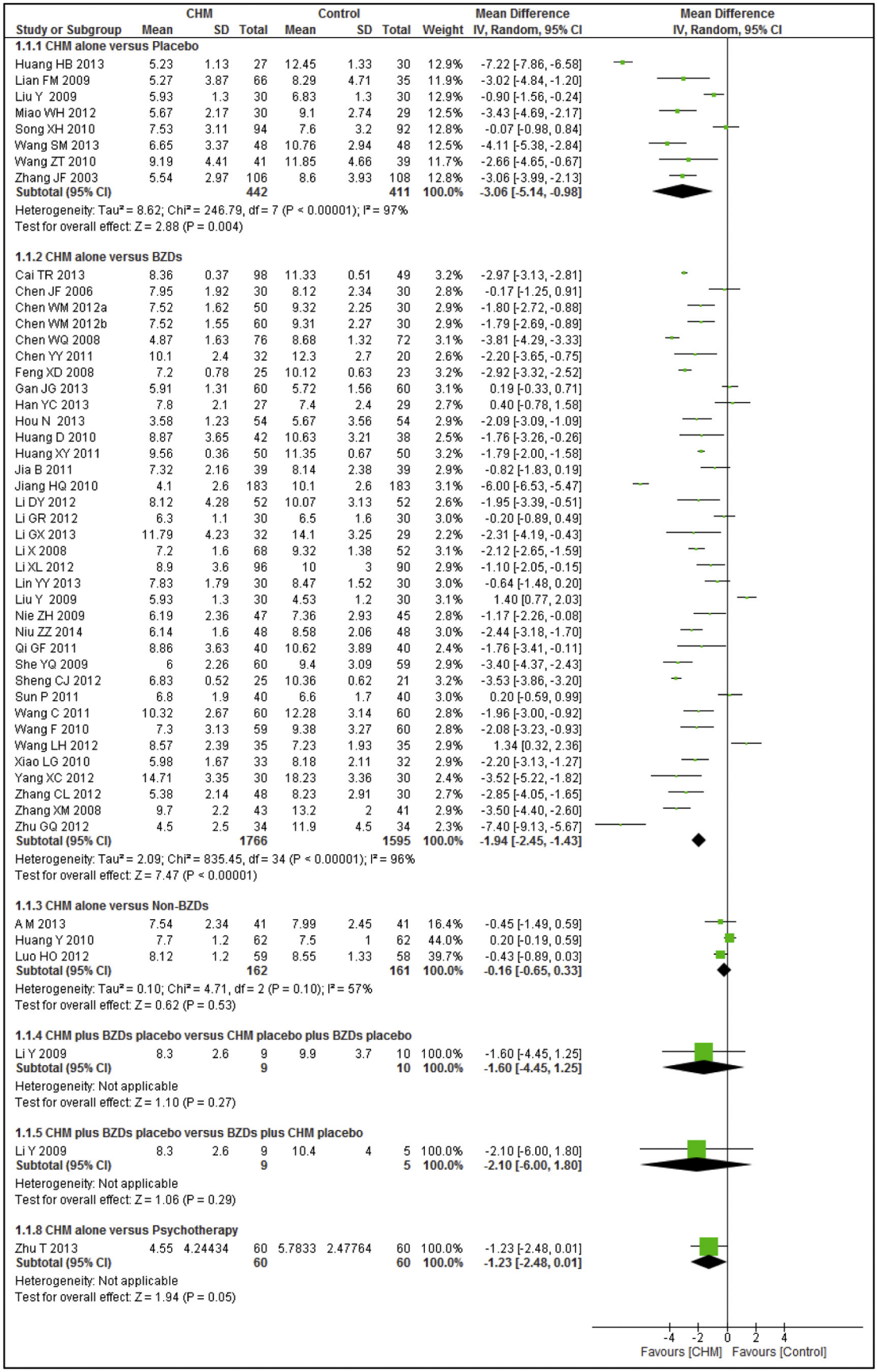

Fig. 3. PSQI of CHM versus control. PSQI: Pittsburgh Sleep Quality Index; CHM: Chinese herbal medicine; BZDs: benzodiazepine drugs; non-BZDs: non-benzodiazepine drugs.

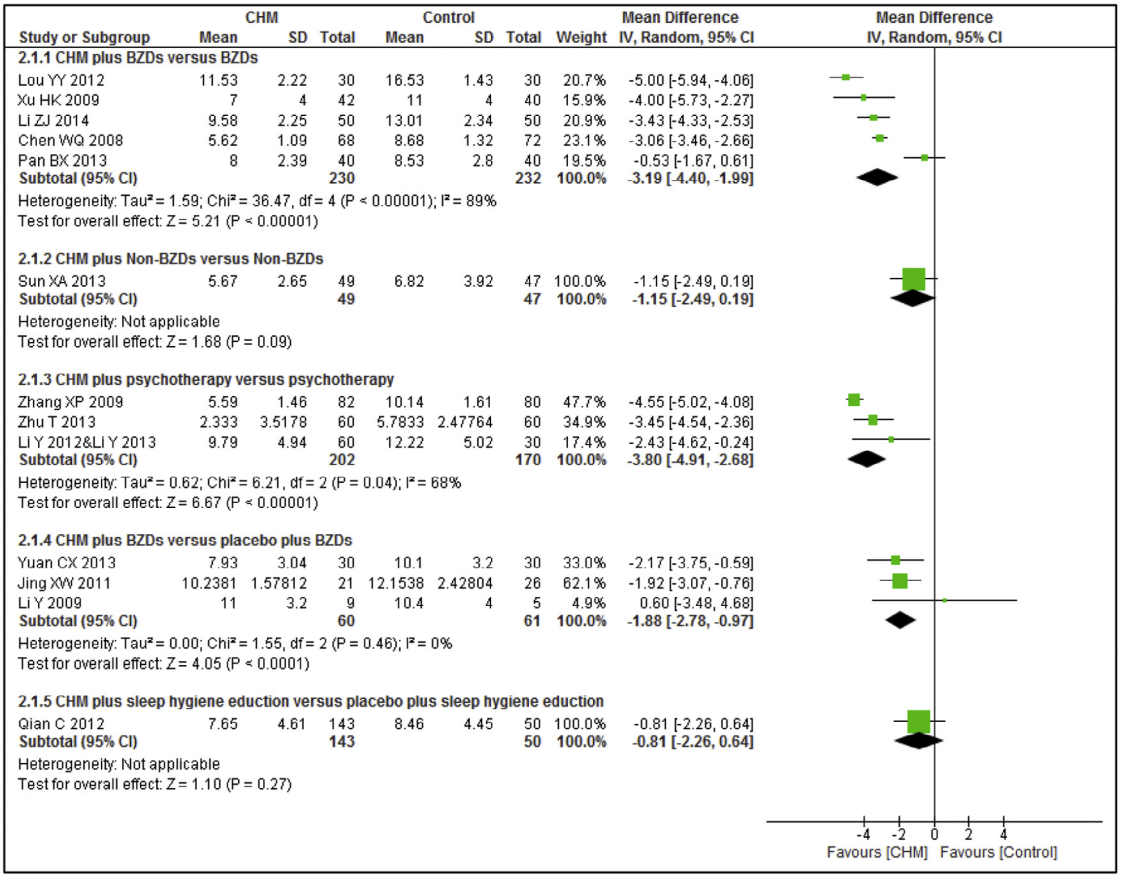

Fig. 4. PSQI of CHM plus conventional medicine versus control. PSQI: Pittsburgh Sleep Quality Index; CHM: Chinese herbal medicine; BZDs: benzodiazepine drugs; non-BZDs: non-benzodiazepine drugs.

3.3.3.3. Sleep efficiency. In terms of sleep efficiency calculated from patient-reporting sleep parameters, CHM was superior to placebo (MD: 9.72%, 95% CI: 6.49–12.96%, $I^2 = 0$; n = two RCTs, 294 participants) [68,95] and BZDs (MD: 19.02%, 95% CI: 18.13–19.92%, $I^2 = 0$; n = two RCTs, 249 participants) [68,103,112]. The results are shown in Supplemental Fig. S8. At the end of a 3-month follow-up period, participants who received CHM reported improved sleep efficiency than those who received BZDs (MD: 20%, 95% CI: 11.23–28.77%; n = one RCT, 84 participants) [103].

3.3.4. Sleep parameters measured by PSG

Sleep parameters measured by PSG were only reported in two RCTs. Data synthesis was not possible because the study design of these two studies varied. According to the only one RCT (96 participants) [94], CHM was not superior to placebo for sleep-onset latency (MD: –1.12 min, 95% CI: –10.31–8.07 min), total sleep duration (MD: 20.33 min, 95% CI: –11.78–52.44 min), sleep efficiency (MD: 3.00%, 95% CI: –2.80–8.80%), or times of awakenings (MD: –0.74 times, 95% CI: –2.88–1.40 times). The four-arm, double-blind, and double-dummy RCT (n = 33 participants) [76] reported no significant difference in sleep-onset latency, total sleep duration, sleep efficiency, or times of awakenings among CHM plus placebo BZDs, BZDs plus placebo CHM, CHM plus BZDs, and placebo CHM plus placebo BZDs.

3.3.5. Clinician global impression

There was no significant difference in the severity of clinician global impression assessed by CGI-S between CHM and BZDs (MD: 0.10, 95% CI: –0.20–0.41, $I^2 = 0\%$; n = three RCTs, 236 participants) [70,89,113] or between CHM plus BZDs and BZDs alone (MD: –0.47, 95% CI: –1.09–0.15; n = one RCT, 86 participants) [107]. The results are shown in Supplementary Fig. S9. At the end of a 1-week follow-up period, the CGI-S score was lower in participants who received CHM than those who received BZDs (MD: –0.89, 95% CI: –1.41 to –0.37; n = one RCT, 100 participants) [89].

3.4. Adverse events

Adverse events were monitored in 43 studies. Eleven of them found no adverse events for the whole study [42,53,59,65,66,80,88,94,95,104,108]. Data of 23 studies were available for the meta-analysis of frequency. There was no significant difference in the frequency of adverse events between CHM and placebo (RR: 1.65, 95% CI: 0.67–4.10, $I^2 = 0$; n = two RCTs, 400 participants) [68,101]. The CHM group had fewer adverse events than the BZD group (RR: 0.15, 95% CI: 0.07–0.28, $I^2 = 76\%$; n = 16 RCTs, 1802 participants) [40,43–45,50,52,54,55,61,74,89,90,93,99,115,118] and the non-BZD group (RR: 0.11, 95% CI: 0.02–0.58, $I^2 = 0$; n = two RCTs, 199 participants) [39,84]. The adjunct CHM treatment did not significantly increase the frequency of adverse events associated with non-BZDs (RR: 0.36, 95% CI: 0.10–1.27; n = one RCT, 96 participants; n = one RCT, 96 participants) [91] or the psychotherapy group (RR: 1.58, 95% CI: 0.08–30.90, $I^2 = 73\%$; n = two RCTs, 372 participants) [41,111]. These results are shown in Figs. 5 and 6. The most frequent types of adverse events in CHM groups were digestive dysfunction such as indigestion and mild increased defecation, dizziness, fatigue, drowsiness, and dry mouth. However, none of the studies assessed whether the reported adverse events were associated with CHM.

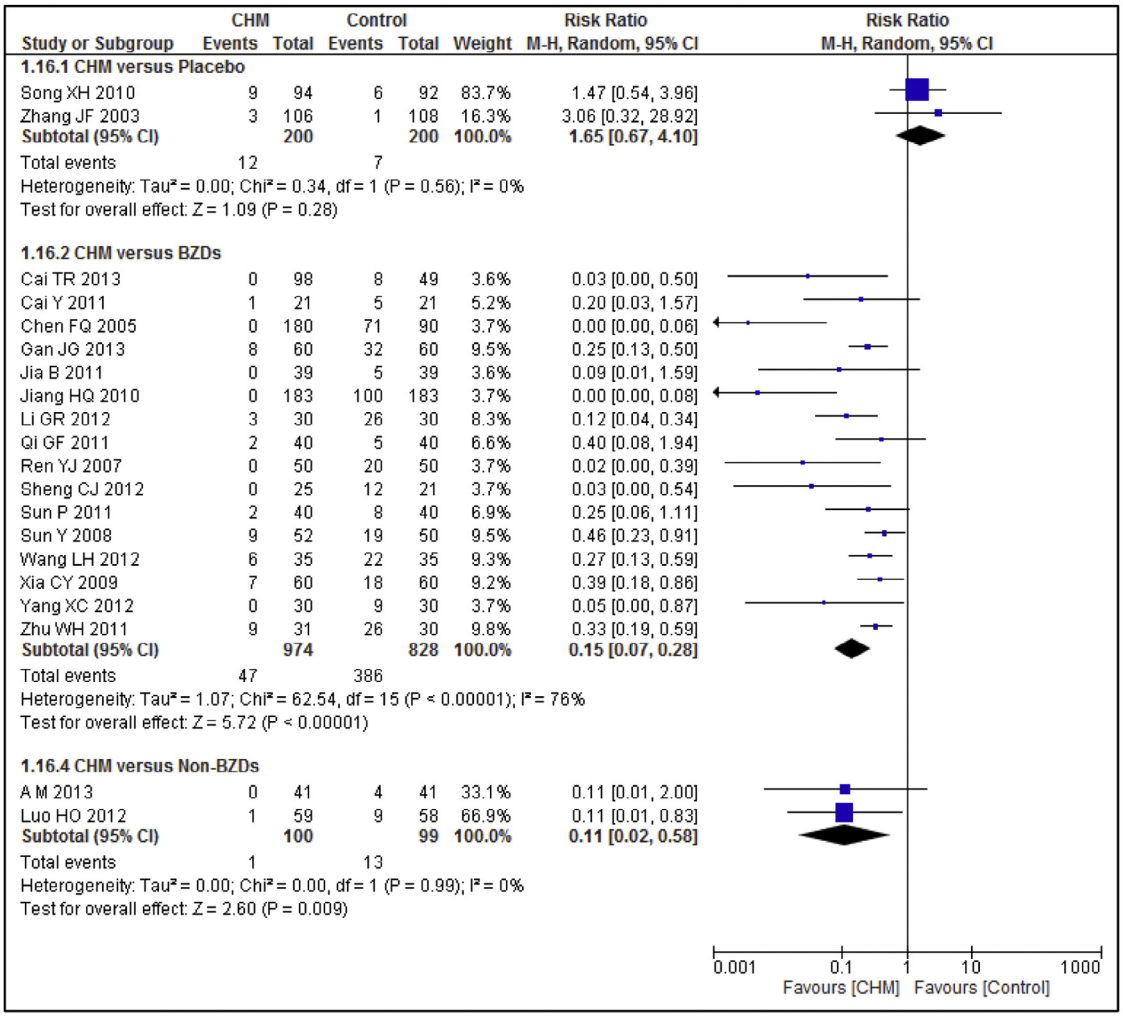

Fig. 5. Frequency of adverse events of CHM versus control. CHM: Chinese herbal medicine; BZDs: benzodiazepine drugs; non-BZDs: non-benzodiazepine drugs.

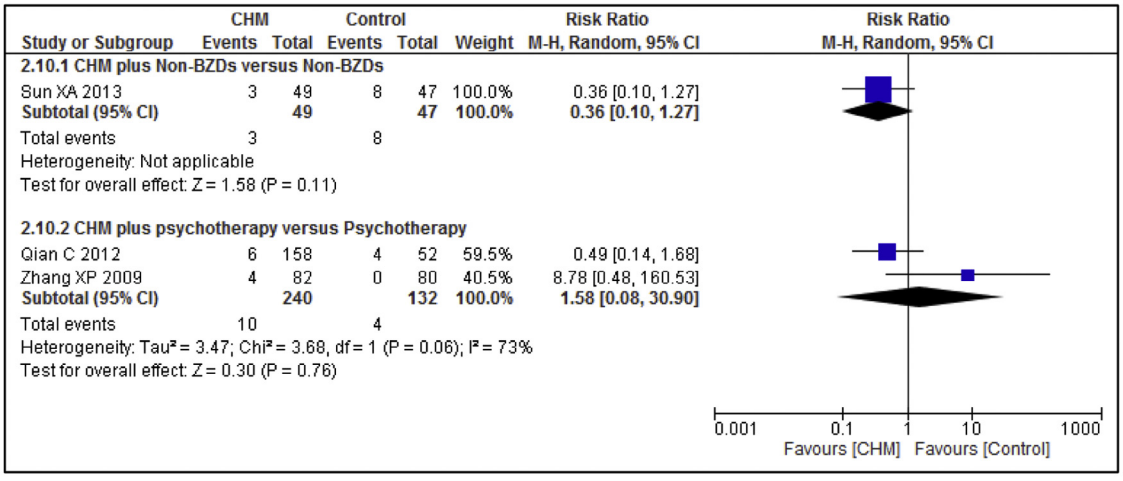

Fig. 6. Frequency of adverse events of CHM plus conventional medicine versus control. CHM: Chinese herbal medicine; non-BZDs: non-benzodiazepine drugs.

3.5. Other analysis

3.5.1. Subgroup analysis of the primary outcome

The subgroup analysis based on treatment duration (≤4 weeks or >4 weeks), insomnia history (<1 year or ≥1 year), and preparation of CHM (decoction or non-decoction) could not address the heterogeneity of meta-analysis for the PSQI scores. The results are shown in Table 3.

3.5.2. Sensitivity analysis

Only four studies (582 participants) had low risk of bias relating to allocation concealment and blinding of participants [68,80,95,101]. All four studies compared non-decoction CHM treatment (≤1 month) with placebo. At the end of the treatment, the PSQI score was lower in participants who received CHM treatment than those who received placebo (MD: –2.13, 95% CI: –3.92 to –0.35, $I^2 = 87\%$).

Eleven studies comparing CHM with BZDs clarified that they excluded the sixth domain (use of sleep medications) when calculating the total scores of PSQI [46,47,53,55,62,67,72,87,93,98,102]. The PSQI scores were significantly lower in the participants treated with CHM than in those with BZDs (MD: –1.46, 95% CI: –2.10 to –0.81, $I^2 = 80\%$; $n = 11$ RCTs, 1046 participants).

Imbalance baseline of PSQI scores was found in three studies in two heterogeneous meta-analyses [50,82,109]. After excluding them, a greater reduction of PSQI scores was observed in the participants treated with CHM (MD: –1.93, 95% CI: –2.46 to –1.39, $I^2 = 96\%$; $n = 33$ RCTs, 3255 participants) and CHM combined with BZDs (MD: –2.72, 95% CI: –3.91 to –1.53, $I^2 = 85\%$; $n =$ four RCTs, 402 participants) than in those with BZDs alone.

3.5.3. Post hoc analysis

The post hoc subgroup analysis on primary outcome was made to explore the estimated effect of individual formula. Four formulae were investigated more than twice in the included RCTs with PSQI scores. The PSQI scores were lower in the participants treated with the *Zao Ren An Shen* capsule (MD: 0.47, 95% CI: –0.43 to –1.36, $I^2 = 85\%$; $n =$ three RCTs, 240 participants) [54,74,83], the *Xue Fu Zhu Yu* decoction (MD: –1.29, 95% CI: –2.09 to –0.49, $I^2 = 0$; $n =$ two RCTs, 266 participants) [62,102], and the *Wuling* capsule (MD: –2.34, 95% CI: –3.45 to –1.23, $I^2 = 96\%$; $n =$ two RCTs, 148 participants) than in those with BZDs [64,100]. There was no significant difference of PSQI scores after the treatment with the *Tian Wang Bu Xin* pill and BZDs (MD: –0.73, 95% CI: –2.87–1.42; $I^2 = 88\%$; $n =$ two RCTs, 146 participants) [46,57].

3.6. Publication bias

Only the comparison between CHM and BZDs in the meta-analysis of PSQI scores included >10 studies. The publication bias was not detected in either the visual funnel plot (Supplementary Fig. S10), Egger's test ($p = 0.708$) or Begger's test ($p = 0.122$).

4. Discussion

4.1. Evidence summary and applicability

In this study, we systematically reviewed 79 RCTs investigating a variety of CHM treatments for participants with insomnia. We also performed meta-analyses to estimate the efficacy of CHM on subjective sleep quality assessed by validated instruments, patient-rated sleep parameters, clinician-reported severity, and PSG results, as well as to determine the safety of CHM. This systematic review provides up-to-date and comprehensive evidence of the efficacy and safety of CHM for insomnia. We also investigated the impact of different treatment strategies, subtypes of participants, various comparators, and methodological designs on the effect, which makes our results clinically meaningful. Overall, this systematic review and

Table 3
Subgroup analysis of PSQI scores based on treatment duration, insomnia history, and preparation of CHM.

Subgroup		No. study	No. participants	Estimated effect (MD, 95% CI)	I [2]	Analysis model
CHM versus BZDs						
Treatment duration	≤4weeks	28	2874	–1.67 (–2.27, –1.08)	94%	Random
	>4 weeks	7	487	–2.95 (–3.84, –2.07)	86%	Random
Duration of insomnia history	<1 year	4	340	–0.55 (–2.62, 1.51)	96%	Random
	≥1 year	20	2144	–1.98 (–2.61, –1.34)	96%	Random
Preparation of CHM	Decoction	21	2175	–2.26 (–3.02, –1.50)	94%	Random
	Non-decoction	14	1186	–1.47 (–2.25, –0.70)	97%	Random
CHM versus placebo						
Treatment duration	≤4 weeks	7	796	–2.40 (–3.61, –1.19)	88%	Random
	>4 weeks	1	57	–7.22 (–7.86, –6.58)	NA	Fixed
Duration of insomnia history	<1 year	1	60	–0.90 (–1.56, –0.24)	NA	Fixed
	≥1 year	5	527	–4.21 (–6.28, –2.15)	95%	Random
CHM versus non-BZDs						
Duration of insomnia history	≥1 year	2	206	0.12 (–0.24, 0.48)	24%	Fixed
	<1 year	0	NA	NA	NA	NA
CHM plus BZDs versus BZDs						
Preparation of CHM	Decoction	2	160	–4.21 (–5.75, –2.68)	82%	Random
	Non-decoction	2	222	–3.11 (–3.50, –2.72)	7%	Fixed
	Combination	1	80	–0.53 (–1.67, 0.61)	NA	Fixed
Duration of insomnia history	≥1 year	4	322	–3.23 (–5.16, –1.31)	92%	Random
	<1 year	0	NA	NA	NA	NA
CHM plus BZDs versus BZDs plus placebo						
Duration of insomnia history	<1 year	1	14	0.60 (–3.48, 4.68)	NA	Fixed
	≥1 year	2	107	–2.00 (–2.93, –1.07)	0%	Fixed
CHM plus psychotherapy versus psychotherapy						
Treatment duration	≤4 weeks	1	120	–3.45 (–4.54, –2.36)	NA	Fixed
	>4 weeks	2	252	–3.77 (–5.77, –1.77)	71%	Random
Preparation of CHM	Decoction	2	210	–3.25 (–4.22, –2.27)	0%	Fixed
	Non-decoction	1	152	–4.55 (–5.02, –4.08)	NA	Fixed

Notes: PSQI: Pittsburgh Sleep Quality Index; CHM: Chinese herbal medicine; BZDs: benzodiazepine drugs; non-BZDs: non-benzodiazepine drugs; NA: not applicable; MD: mean difference; CI: confidential intervals. For some comparison, the subgroup analysis could not be achieved because of insufficient information related to treatment duration, duration of insomnia history, or preparation of CHM.

meta-analysis showed that CHM was superior to placebo and BZDs when used as a monotherapy and was superior to BZDs and psychotherapy alone as an adjunct therapy in terms of subjective sleep quality and quantity and safety. CHM was not associated with more benefit than non-BZDs, although the risks were less. These results suggest that CHM could be a promising alternative therapy with a good benefit–risk ratio.

In this systematic review, the most homogeneous meta-analysis of primary outcome was the comparison of CHM plus BZDs with placebo CHM plus BZDs. It showed that the adjunct use of CHM resulted in a larger reduction of PSQI scores by 1.88 points, which was greater than the MCID of PSQI scores [33]. This result suggests that the estimated effect of CHM as a co-intervention to BZDs is relevant and potentially important to the insomnia patients in real clinical practice.

As this systematic review only included participants primarily diagnosed with insomnia, the evidence on CHM generated from this systematic review cannot be generalized to the population with comorbid insomnia or medication/substance-induced insomnia. In addition, the longest follow-up duration of the CHM treatment was 6 months; thus, the evidence of safety related to CHM could not be generalized to a longer therapy.

4.2. Overall completeness of evidence and clinical implications

A placebo effect is commonly observed for self-reported outcomes related to insomnia where placebo treatment significantly improved the total scores of PSQI by 2.0 points, increased total sleep duration by 23.0 min, and decreased sleep-onset latency by 15.1 min, compared with no treatment [120]. In this systematic review, our primary finding was that CHM was superior to placebo in terms of the improvement of PSQI scores, sleep-onset latency, total sleep duration, and sleep efficiency in participants with insomnia. In the sensitivity analysis, the positive trend of CHM was robust after the studies with inadequate randomization, allocation concealment, or insufficient blinding were removed. This study provides new evidence of the effect of CHM on subjective insomnia. This result also suggests that CHM could be an alternative treatment for individuals with insomnia when CBT-i or pharmacotherapies are unavailable in clinical settings.

Previous studies showed that short-term use of BZDs was effective for insomnia [8]. However, the risks and side effects associated with BZDs, such as daytime drowsiness and drug dependency, have been noted in both research and clinical practice [9,121–123]. Another striking finding of our systematic review was that CHM was associated with more benefit in terms of subjective sleep quality, total sleep duration, and sleep efficiency than BZDs, and these results remained robust in sensitivity analysis. Furthermore, the meta-analysis indicated that the frequency of adverse events in participants treated with short-to-medium CHM was significantly lesser than that of participants treated with BZDs, and no serious adverse events were reported in any study. These results suggest that CHM might be an alternative to BZDs for individuals whose predominant complaint is dissatisfaction with overall sleep quality and total sleep quantity, although to what extent CHM was better than BZDs remains uncertain. However, CHM did not have a better effect than non-BZDs on subjective outcomes of insomnia, although it was associated with less adverse events.

Insomnia management is complex as a sequential or integrative approach is used, particularly for persistent and chronic insomnia [124,125]. In this systematic review, we also investigated the add-on effect of CHM on conventional medicine. The meta-analysis showed that the adjunct use of CHM to conventional medicine resulted in greater improvement of subjective sleep quality compared with BZDs, non-BZDs, and CBT-i. The highest level of evidence was attained from the homogeneous meta-analysis comparing CHM plus BZDs with BZDs plus placebo. In addition, the adjunct use of CHM to CBT or non-BZDs did not increase the adverse events in participants with insomnia. These results provide new knowledge that CHM could be used as a complementary therapy for insomnia patients with a predominant complaint of dissatisfaction with overall sleep quality.

Drug tolerance is commonly encountered in pharmacotherapies for insomnia [126]. Our systematic review showed that the effect of CHM was well sustained in the medium-to-long-term follow-up, and this effect was significantly better than placebo, BZDs, and non-BZDs in terms of PSQI scores. This result also adds new knowledge to the field.

This systematic review showed that there was no significant difference between CHM and BZRAs for increasing sleep-onset latency or for reducing clinician-rated severity. This indicates that the conscientious and judicious implementation of the CHM evidence is required in clinical practice because the effect of CHM on insomnia varies according to the outcome measurement.

There was insufficient evidence addressing two important clinical questions: (1) whether CHM was more beneficial than CBT-i for participants with insomnia and (2) whether CHM changed the insomnia electrophysiology detected by PSG.

4.3. Limitations and implications for research

Proper randomization and allocation to reduce the selection bias are necessary for an RCT. We noted that appropriate randomization methods were only used in 34.18% of studies, and adequate allocation concealment in 6.33%. The poor status of randomization may be due to the low methodological quality or low report quality. However, both are likely to exaggerate the estimate of efficacy [127,128]. Therefore, prospective registration of clinical trials and improvement of reporting quality according to CONSORT statement for herbal interventions are required in the future to present full transparency for the study design, implementation, and data-analysis [129–131].

Insufficient blinding can also lead to overestimation of the effect size [128]. Although double blinding is encouraged in RCTs, it is difficult to practice it for herbal intervention because of the different shape, smell, taste, and administration of CHM products from pharmacotherapy. Considering this challenge, the efficacy of any CHM product should be assessed in the comparison with placebo before its effectiveness is evaluated by using pharmacotherapy as its comparator. Sixty-six different CHM treatments were found in the pool of RCTs, but only 13 of them used placebo as comparators and only 10 used blinding. This indicates that more RCTs using placebo and blinding are needed. In addition, only two RCTs used placebo to CHM decoction, which suggests that the research and development of a placebo to CHM decoction is need.

PROs such as PSQI and patient-rated sleep parameters directly measure the core treatment benefits from patients' perspective in a natural setting [132], which have been comprehensively analyzed in this meta-analysis. However, the treatment effect on PROs is easily changed by insufficient allocation concealment and blinding [133]. In light of the difficulty in blinding RCTs for Chinese herbal intervention, the increasing use of CROs such as CGI-s and CGI-I performed by blinded assessors is needed to provide the overall assessment of insomnia progression. Sleep laboratory studies such as PSG and actigraphy should also be encouraged to explore the mechanism of CHM's action in sleep structures.

Heterogeneity across studies often results in unsuccessful meta-analysis [134]. In this systematic review, we included RCTs of various interventions to gain a broad perspective on the evidence regarding the use of CHM for insomnia, and this caused heterogeneity in some meta-analyses. In addition, clinical and methodological heterogeneity could not be well addressed by subgroup or sensitivity

analysis. Therefore, most results presented in this systematic review were the average effects of CHM on insomnia estimated by a random-effect model, rather than the typical effect. This solution to heterogeneity was based on the assumption that effect being estimated in different CHM treatments may not be identical, but it follows some distribution [135,136]. We noted that the effect size of formulae varied in the post hoc analysis, which agreed with our assumption. Therefore, further comprehensive searches and appraisals of the evidence for each CHM formula for insomnia are needed in the future.

4.4. Agreements and disagreements with other reviews

A previous high-quality systematic review with meta-analysis on standardized CHM for insomnia also suggested that CHM was superior to placebo and safe for individuals with insomnia [21]. However, our study is different from the previous study in four main areas. First, the previous study used Jadad scale [137] to examine the study quality, and it concluded that the poor methodological quality of the studies limited their ability to draw definitive conclusions. However, the use of Jadad scale is increasingly discouraged because the total score is an unreliable assessment of validity [138–140]. We used Cochrane risk and bias instrument to assess the domain-specific methodological quality, thus avoiding this problem. Second, we conducted the search up to May 2014 and therefore collected more up-to-date evidence. Third, we only included the participants diagnosed by standard instruments of insomnia, whereas the previous review treated insomnia as a complaint, which results in a different generalized population. Fourth, we used a comprehensive list of sleep measurements as outcomes, which provides more information for clinical practice and research.

5. Conclusion

Overall, oral CHM alone or when combined with routine care can safely improve subjective sleep in people with insomnia. However, the typical effect of CHM cannot be determined when compared with BRADs and CBT-i due to heterogeneity. Further systematic review focusing on individual formula for insomnia is needed. The development of a comparable placebo to traditional decoction is encouraged as well to ensure the successful blinding in clinical trials.

Authors' contributions

XN conceived the study and drafted the manuscript. XN and JS designed, screened, and analyzed the studies. XN, JS, XG, AZ, and YL interpreted the evidence from methodological and clinical perspective. CL and CX oversaw the conduct of the study, and they contributed to the overall design, analysis, and write-up. All authors read, critically reviewed, and approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.08.012.

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Appendix A

Comprehensive English search strategy

#1: Sleep Initiation and Maintenance Disorders OR Sleep Disorders OR DIMS OR Early Awakening OR Nonorganic Insomnia OR Primary Insomnia OR Secondary Insomnia OR Transient Insomnia OR Rebound Insomnia OR Sleep Initiation Dysfunction OR Sleep Initiation Dysfunctions OR Sleeplessness OR Insomnia Disorder OR Insomnia Disorders OR Insomnias OR Chronic Insomnia OR Psychophysiological Insomnia OR Dyssomnia
#2: Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs, Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Herbs OR Chinese Medicine Herb OR Herbal Medicine
#3: Acupuncture OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR plum blossom OR acupressure OR ear acupuncture OR ear acupressure OR acupuncture, ear OR acupuncture therapy OR moxa OR laser acupuncture OR seven-star needle OR acupuncture analgesia OR acupuncture points OR electroacupuncture OR electroacupuncture OR TENS OR transcutaneous nerve stimulation OR transcutaneous electric nerve stimulation OR transcutaneous electrical nerve stimulation OR electrostimulation OR electrostimulation OR pharmacopuncture OR point injection OR catgut embedding
#4: Tai Ji OR Tai chi OR Breathing exercises OR Qi gong OR Qigong OR Chi Kung OR Tuina OR anmo Tuina OR Chinese massage OR cupping OR guasha OR blood letting OR bloodletting OR diet therapy OR therapy, diet OR therapies, diet OR phlebotomy
#5: #2 OR #3 OR #4
#6: #1 AND #5

Comprehensive Chinese search strategy

#1: 入睡和睡眠障碍 OR失眠 OR 睡眠 OR 不寐;
#2: 中医 OR 中西医 OR 中医疗法 OR 辨病论治 OR 辨证 OR 辨证论治 OR 辨症 OR 辩证 OR 汉方 OR 祖国医学 OR 传统医学 OR 传统治疗 OR 传统疗法 OR 替代医学 OR 替代治疗 OR 中国传统医学 OR 民族医药 OR 民族医学 OR 草药 OR 中草药 OR 中药 OR 中药疗法 OR 中西药 OR 传统医药 OR 中成药 OR 植物药 OR 中医治法 OR 治则 OR 中医疗法 OR 熏洗 OR 薰洗 OR 药浴 OR 外洗 OR 沐足 OR 足浴 OR 浴足 OR 灌肠 OR 药熨 OR热熨 OR热敷 OR 敷脐 OR 药枕 OR 足疗 OR外敷
#3: 针刺 OR 针灸 OR 针灸疗法 OR 针灸治疗 OR 灸 OR 针法 OR 刺法 OR 体针 OR 腹针OR 温针 OR 火针 OR 电针 OR 梅花针 OR 水针 OR 穴位注射 OR 经络注射 OR 穴位按压 OR 穴位按摩 OR 穴位疗法 OR 指压 OR 耳压 OR 耳针OR 耳穴 OR 耳豆 OR 压豆 OR 点穴 OR 埋线 OR 埋针 OR 头针 OR 眼针 OR 蜂针 OR穴位贴敷 OR 小针刀 OR 皮肤针
#4: 外治 OR 外治法 OR 推拿OR 按摩 OR 拔罐 OR 药罐 OR 推罐 OR 闪罐 OR 火罐 OR 针罐 OR 砭石 OR 刮痧 OR 挑治 OR 发泡 OR 导引 OR 吐纳 OR 气功 OR 太极 OR 八段锦 OR 刺络 OR 刺血OR 刺血疗法 OR 放血 OR 三棱针 OR 离子导入 OR 理疗 OR 情志疗法 OR 中医音乐 OR 五行音乐
#5: #2 OR #3 OR #4
#6: #1 AND #5

Appendix B: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2015.08.012.

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