European Journal of Integrative Medicine 30 (2019) 100961

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Systematic review

Herbal medicine for insomnia in elderly with hypertension: A systematic review and meta-analysis

Chan-Young Kwon[a,1], Boram Lee[a,1], Sun-Yong Chung[a,b], Jong Woo Kim[a,b], Sang-Ho Kim[c,*]

[a] Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, Republic of Korea
[b] Department of Korean Medicine, Kyung Hee University Korean Medicine Hospital at Gangdong, 892, Dongnam-ro, Gangdong-gu, Seoul, Republic of Korea
[c] Department of Neuropsychiatry of Korean Medicine, Pohang Korean Medicine Hospital, Daegu Haany University, 411 Saecheonnyeon-daero, Nam-gu, Pohang-si, Gyeongsangbuk-do, Republic of Korea

ARTICLE INFO

Keywords:
Aged
Herbal medicine
Hypertension
Insomnia
Polypharmacy
Systematic review

ABSTRACT

Introduction: Herbal medicine (HM) may be beneficial for geriatrics with multiple pathological conditions. The objective of this study was to systematically analyze the effectiveness and safety of HM for insomnia in the hypertensive elderly.

Methods: Thirteen databases were comprehensively searched from their inception dates to August 28, 2018, to identify relevant randomized control trials (RCTs). The results of meta-analyses were presented as relative risk (RR) or mean difference (MD) with 95% confidence intervals. The quality of evidence (QoE) was evaluated using the GRADE approach.

Results: Eight RCTs were included in this review. Based on routine antihypertensive therapies in most cases, compared to the hypnotics group, HM group had a significantly higher total effective rate (TER) for improvement of insomnia (RR 1.24 [1.12, 1.39]). Compared to no intervention group, HM group showed a significantly higher TER for improving insomnia (RR 1.70 [1.25, 2.33]), and lowering systolic (MD -5.63 mmHg [-7.18, -4.09]) and diastolic blood pressures (MD -4.40 mmHg [-5.63, -3.18]). Pittsburgh sleep quality index (MD -4.11 [-5.72, -2.50]), Zung self-rating anxiety scale (MD -6.60 [-7.79, -5.41]), and Zung self-rating depression scale (MD -6.15 [-7.43, -4.87]). There was no significant difference in the incidence of adverse events between the HM and no intervention groups. The QoE ranged from "Very low" to "Moderate."

Conclusion: HM might have some beneficial effects including improving insomnia, blood pressure, and mental health, for the hypertensive elderly with insomnia. Since the methodological quality of the included studies and QoE were not high, well-designed RCTs are important to confirm these results.

1. Introduction

Hypertension and insomnia are common diseases in elderly populations, with prevalence of 9–34% [1–3] and 40–75% [4–6], respectively. According to the American Academy of Sleep Medicine, insomnia is defined as "a complaint of trouble initiating or maintaining sleep which is associated with daytime consequences and is not attributable to environmental circumstances or inadequate opportunity to sleep" [7]. Hypertension is defined as the state of having a blood pressure (BP) of 130/80 mmHg or more according to the American College of Cardiology/American Heart Association [8].

Several studies have revealed that the two diseases are associated with significant negative outcomes for the health status among the population, such as memory impairment [9], dementia [10], depression [11], cardiovascular diseases [12], metabolic disorders [13], frailty [14], and even mortality [15,16]. Interestingly, growing evidence has revealed the association between the two diseases [17]. Dysfunction of the hypothalamic-pituitary-adrenal axis has been proposed as a mechanism underlying the association [18]. It has also been suggested that some psychological and biological factors such as emotional distress and excessive activity of the arousal-related neural pathways are involved [18]. In addition, lower sleeping times and fragmented sleep can increase the risk of atherosclerosis and consequently may threaten cardiovascular health, thus emphasizing sleep health in the prevention of cardiovascular disease [19]. Furthermore, the analysis of the American Heart Association's Strategically Focused Research Network, a

* Corresponding author.
E-mail addresses: beanalogue@naver.com (C.-Y. Kwon), qhfka9357@naver.com (B. Lee), lovepwr@khu.ac.kr (S.-Y. Chung), aromaqi@khu.ac.kr (J.W. Kim), omed22@naver.com (S.-H. Kim).
[1] These authors contributed equally to this work (co-first authors).

https://doi.org/10.1016/j.eujim.2019.100961
Received 1 November 2018; Received in revised form 15 August 2019; Accepted 15 August 2019

population-based prospective cohort, found that sleep disorders are associated with increased BP as well as endothelial inflammation, a key mechanism underlying an increasing cardiovascular burden [20]. Therefore, in a therapeutic context, the need to improve the sleep of patients, as well as to improve cardiovascular conditions, such as hypertension, is emphasized to reduce the cardiovascular burden.

Another important topic in treating these two diseases at the same time is polypharmacy. Elucidating the relationship between two or more diseases may be the key to addressing the polypharmacy issue, which generally leads to patients taking five or more medications daily [21], and has been highlighted recently, especially in the elderly [22]. This is because the potential for treatments targeting pathological processes common to both diseases can lead to the development of strategies to reduce the number of medications taken. However, many synthetic drugs with a single active component acting on a single target are limited in this respect. In the case of elderly patients suffering from both insomnia and hypertension, for example, the use of hypnotics or sleep inducers and antihypertensives is common according to their respective clinical practice guidelines, which may increase the risk of harm from polypharmacy [23].

Moreover, the simultaneous use of these drugs has also been associated with some side effects. Specifically, benzodiazepines and other sedative-hypnotic drugs are known to be associated with increased risks of falls and hip fractures in the elderly [24]. The American Geriatrics Society called on clinicians to avoid using benzodiazepines in the elderly in their recent Beers Criteria [25]. Although relatively safe, antihypertensives may also be associated with adverse events (AEs) such as hypotension, syncope and bradycardia [26], and a recent systematic review has suggested the possibility of the withdrawal symptoms of these drugs [27].

In East Asia, herbal medicine (HM) has been used as a primary mode of care for centuries. Recently, HM has attracted attention as a promising candidate to complement the limit of conventional pharmacotherapy in geriatrics [28,29]. Several studies have also confirmed the safety and effectiveness of HM for insomnia and hypertension [30,31]. Importantly, HM contains multiple active components that act on multiple targets [32], thus overcoming the limitations of conventional synthetic drugs with a single active constituent. This means that HM can potentially affect both hypertension and insomnia at the same time, reducing the risk of polypharmacy and its consequent complications.

However, the use of HM for insomnia in hypertensive elderly patients has not yet been systematically and critically reviewed. Therefore, the objective of this review was to comprehensively assess the therapeutic effectiveness and safety of HM in elderly with both insomnia and hypertension, and to discuss the possibilities of HM in terms of the polypharmacy issue.

2. Materials and methods

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [33]. The protocol for this systematic review was published [34] and registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number, CRD42018104095).

2.1. Data sources and search strategy

The following databases were comprehensively searched from their inception dates to August 28, 2018 by two independent researchers (CY Kwon and B Lee): six English-language databases (Medline via PubMed, EMBASE via Elsevier, the Cochrane Central Register of Controlled Trials [CENTRAL], Allied and Complementary Medicine Database [AMED] via EBSCO, Cumulative Index to Nursing and Allied Health Literature [CINAHL] via EBSCO, and PsycARTICLES via ProQuest), three Korean-language databases (Oriental Medicine Advanced Searching Integrated System [OASIS], Research Information Service System [RISS], and Korea Citation Index [KCI]), three Chinese databases (China National Knowledge Infrastructure [CNKI], Wanfang Data, and VIP), and one Japanese database (CiNii). In addition, the reference lists of the relevant articles were checked, and a manual search of Google Scholar was conducted to identify any additional studies. In addition to the studies published in the journal, we also included gray literature, such as theses and conference proceedings. The following search terms were used in Medline: (Hypertension[mh] OR hypertens* OR Blood Pressure [mh] OR blood pressure OR bloodpressure) AND (Sleep[mh] OR Sleep Disorders[mh] OR sleep* OR insomnia* OR wakeful* OR sleepless* OR dyssomn*) AND (Plants, Medicinal[mh] OR Drugs, Chinese Herbal[mh] OR Medicine, Chinese Traditional[mh] OR Medicine, Kampo[mh] OR Medicine, Korean Traditional[mh] OR Herbal Medicine[mh] OR Prescription Drugs[mh] OR traditional Korean medicine OR traditional Chinese medicine OR Traditional oriental medicine OR Kampo medicine OR alternative medicine OR complementary medicine OR herb* OR decoction* OR botanic*) (Appendix 1 in Supplementary materials).

2.2. Inclusion criteria

2.2.1. Types of studies

We included only randomized controlled trials (RCTs) and excluded quasi-RCTs using inappropriate random sequence generation methods such as alternate allocation or allocation by birthdate. If only the expression “randomization” (随机) was mentioned without a detailed randomization method, it was regarded as an RCT and included in this review. We included both parallel and crossover studies. In crossover designs, only first-phase data was used in calculating the effect size and conducting the meta-analysis. There was no language restriction.

2.2.2. Types of participants

We included studies on patients with a diagnosis of both hypertension and insomnia, diagnosed using standardized diagnostic tools, assessment tools, textbook, or clinical symptoms. Studies not providing diagnostic criteria for hypertension and insomnia in participants were excluded. We included studies on elderly people with an average age of 60 years or older, regardless of sex or race. Studies were excluded if participants had serious systemic disease, congenital disease, cognitive dysfunction, or drug allergies.

2.2.3. Types of interventions

We included only those studies using HM as the experimental intervention. In this review, HM is defined as herbal medicine prescribed based on the theory of East Asian traditional medicines such as traditional Chinese medicine (TCM), Kampo medicine, and traditional Korean medicine. We allowed any formulation (e.g., decoction, tablets, capsules, pills, powders, and extracts) of HM. Studies involving HM combined with other therapies as experimental interventions were included if the other therapies were used equally in both the experimental and the control groups. Except for patented drugs, studies that did not list the composition of the HM used were excluded. We excluded studies comparing different types of HM. As control interventions, we included Western medication, placebo, or no treatment. There were no other restrictions regarding the control interventions.

2.2.4. Types of outcome measures

The primary outcome measures were (1) change in the degree of insomnia as measured using validated assessment tools, such as the Pittsburgh Sleep Quality Index (PSQI) [35] and the Insomnia Severity Index [36] and (2) change in drug use. The secondary outcome measures included (1) change in BP, (2) change in mental health as measured using validated assessment tools, such as the Hamilton Anxiety Rating Scale (HAMA) [37], Hamilton Depression Rating Scale (HAMD) [38], and Geriatric Depression Scale (GDS) [39], and (3) total effective rate (TER), a non-validated outcome measure that is processed secondarily according to certain evaluation criteria such as clinical symptom

improvement or the improvement rates of other quantified outcomes. In the assessment of TER, participants are generally classified as “cured” (痊愈), “markedly improved” (顯效), “improved” (有效), or “non-responder” (無效) after treatment. TER was calculated consistently using the following formula: $TER = N1 + N2 + N3 / N$, where $N1$, $N2$, $N3$, and N were the number of patients who were cured, markedly improved, improved, and the total sample size, respectively. We also evaluated AEs as measured using the Treatment Emergent Symptom Scale [40] or the incidence as secondary outcome measures.

2.3. Study selection

Two researchers (CY Kwon and B Lee) independently conducted the study selection process according to the above inclusion criteria. After removing duplicates, we screened the titles and abstracts of the searched studies for initial candidate studies for inclusion. We then evaluated the full-text of the remaining articles for final inclusion. Any disagreement on study selection was resolved through discussion with other researchers.

2.4. Data extraction

Using a standardized data collection form in Excel 2010 (Microsoft, Redmond, WA, USA), two researchers (CY Kwon and B Lee) independently performed and cross-checked the data extraction. Discrepancies were resolved through discussion with other researchers. The extracted items included the first author’s name; year of publication; country; sample size and number of dropouts; details about the participants, experimental intervention, and comparisons; duration of the intervention; outcome measures; and AEs associated with interventions.

2.5. Quality assessment

Two researchers (CY Kwon and B Lee) independently assessed the methodological quality of the included studies and the quality of evidence for each main finding. Discrepancies were resolved through discussion with other researchers.

We assessed the methodological quality of the included RCTs using the Cochrane Collaboration’s risk of bias tool [41]. The following domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other sources of bias. Each item was evaluated and categorized into three groups: “low risk,” “unclear,” or “high risk.” When only the expression “randomization” (随机) was mentioned without specifying the randomization methods, we judged the study to be at high risk of bias in the random sequence generation domain. We also assessed other potential biases with particular emphasis on baseline imbalances between experimental and control group such as participant characteristics, which includes mean age and baseline insomnia or hypertension level, because baseline imbalance in factors that are strongly related to outcome measures can cause bias in the estimation of the intervention effect in RCTs.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the quality of evidence for each main finding [42]. Using the online program GRADEpro (https://gradepro.org/), we assessed the risk of bias; inconsistency, indirectness, and imprecision of the results; and the probability of publication bias using a four-item scale (“Very low,” “Low,” “Moderate,” or “High”).

2.6. Data synthesis and analysis

Descriptive analyses of the details of the participants, interventions, and outcomes were conducted for all included studies. Quantitative synthesis was performed if there were studies using the same type of experimental intervention, comparison, and outcome measure. We pooled the continuous outcomes as a mean difference (MD) with 95% confidence intervals (CIs) and the dichotomous outcomes as a risk ratio (RR) with 95% CIs.

Heterogeneity between the studies in terms of effect measures was assessed using both the chi-squared test and the I-squared statistic. We considered I-squared values greater than 50% and 75% indicative of substantial and high heterogeneity, respectively. In the meta-analyses, a random effects model was used when the heterogeneity was significant (I-squared value > 50%), while a fixed effects model was used when the heterogeneity was non-significant. The fixed-effect model was also used when the number of studies included in a meta-analysis was very small, where the estimates of inter-study variance had poor accuracy [43].

All statistical analyses were conducted using the Cochrane Collaboration’s software program Review Manager (RevMan) version 5.3 for Windows (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012). We contacted the corresponding authors of the included studies via e-mail to request additional information if the data were insufficient or ambiguous.

2.6.1. Subgroup analysis

If the necessary data were available, we conducted a subgroup analysis to explore the possible cause of the heterogeneity according to the disease severity and treatment period.

2.6.2. Assessment of reporting biases

If there were more than 10 trials included in the meta-analysis, reporting biases, such as publication bias, were assessed by using funnel plots. When there was an asymmetry of the funnel plot, we tried to explain the possible reasons.

3. Results

3.1. Description of included studies

We identified 7355 records through database searches and no additional records through other sources. After removing duplicates, 6901 records remained. After screening the titles and abstracts, 64 articles were considered to be relevant and the full texts of those were obtained and reviewed. Consequently, eight RCTs [44–51] were included in this systematic review. Among them, the meta-analyses were conducted on six studies [44–46,48–50] with 628 participants (Fig. 1).

The general characteristics of the included studies are summarized in Table 1. All included studies were conducted in China. There were two dissertations [48,50], while the remaining six [44–47,49,51] were journal articles. Based on routine antihypertensive therapies, three [44–46], one [47], and three [48–50] compared HM with hypnotics, HM plus hypnotics with hypnotics alone, and HM with no additional intervention, respectively. The remaining study [51] compared HM with antihypertensive treatment plus hypnotics. The sample sizes ranged from 60 to 224, with a median of 94. In the case of Li [50], 224 participants were initially enrolled and randomized to experimental group or control group after classification of their BP levels from grade 1 to 3. However, Li did not list the initial number assigned to each group and only listed the number who completed the study as 180: 30 in the treatment group and 30 in the control group for each comparison (treatment group versus control group in grade 1, 2, and 3 hypertensive patients). The treatment duration ranged from 3 to 12 weeks, with a median of 4. Two studies [48,50] recruited participants with specific TCM patterns; both were related to liver depression. Regarding the antihypertensive treatment, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and calcium channel blockers plus angiotensin receptor blockers (ARBs) were used in one [47], one [49], and two studies [50,51], respectively. Three studies [44,45,48]

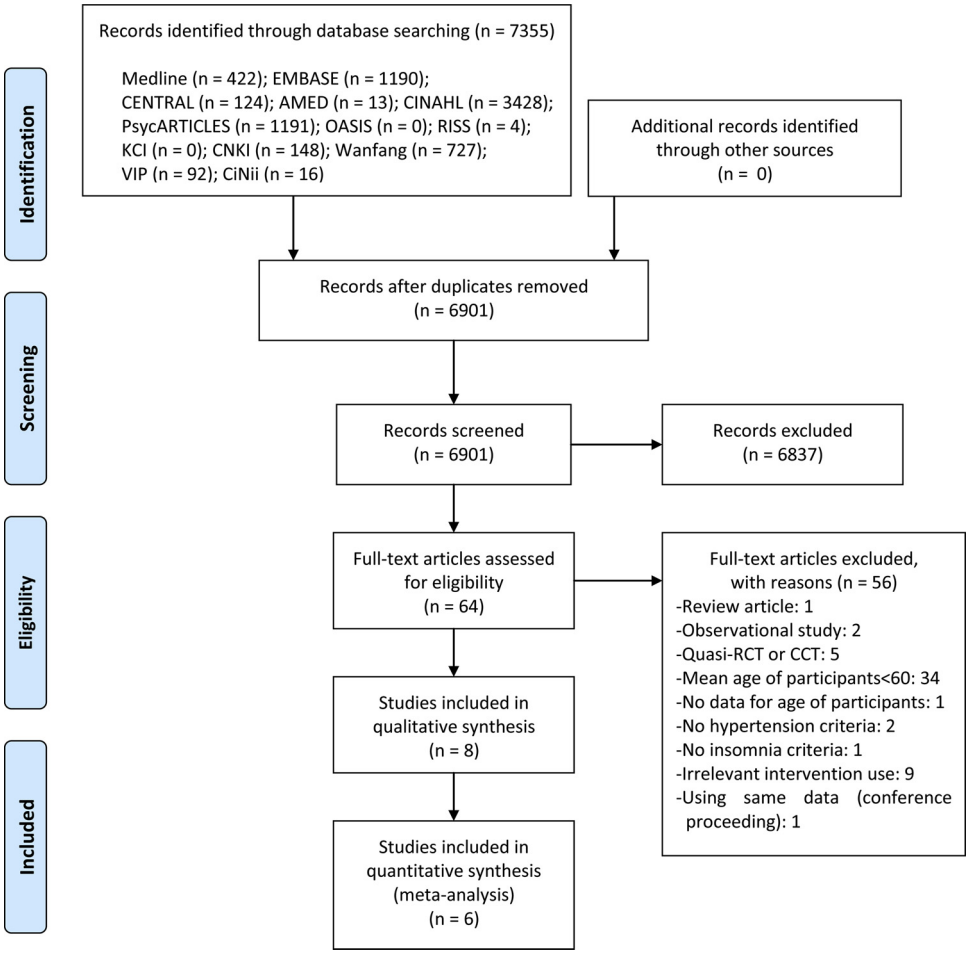

Fig. 1. PRISMA flow chart for the study selection.
AMED, Allied and Complementary Medicine Database; CCT, controlled clinical trial; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CNKI, China National Knowledge Infrastructure; KCI, Korea Citation Index; OASIS, Oriental Medicine Advanced Searching Integrated System; RCT, randomized controlled trial; RISS, Research Information Service System

reported using "routine" antihypertensives, one [48] of which described this as calcium channel blockers; ACE inhibitors or ARBs; and β-blockers. All five studies [44–47,51] using hypnotics as an intervention used benzodiazepines and, among them, one study [44] used alprazolam, while the rest [45,45,46,47,51] used estazolam. TER [44–49,51] and BP [44,45,47–51] were the most frequently used outcome in seven studies, and PSQI was used in four [46,48–50]. The TCM syndrome score [45,48], Zung Self-Rating Anxiety Scale (SAS) [46,50], and Zung Self-Rating Depression Scale (SDS) [46,50] were used in two studies. Sleep Dysfunction Rating Scale (SDRS) [51], recurrence rate of insomnia [46], and HAMA [51] were also used as outcomes once each. Three different calculation methods of TER were used: seven [44–49,51] according to improvement of insomnia, one [48] according to improvement of hypertension, and one [48] according to improvement TCM syndrome score. Two studies [45,50] reported the approval of the institutional review board, and five [44–46,48,50] reported that they had received consent from the participants.

3.2. Methodological quality

Four studies [44–46,51] described an appropriate method of random sequence generation, such as a computerized random number table, and were assessed to have low risk of bias on the random sequence generation domain. The remaining four studies [47–50] with no description of the random sequence generation method were considered to be at high risk of bias. No studies reported the allocation concealment and blinding of participants, personnel, or outcome assessors. Since no studies used a placebo treatment, the domain of the blinding of participants and personnel in all studies was assessed to be at high risk of bias. In the domain of incomplete outcome data, one study [50] was assessed to have a high risk of bias because they processed the missing data with a per-protocol analysis method. Five studies [44,48–51], reporting both outcomes of insomnia and hypertension with their raw data, were considered to have a low risk of bias on the selective reporting domain. In the domain of other sources of bias, all studies reported that there was no statistical heterogeneity of demographic data between groups and were assessed to have low risk of bias (Fig. 2, Appendix 2 in Supplementary materials).

3.3. Details of HM used

Details of the HM used for insomnia in elderly with hypertension are summarized in Appendix 3 in Supplementary materials. Six studies [44–48,51] used decoctions, and the remaining two [49,50] used Chinese herbal patented medicine capsules. Except for one study [49] that instructed that the HM should be taken once a day, all others instructed participants to take HM twice a day. There were no studies using the same HM. In four studies [45–47,51], in addition to the basic components of the HM, some herbs were added according to the participants' symptoms or specific TCM patterns.

Based on the basic components, 43 different herbs were used. The most frequently used herbs were *Salviae miltiorrhizae radix*, *Zizyphi*

Table 1
Characteristics of included studies.

Study	Sample size (included →analyzed)	Mean age (range) (years)	Diagnostic criteria	Pattern identification	(A) Experimental intervention	(B) Control intervention	Outcome	Results reported	Adverse events
HM vs. Hypnotics									
Huang 2005 [44]	108(72:36)→108(72:36)	(A) NR (65–90) (B) NR (62–86)	-Insomnia: CCMD-2-R -Hypertension: WHO/ISH criteria	NR	(1) HM (2) routine antihypertensives	(1) Hypnotics (Alprazolam 0.4 mg qd) (2) routine antihypertensives	1. Ambulatory BP (ratio of the dipper type and non-dipper type) 2. Improvement of insomnia (sleep onset latency, number of awakenings, daytime sleepiness, and dreaming) 3. TER (improvement of insomnia)	1. (A) > (B)* (dipper type ratio) 2. (A) > (B)* 3. (A) > (B)*	NR
Li 2017 [45]	110(55:55)→110(55:55)	(A) 66.4 ± 4.3 (64–77) (B) 66.3 ± 5.2 (65–72)	-Insomnia: Guiding principles for clinical study of new Chinese medicines, PSQI > 7 -Hypertension: Practical internal medicine (170 ≥ sBP≥ 140 mmHg and dBP≥110 mmHg)	NR	(1) HM (2) routine antihypertensives	(1) Hypnotics (Estazolam 1 mg qd) (2) routine antihypertensives	1. TCM syndrome score 2. BP 3. TER (improvement of insomnia and PSQI score)	1. (A) < (B)* 2. (A) < (B)* 3. (A) > (B)*	NR
Zhang 2017 [46]	110(55:55)→110(55:55)	(A) 65.39 ± 3.21 (56–78) (B) 64.75 ± 2.04 (54–75)	-Insomnia, hypertension: Diagnostic criteria for complications, "insomnia" caused by hypertension	NR	(1) HM	(1) Hypnotics (Estazolam 1 mg qd)	1. SAS 2. SDS 3. PSQI 4. TER (improvement of PSQI score) 5. Insomnia recurrence rate (1 yr f/u)	1. (A) < (B)* 2. (A) < (B)* 3. (A) < (B)* 4. (A) > (B)* 5. (A) < (B)*	NR
HM + Hypnotics vs. Hypnotics									
Jiang 2006 [47]	80(40:40)→80(40:40)	(A) 63.8 (44–83) (B) 62.6 (45–81)	-Insomnia: Guiding principles for clinical study of new Chinese medicines -Hypertension: WHO/ ISH criteria	NR	(1) HM (2) Antihypertensives (Captopril 12.0 mg tid) (3) Hypnotics (Estazolam 2 mg qd)	(1) Antihypertensives (Captopril 12.0 mg tid) (2) Hypnotics (Estazolam 2 mg qd)	1. TER (improvements of insomnia and Spiegel scale score) 2. TER (total sleep time, sleep onset latency, number of awakenings, sleep depth, dreaming, and feel after waking up) 3. BP	1. (A) > (B)* 2. (A) > (B) + (dreaming), (A) > (B)* (others) 3. (A) < (B) +	NR
HM vs. no additional intervention									
Ruan 2015 [48]	60(30:30)→60(30:30)	(A) 62.50 ± 5.80 (NR) (B) 63.10 ± 6.35 (NR)	-Insomnia: CCMD-3, PSQI ≥ 7 -Hypertension: 2010 China guidelines for the prevention and treatment of hypertension (sBP≥140 mmHg and/or dBP≥90 mmHg)	liver depression, spleen deficiency and blood stasis	(1) HM (2) Antihypertensives (Calcium channel blockers; ACE inhibitors or Angiotensin II receptor blockers; β-blockers)	(1) Antihypertensives (Calcium channel blockers; ACE inhibitors or Angiotensin II receptor blockers; β-blockers)	1. Ambulatory BP 2. Ambulatory HRV 3. PSQI 4. TCM syndrome score 5. TER (improvement of ambulatory BP) 6. TER (improvement of insomnia and PSQI score) 7. TER (improvement of TCM syndrome score)	1. (A) < (B)* (24 h sBP, dBP and night time sBP, dBP), N.S (others) 2. (A) < (B)* (average heart rate, rMSSD), (A) > (B)* (SDNN, SDANN, PNN50) 3. (A) < (B) + 4. (A) < (B)* 5. N.S 6. (A) > (B)* 7. (A) > (B)*	(A) bland taste in the mouth and dry mouth (1 case, relieved after drinking more water) (B) flushing of the face (1 case), mild edema of the ankle (2 cases) *N.S between (A) and (B)
Zhang 2015 [49]	60(30:30)→60(30:30)	(A) 63.07 ± 8.06 (NR) (B) 63.67 ± 7.35 (NR)	-Insomnia: The Chinese medical association's 2012 guidelines for the diagnosis and treatment of adult insomnia, PSQI > 7	NR	(1) HM (2) Antihypertensives (Amlodipine 5 mg qd or Levamlodipine 2.5 mg qd)	(1) Antihypertensives (Amlodipine 5 mg qd or Levamlodipine 2.5 mg qd)	1. Sleep efficiency 2. Sleep onset latency 3. Total sleep time 4. PSQI 5. BP 6. TER (improvement of	1. (A) > (B)* 2. (A) < (B) + 3. (A) > (B) + 4. (A) < (B) + 5.	(A) stomach distension and pain (3 cases, relieved after adding antacid)

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size (included →analyzed)	Mean age (range) (years)	Diagnostic criteria	Pattern identification	(A) Experimental intervention	(B) Control intervention	Outcome	Results reported	Adverse events
			-Hypertension: JNC 8 hypertension guideline				insomnia and PSQI score)	(A) < (B) + 6. (A) > (B)*	
Li 2018 [50]	α→60(30:30)	(A) 66.1 ± 5.61 (NR) (B) 65.2 ± 5.01 (NR)	-Insomnia: Clinical symptoms, PSQI > 7 -Hypertension: 2010 China guidelines for the prevention and treatment of hypertension, stage 1 hypertension (159 ≥ sBP ≥ 140 mmHg or 99 ≥ dBP ≥ 90 mmHg)	liver qi depression	(1) HM (2) Antihypertensives (Amlodipine Besylate 2.5 mg bid, Valsartan 80 mg 1 T)	(1) Antihypertensives (Amlodipine Besylate 2.5 mg bid, Valsartan 80 mg 1 T)	1. Ambulatory BP 2. PSQI 3. SAS 4. SDS	1. (A) < (B)* (24 h sBP, dBP) 2. (A) < (B)* 3. (A) < (B)* 4. (A) < (B)*	None
	β→60(30:30)	(A) 64.0 ± 3.91 (NR) (B) 63.6 ± 4.01 (NR)	-Insomnia: Clinical symptoms, PSQI > 7 -Hypertension: 2010 China guidelines for the prevention and treatment of hypertension, stage 2 hypertension (179 ≥ sBP ≥ 160 mmHg or 109 ≥ dBP ≥ 100 mmHg)	liver qi depression	(1) HM (2) Antihypertensives (Amlodipine Besylate 2.5 mg bid, Valsartan 80 mg 1 T)	(1) Antihypertensives (Amlodipine Besylate 2.5 mg bid, Valsartan 80 mg 1 T)	1. Ambulatory BP 2. PSQI 3. SAS 4. SDS	1. (A) < (B)* (24 h sBP, dBP) 2. (A) < (B)* 3. (A) < (B)* 4. (A) < (B)*	(A) nausea and vomiting (1 case)
	γ→60(30:30)	(A) 67.1 ± 5.61 (NR) (B) 66.7 ± 5.41 (NR)	-Insomnia: Clinical symptoms, PSQI > 7 -Hypertension: 2010 China guidelines for the prevention and treatment of hypertension, stage 3 hypertension (sBP ≥ 180 mmHg or dBP ≥ 110 mmHg)	liver qi depression	(1) HM (2) Antihypertensives (Amlodipine Besylate 5 mg bid, Valsartan 80 mg 1 T)	Antihypertensives (Amlodipine Besylate 5 mg bid, Valsartan 80 mg 1 T)	1. Ambulatory BP 2. PSQI 3. SAS 4. SDS	1. (A) < (B)* (24 h sBP, dBP) 2. (A) < (B)* 3. (A) < (B)* 4. (A) < (B)*	(B) nausea and vomiting (1 case)
HM vs. Antihypertensives + Hypnotics									
Wang 2012 [51]	60(30:30)→60(30:30)	(A) 70.4 ± 7.4 (NR) (B) 70.7 ± 8.3 (NR)	-Insomnia: CCMD-3 -Hypertension: WHO criteria	NR	(1) HM	(1) Antihypertensives (Amlodipine 5 mg qd or Losartan Potassium 50 mg qd) (2) Hypnotics (Estazolam 1–2 mg qd)	1. TER (improvement of SDRS score) 2. SDRS 3. HAMA 4. BP	1. N.S 2. (A) < (B)* 3. N.S 4. N.S	NR

'*' and '+' mean significant differences between two groups, $p < 0.05$ and $p < 0.01$, respectively. 'N.S' means no significant difference between two groups, $p > 0.05$.

Li (2018), $\alpha + \beta + \gamma = 224$. '$\alpha + \beta + \gamma$' refers to initially enrolled participants. They were then classified according to their BP levels before the randomization. The authors only described this process, and did not specify the numbers corresponding to α, β, and γ.

Abbreviations. ACE, angiotensin converting enzyme; BP, blood pressure; CCMD, Chinese classification of mental disorders; dBP, diastolic blood pressure; HAMA, Hamilton anxiety rating scale; HM, herbal medicine; HRV, heart rate variability; ISH, the international society of hypertension; JNC, joint national committee; NR, not recorded; PSQI, Pittsburgh sleep quality index; SAS, Zung self-rating anxiety scale; sBP, systolic blood pressure; SDRS, Sleep dysfunction rating scale; SDS, Zung self-rating depression scale; TCM, traditional Chinese medicine; TER, total effective rate; WHO, world health organization.

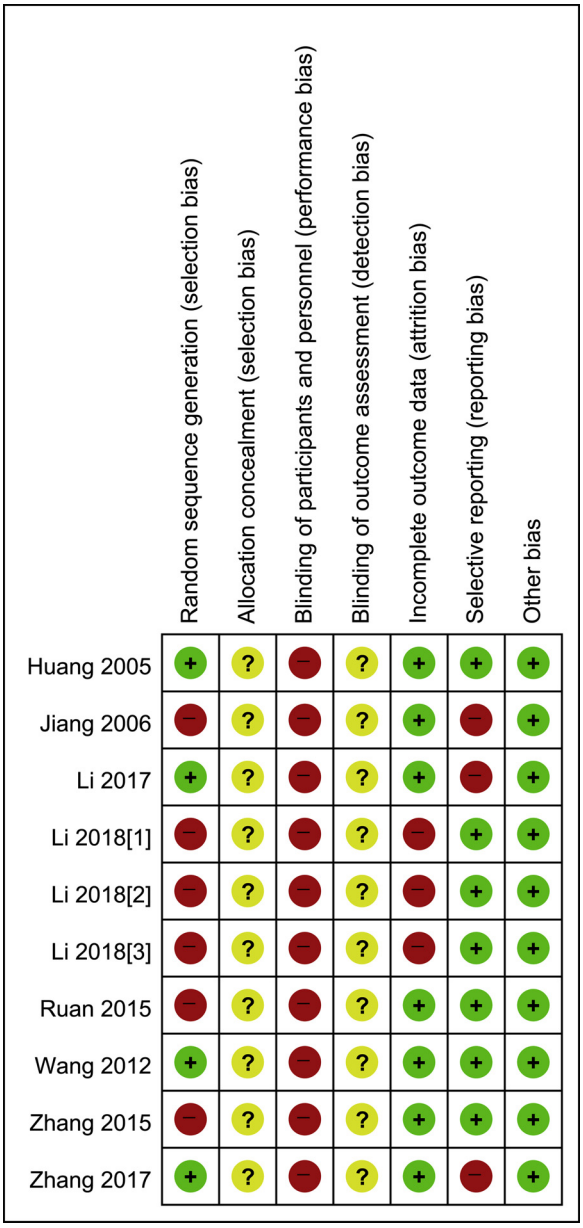

Fig. 2. Risk of bias summary for all included studies.
Low, unclear, and high risk, respectively, are represented with the following symbols: "+", "?", and "-"

spinosae semen, and *Ligustici rhizoma,* which were used in four studies (50%) each. In addition, *Paeoniae radix alba* was used in three studies (37.5%) and other all herbs were used once or twice.

3.4. Effectiveness of HM for insomnia in elderly with hypertension

3.4.1. HM vs. hypnotics (three RCTs)

Meta-analysis was available only in TER based on improvement of insomnia. The results showed that the HM group had significantly higher TER without significant heterogeneity (328 participants; RR 1.24, 95% CI 1.12–1.39, I^2 = 0%) (Appendix 4 in Supplementary materials).

Zhang et al. [46] prescribed HM for 4 weeks and reported the PSQI, recurrence rate of insomnia at 1-year follow-up, SAS, and SDS as their outcomes. They found that the HM group was associated with significantly lower PSQI, SAS, and SDS scores at post-intervention and lower recurrence rate at 1-year follow-up (all, P < 0.05). Li [45] prescribed HM for 4 weeks and reported BP and TCM syndrome score as their outcomes. They found that the HM group was associated with significantly lower systolic BP (sBP), diastolic BP (dBP), and TCM syndrome score post-intervention (all, P < 0.05).

3.4.2. HM plus hypnotics vs. hypnotics alone (1 RCT)

Jiang et al. [47] prescribed HM plus hypnotics or hypnotics alone for 3 weeks and reported TER based on the improvement of insomnia and BP as their outcomes. The results showed that the combined therapy group was associated with significantly higher TER and lower sBP and dBP (P < 0.05 or P < 0.01).

3.4.3. HM vs. no intervention (3 RCTs)

Of the studies included in this category, Li [50] divided the participants into three groups according to their baseline BP and reported the data separately. Therefore, we regarded these as individual data and conducted meta-analyses. Among the outcomes reported, meta-analyses were performed on TER based on the improvement of insomnia, BP, PSQI, SAS, and SDS. The synthesized results showed that the HM group showed significantly higher TER (120 participants; RR 1.70, 95% CI 1.25 to 2.33, I^2 = 0%), and lower sBP (300 participants; MD -5.63 mmHg, 95% CI -7.18 to -4.09, I^2 = 54%), dBP (300 participants; MD -4.40 mmHg, 95% CI -5.63 to -3.18, I^2 = 55%), PSQI (300 participants; MD -4.11 score, 95% CI -5.72 to -2.50, I^2 = 91%), SAS (180 participants; MD -6.60 score, 95% CI -7.79 to -5.41, I^2 = 90%), and SDS scores (180 participants; MD -6.15 score, 95% CI -7.43 to -4.87, I^2 = 63%) (Fig. 3, Appendix 4 in Supplementary materials).

The results regarding sBP, dBP, PSQI, SAS, and SDS scores showed substantial heterogeneities; however, subgroup analysis according to treatment duration could not explain the heterogeneities except in the case of sBP. In most cases, the statistical significances were maintained when sub-analyzed according to the treatment durations; however, significant statistical differences in PSQI scores disappeared when HM was prescribed within 4 weeks.

Ruan [48] prescribed HM for 4 weeks and reported TERs based on the improvement of hypertension or the TCM syndrome and TCM syndrome score as their outcomes. The results showed that the HM group was associated with significantly higher TER based on the improvement of the TCM syndrome and lower TCM syndrome scores (both P < 0.05) than that of the no treatment group. However, there was no significant difference between groups regarding the TER based on the improvement of hypertension (P > 0.05).

3.4.4. HM vs. antihypertensives plus hypnotics (1 RCT)

Wang et al. [51] compared HM with antihypertensives plus hypnotics during a 4-week period and reported TER based on improvement of insomnia, BP, SDRS, and HAMA as their outcomes. The results showed that the HM group was associated with significantly lower SDRS score (P < 0.05). However, there were no significant differences between groups regarding TER based on the improvement of insomnia, BP, and HAMA (P > 0.05).

3.5. Safety profile

There were only three studies that reported safety data [48–50]. They all compared HM with no intervention. According to the results of the meta-analysis, there was no significant difference between groups with respect to the incidence of AEs with no significant heterogeneity (300 participants; RR 1.44, 95% CI 0.44–4.72, I^2 = 0%) (Fig. 4). This result was maintained in the subgroup analysis according to the treatment period.

3.6. Quality of evidence

In the comparison between HM and hypnotics, the quality of evidence of TER based on the improvement of insomnia was assessed to be

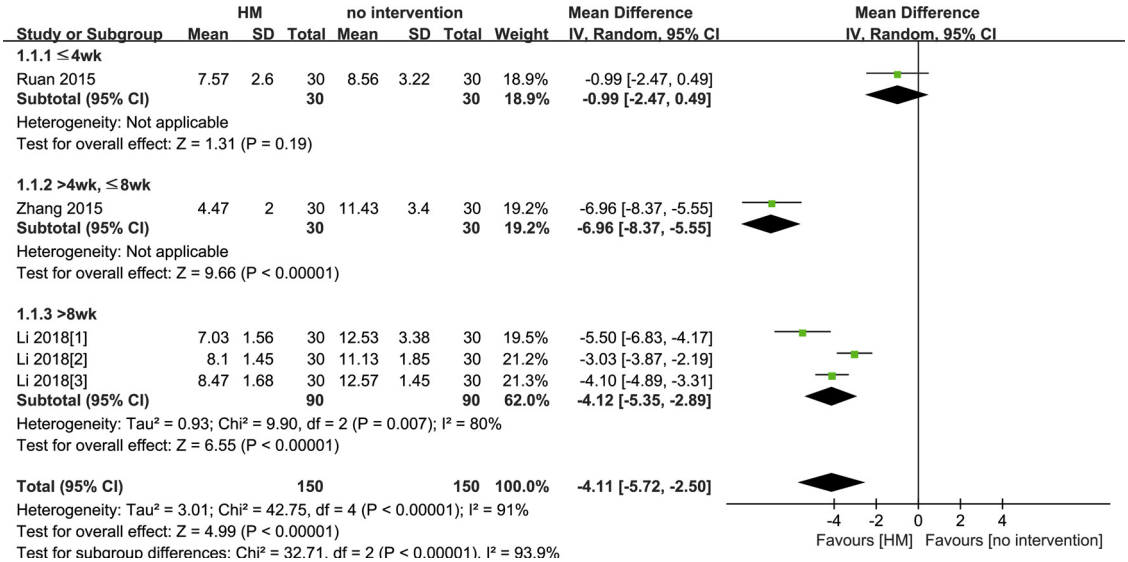

Fig. 3. Forest plot for the comparison of HM with no intervention. Outcome: PSQI score.
HM, herbal medicine; PSQI, Pittsburgh sleep quality index

"Low." The reasons for this were the high risk of bias of the included RCTs and indirectness of the outcome measure (Table 2). Meanwhile, in the comparison between HM and no intervention, the quality of evidence for TER based on the improvement of insomnia, sBP, dBP, PSQI, SAS, SDS, and AEs were assessed and graded as "Very low" to "Moderate." The main reasons for this grading were the high risk of bias of the included RCTs and low precision of the results because they did not satisfy the optimal sample size and had wide CIs (Table 3).

3.7. Publication bias

Because the meta-analysis did not involve more than ten studies, evaluation of publication bias using funnel plots was impossible.

4. Discussion

This review aimed to evaluate the effectiveness and safety of HM for insomnia in elderly with hypertension. Through comprehensive searches, eight RCTs were included in this review.

According to the results of the meta-analyses, based on routine antihypertensive therapies, HM group showed significantly higher TER based on the improvement of insomnia than treatment with hypnotics. Moreover, the HM group showed significantly higher TER based on the improvement of insomnia and lower sBP, dBP, PSQI, SAS, and SDS scores than the no intervention group. In most cases, subgroup analysis according to the treatment duration did not show meaningful changes in significance level; however, there was no significant difference in PSQI score when HM was prescribed within 4 weeks compared with no

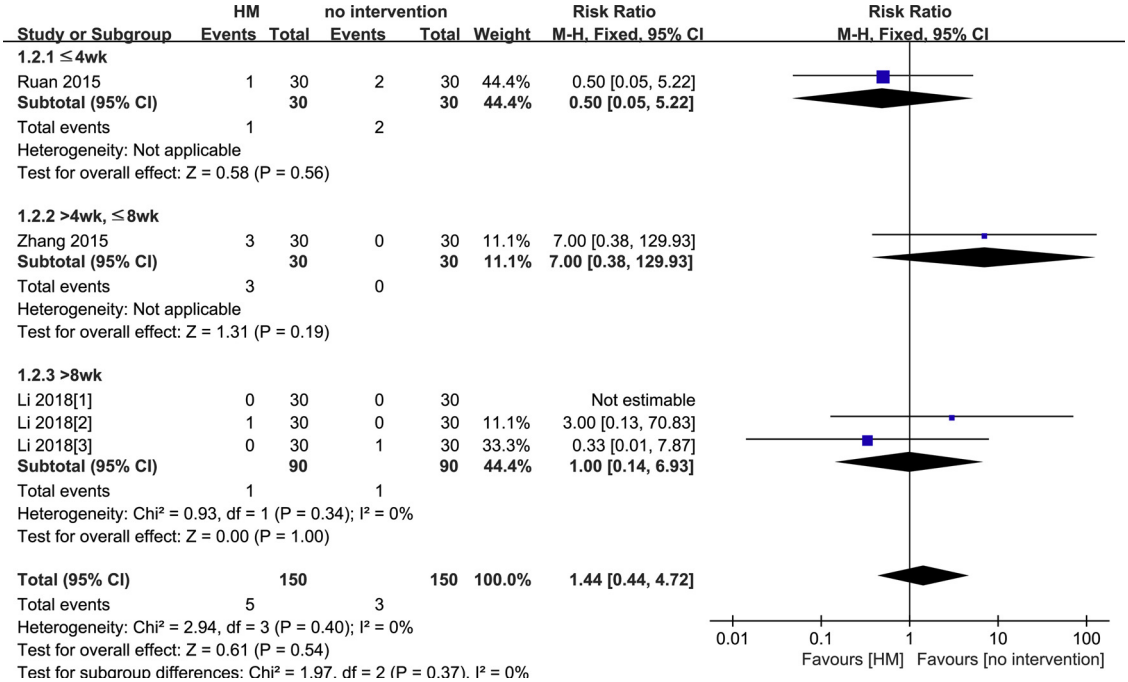

Fig. 4. Forest plot for the comparison of HM with no intervention. Outcome: incidence of adverse events.
HM, herbal medicine

Table 2
Summary of findings table: HM compared to hypnotics.

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Hypnotics	Risk with HM				
TER (insomnia)	740 per 1,000	917 per 1,000 (828 to 1,000)	RR 1.24 (1.12 to 1.39)	328 (3 RCTs)	⊕⊕◯◯ (Low)	Risk of bias (-1) Indirectness (-1)

Abbreviations. CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HM, herbal medicine; RCT, randomized controlled trial; RR, risk ratio; TER, total effective rate.

Table 3
Summary of findings table: HM compared to no intervention.

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with No intervention	Risk with HM				
TER (insomnia)	450 per 1,000	765 per 1,000 (563 to 1,000)	RR 1.70 (1.25 to 2.33)	120 (2 RCTs)	⊕◯◯◯ (Very Low)	Risk of bias (-1) Indirectness (-1) Imprecision (-1)
sBP	–	MD 5.63 mmHg lower (7.18 to 4.09 lower)	–	300 (5 RCTs)	⊕⊕⊕◯ (Moderate)	Risk of bias (-1)
dBP	–	MD 4.40 mmHg lower (5.63 to 3.18 lower)	–	300 (5 RCTs)	⊕⊕⊕◯ (Moderate)	Risk of bias (-1)
PSQI	–	MD 4.11 score lower (5.72 to 2.50 lower)	–	300 (5 RCTs)	⊕⊕⊕◯ (Moderate)	Risk of bias (-1)
SAS	–	MD 6.60 score lower (7.79 to 5.41 lower)	–	180 (3 RCTs)	⊕⊕◯◯ (Low)	Risk of bias (-2)
SDS	–	MD 6.15 score lower (7.43 to 4.87 lower)	–	180 (3 RCTs)	⊕⊕◯◯ (Low)	Risk of bias (-2)
AEs	20 per 1,000	29 per 1,000 (9 to 94)	RR 1.44 (0.44 to 4.72)	300 (5 RCTs)	⊕◯◯◯ (Very Low)	Risk of bias (-1) Imprecision (-2)

Abbreviations. AEs, adverse events; CI, confidence interval; dBP, diastolic blood pressure; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HM, herbal medicine; MD, mean difference; RCT, randomized controlled trial; RR, risk ratio; PSQI, Pittsburgh Sleep Quality Index; SAS, Zung self-rating anxiety scale; sBP, systolic blood pressure; SDS, Zung self-rating depression scale; TER, total effective rate.

intervention. In addition to the studies included in the meta-analysis, two different studies compared HM plus hypnotics with hypnotics alone [47], and HM with antihypertensives plus hypnotics [51]. In the former study, the combined therapy group was associated with significantly higher TER based on the improvement of insomnia, and significantly lower sBP and dBP. In the latter study, the HM group was associated with significantly lower SDRS score, while there were no significant differences in TER based on the improvement of insomnia, BP, and HAMA score between groups.

There were only three studies [48–50] that reported whether AEs occurred. They all compared HM with no intervention and there were no significant differences in the incidence of AEs between the two groups. However, since HM is also a type of medicine, the fact that there was no significant difference in the incidence of AEs relative to no intervention may be circumstantial evidence that HM is relatively safe.

We explored the possibility of using HM for the two concomitant diseases, insomnia and hypertension in elderly patients to overcome the one-drug-one target paradigm of conventional synthetic drugs [52], taking into account the characteristic that HM comprises multiple active components. In order to reduce the use of harmful drugs in the elderly, non-pharmacological interventions, such as patient education and cognitive behavioral therapy, have been shown to be effective; however, more acceptable adjuvant intervention is needed [53]. In this regard, HM may be a solution. This review suggests that HM as an adjunctive therapy to routine antihypertensives for the treatment of insomnia in hypertensive elderly patients might have some benefits in improving anxiety and depression as well as in relieving symptoms of insomnia and lowering BP compared with antihypertensives combined with hypnotics or antihypertensives alone. When compared with antihypertensives and hypnotics, HM alone might improve insomnia, but it seemed that there is no significant difference in BP or anxiety level. In other words, current evidence suggests that HM alone is not yet sufficient to replace both hypnotics and antihypertensives for insomnia in elderly with hypertension. However, the number of included studies was small and the methodological quality of them was generally low. Above all, the quality of the evidence assessed using the GRADE approach was “Very low” to “Moderate” and there was no high quality of evidence. Therefore, our confidence in the estimated effect is limited and attention should be paid to interpreting the results.

This study has the following limitations. As described previously, the reliability of the results is markedly limited because the methodological quality of the included studies and quality of evidence for the main findings were generally low. This means that our conclusion may be significantly changed by rigorous further studies. In our protocol, “change in drug use” was the primary outcome measure to assess the impact of HM on the polypharmacy risk of elderly patients; however, none of the included studies reported this. Therefore, the impact of HM on this issue could only be indirectly assessed through the multiple components acting on multiple targets. There was also a lack of adequate studies to perform subgroup analysis according to the severity of insomnia, as described in our protocol. Because all of the included studies were conducted in China, potential publication bias was suspected; however, the lack of studies made it impossible to assess the publication bias using funnel plots. None of the included studies had pre-registered the study protocols or used placebo as a control intervention. This indicates that the results from these studies are highly likely to be over-estimated. Despite subgroup analysis, heterogeneity between studies was not solved. In addition, the differences in the baseline BP level, diagnostic criteria of insomnia, and specific TCM patterns between participants suggested clinical heterogeneity among the included studies.

Therefore, the following should be considered in future studies. (1) Larger RCTs implemented using rigorous methodology are needed on this topic. In particular, protocols should be registered prior to study

initiation to reduce potential reporting bias, and a placebo control should be used to reduce potential performance bias. (2) If the possibility of drug withdrawal or tapering of the participants is evaluated under the judgment of the clinician during the study period, more practical findings will be obtained. (3) Using recently emerged advanced research methods such as network pharmacology, with advances in computer technology [54], the underlying molecular mechanisms of HMs for multiple diseases need to be explored. (4) The herb-drug interaction induced by unregulated use of herbs has attracted attention as another risk factor of polypharmacy [55–58]. To explain this interaction, previous studies have focused on cytochrome P450 regulation, but currently there is a multidimensional approach, involving factors such as examining the roles of drug transport proteins at the blood-cerebrospinal fluid barrier and blood-brain barrier [59]. Therefore, the safety evaluation of HM should be reported more elaborately, especially in elderly patients. This should include not only clinical symptoms and signs, routine liver and renal function tests, vital signs, but also cardiac function, risk of falls, motor function, and frailty, as needed. (5) Finally, to be adopted at the level of government policy, the economic evaluation of such interventions should be performed.

5. Conclusion

The current evidence suggests that based on routine antihypertensive therapies, HM might have some beneficial effects in improving insomnia, lowering BP, and improving mental health in the elderly patients with both insomnia and hypertension, compared to hypnotics or no intervention. Our findings suggest that HM might have potential to help withdrawal from conventional drugs as a complement, but not as a substitute, in this population having high risk of polypharmacy. However, since the methodological quality of the included studies was poor and the quality of evidence was generally low, the results should be interpreted with caution. Given polypharmacy issues in elderly, further larger, well-designed RCTs are necessary to confirm the benefits of HM.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

The study was conceptualized by CYK. CYK and BL searched and selected the trials, and extracted, analyzed, and interpreted the data. CYK and BL drafted the manuscript. SYC, JWK, and SHK helped with the study design and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eujim.2019.100961.

References

[1] J. López-Torres Hidalgo, B. Navarro Bravo, I. Párraga Martínez, F. Andrés Pretel, J. Téllez Lapeira, C. Boix Gras, Understanding insomnia in older adults, Int. J. Geriatr. Psychiatry 27 (1) (2012) 1086–1093.
[2] D.J. Foley, A.A. Monjan, S.L. Brown, E.M. Simonsick, R.B. Wallace, D.G. Blazer, Sleep complaints among elderly persons: an epidemiologic study of three communities, Sleep 18 (6) (1995) 425–432.
[3] A.I. Ayoub, M. Attia, H.M. El Kady, A. Ashour, Insomnia among community dwelling elderly in Alexandria, Egypt, J. Egypt. Public Health Assoc. 89 (3) (2014) 136–142.
[4] R.V. Picon, F.D. Fuchs, L.B. Moreira, S.C. Fuchs, Prevalence of hypertension among elderly persons in urban Brazil: a systematic review with meta-analysis, Am. J. Hypertens. 26 (4) (2013) 541–548.
[5] L. Wu, Y. He, B. Jiang, D. Sun, J. Wang, M. Liu, S. Yang, Y. Wang, Trends in prevalence, awareness, treatment and control of hypertension during 2001-2010 in an urban elderly population of China, PLoS One 10 (8) (2015) e0132814.
[6] T. Zdrojewski, B. Wizner, A. Więcek, P. Ślusarczyk, J. Chudek, M. Mossakowska, P. Bandosz, M. Bobak, K. Kozakiewicz, G. Broda, B. Wyrzykowski, T. Grodzicki, Prevalence, awareness, and control of hypertension in elderly and very elderly in Poland: results of a cross-sectional representative survey, J. Hypertens. 34 (3) (2016) 532–538.
[7] M.J. Sateia, D.J. Buysse, A.D. Krystal, D.N. Neubauer, J.L. Heald, Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline, J. Clin. Sleep Med. 13 (2) (2017) 307–349.
[8] P.K. Whelton, R.M. Carey, W.S. Aronow, D.E. Casey Jr, K.J. Collins, C. Dennison Himmelfarb, S.M. DePalma, S. Gidding, K.A. Jamerson, D.W. Jones, E.J. MacLaughlin, P. Muntner, B. Ovbiagele, S.C. Smith Jr, C.C. Spencer, R.S. Stafford, S.J. Taler, R.J. Thomas, K.A. Sr Williams, J.D. Williamson, J.T. Wright Jr, ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines, J. Am. Coll. Cardiol. 71 (19) (2017) e127–e248 2018.
[9] I. Haimov, Association between memory impairment and insomnia among older adults, Eur. J. Ageing 3 (2) (2006) 107.
[10] K.M. de Almondes, M.V. Costa, L.F. Malloy-Diniz, B.S. Diniz, Insomnia and risk of dementia in older adults: systematic review and meta-analysis, J. Psychiatr. Res. 77 (2016) 109–115.
[11] I. Okajima, Y. Komada, T. Nomura, K. Nakashima, Y. Inoue, Insomnia as a risk for depression: a longitudinal epidemiologic study on a Japanese rural cohort, J. Clin. Psychiatry 73 (3) (2012) 377–383.
[12] C.Y. Hsu, Y.T. Chen, M.H. Chen, C.C. Huang, C.H. Chiang, P.H. Huang, J.W. Chen, T.J. Chen, S.J. Lin, H.B. Leu, W.L. Chan, The association between insomnia and increased future cardiovascular events: a nationwide population-based study, Psychosom. Med. 77 (7) (2015) 743–751.
[13] N. Alwardat, L. Di Renzo, R.C. de Miranda, S. Alwardat, P. Sinibaldi Salimei, A. De Lorenzo, Association between hypertension and metabolic disorders among elderly patients in North Jordan, Diabetes Metab. Syndr. 12 (5) (2018) 661–666.
[14] M.G. Kang, S.W. Kim, S.J. Yoon, J.Y. Choi, K.I. Kim, C.H. Kim, Association between frailty and hypertension prevalence, treatment, and control in the elderly Korean population, Sci. Rep. 7 (1) (2017) 7542.
[15] S. Parthasarathy, M.M. Vasquez, M. Halonen, R. Bootzin, S.F. Quan, F.D. Martinez, S. Guerra, Persistent insomnia is associated with mortality risk, Am. J. Med. 128 (3) (2015) 268–275.
[16] D. Zhou, B. Xi, M. Zhao, L. Wang, S.P. Veeranki, Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III linked mortality study, Sci. Rep. 8 (1) (2018) 9418.
[17] D.C. Jarrin, P.K. Alvaro, M.A. Bouchard, S.D. Jarrin, C.L. Drake, C.M. Morin, Insomnia and hypertension: a systematic review, Sleep Med. Rev. 41 (2018) 3–38.
[18] S.J. Thomas, D. Calhoun, Sleep, insomnia, and hypertension: current findings and future directions, J. Am. Soc. Hypertens. 11 (2) (2017) 122–129.
[19] F. Domínguez, V. Fuster, J.M. Fernández-Alvira, L. Fernández-Friera, B. López-Melgar, R. Blanco-Rojo, A. Fernández-Ortiz, P. García-Pavía, J. Sanz, J.M. Mendiguren, B. Ibañez, H. Bueno, E. Lara-Pezzi, J.M. Ordovás, Association of sleep duration and quality with subclinical atherosclerosis, J. Am. Coll. Cardiol. 73 (2) (2019) 134–144.
[20] B. Aggarwal, N. Makarem, R. Shah, M. Emin, Y. Wei, M.P. St-Onge, S. Jelic, Effects of inadequate sleep on blood pressure and endothelial inflammation in women: findings from the American Heart Association Go Red for Women Strategically Focused Research Network, J. Am. Heart Assoc. 7 (12) (2018).
[21] D. Gnjidic, S.N. Hilmer, F.M. Blyth, V. Naganathan, L. Waite, M.J. Seibel, A.J. McLachlan, R.G. Cumming, D.J. Handelsman, D.G. Le Couteur, Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes, J. Clin. Epidemiol. 65 (2012) 989–995.
[22] J. Kim, A.L. Parish, Polypharmacy and medication management in older adults, Nurs. Clin. North Am. 52 (3) (2017) 457–468.
[23] M.J. Rawle, R. Cooper, D. Kuh, M. Richards, Associations between polypharmacy and cognitive and physical capability: a British birth cohort study, J. Am. Geriatr. Soc. 66 (5) (2018) 916–923.
[24] J.M. McMillan, E. Aitken, J.M. Holroyd-Leduc, Management of insomnia and long-term use of sedative-hypnotic drugs in older patients, CMAJ 185 (17) (2013) 1499–1505.
[25] By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, J. Am. Geriatr. Soc. 63 (11) (2015) 2227–2246.
[26] T.M. Alhawassi, I. Krass, L.G. Pont, Antihypertensive-related adverse drug reactions among older hospitalized adults, Int. J. Clin. Pharm. 40 (2) (2018) 428–435.
[27] V. van der Wardt, J.K. Harrison, T. Welsh, S. Conroy, J. Gladman, Withdrawal of antihypertensive medication: a systematic review, J. Hypertens. 35 (9) (2017) 1742–1749.
[28] J. Luo, H. Xu, K.J. Chen, Potential benefits of Chinese herbal medicine for elderly

patients with cardiovascular diseases, J. Geriatr. Cardiol. 10 (4) (2013) 305–309.
[29] S. Takayama, K. Iwasaki, Systematic review of traditional Chinese medicine for geriatrics, Geriatr. Gerontol. Int. 17 (5) (2017) 679–688.
[30] X. Ni, J.L. Shergis, X. Guo, A.L. Zhang, Y. Li, C. Lu, C.C. Xue, Updated clinical evidence of Chinese herbal medicine for insomnia: a systematic review and meta-analysis of randomized controlled trials, Sleep Med. 16 (12) (2015) 1462–1481.
[31] Z. Chen, L. Wang, G. Yang, H. Xu, J. Liu, Chinese herbal medicine combined with conventional therapy for blood pressure variability in hypertension patients: a systematic review of randomized controlled trials, Evid. Complement. Alternat. Med. 2015 (2015) 582751.
[32] O. Pelkonen, Q. Xu, T.P. Fan, Why is research on herbal medicinal products important and how can we improve its quality? J. Tradit. Complement. Med. 4 (1) (2014) 1–7.
[33] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009) e1000097.
[34] C.Y. Kwon, B. Lee, S.Y. Chung, J.W. Kim, S.H. Kim, Oriental herbal medicine for insomnia in the elderly with hypertension: a systematic review protocol, Medicine (Baltimore) 97 (36) (2018) e12200.
[35] A.P. Spira, S.A. Beaudreau, K.L. Stone, E.J. Kezirian, L.Y. Lui, S. Redline, S. Ancoli-Israel, K. Ensrud, A. Stewart, Osteoporotic fractures in men study, reliability and validity of the Pittsburgh sleep quality index and the epworth sleepiness scale in older men, J. Gerontol. A Biol. Sci. Med. Sci. 67A (4) (2012) 433–439.
[36] C.H. Bastien, A. Vallières, C.M. Morin, Validation of the Insomnia Severity Index as an outcome measure for insomnia research, Sleep Med. 2 (2001) 297–307.
[37] D.B. Clark, J.E. Donovan, Reliability and validity of the Hamilton Anxiety Rating Scale in an adolescent sample, J. Am. Acad. Child Adolesc. Psychiatry 33 (3) (1994) 354–360.
[38] M. Hamilton, A rating scale for depression, J. Neurol. Neurosurg. Psychiatry 23 (1960) 56–62.
[39] J.A. Yesavage, T.L. Brink, T.L. Rose, O. Lum, V. Huang, M. Adey, V.O. Leirer, Development and validation of a geriatric depression screening scale: a preliminary report, J. Psychiatr. Res. 17 (1) (1982) 37–49 1983.
[40] National Institute of Mental Health, TESS (Treatment emergent symptom scale-write-in), Psychopharmacol. Bull. 21 (1985) 1069–1072.
[41] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, Cochrane Bias Methods Group, Cochrane Statistical Methods Group, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[42] H. Balshem, M. Helfand, H.J. Schünemann, A.D. Oxman, R. Kunz, J. Brozek, G.E. Vist, Y. Falck-Ytter, J. Meerpohl, S. Norris, G.H. Guyatt, GRADE guideline: 3. Rating the quality of evidence, J. Clin. Epidemiol. 64 (4) (2011) 401–406.
[43] M. Borenstein, L.V. Hedges, J.P. Higgins, H.R. Rothstein, A basic introduction to fixed-effect and random-effects models for meta-analysis, Res. Synth. Methods 1 (2) (2011) 97–111.
[44] J.H. Huang, Effect of integrated Chinese and Western medicine on blood pressure circadian rhythm and nighttime sleep in 72 hypertensive patients, TCM Res. 18 (6) (2005) 33–35.
[45] X.F. Li, Clinical study on the treatment of senile essential hypertension with insomnia caused by self-made Erxia decoction, Yunnan J. TCM Materia Medica 38 (12) (2017) 40–41.
[46] L. Zhang, Z.D. Zhang, Y.D. Li, C.H. Yin, F.D. Xue, Observation on the effect of Xuefu zhuyu decoction on the treatment of hypertension with insomnia, Nei Mongol J. TCM 36 (8) (2017) 38–39.
[47] M.Q. Jiang, X.G. Zhou, F. Wang, Treatment of 40 cases of essential hypertension with insomnia by integrative Chinese and Western Medicine, SH J. TCM 27 (2) (2006) 160–161.
[48] J.J. Ruan, Clinical Observation of Common Cardiovascular Diseases Complicated With Insomnia Investigatiomnia, Thesis of Master's degree in Anhui University of Chinese Medicine, 2015.
[49] M.L. Zhang, Therapeutic effect of Zaoren anshen capsule on patients with hypertension and insomnia, Chin. J. Integ. Med. Cardio-/Cerebrovasc. Dis. 13 (15) (2015) 1789–1791.
[50] X.B. Li, Effect of Shuganjieyu Capsule on Hypotensive Effect in Patients With Essential Hypertension with Insomnia, Thesis of Master's degree in Shenyang Medical College, 2018.
[51] L. Wang, Y.M. Cheng, Q.C. Wang, Treatment of senile hypertension with insomnia by "Erbai Jiangya Decoction": a report of 30 cases, SH J. TCM 46 (5) (2012) 47–48.
[52] C.T. Che, Z.J. Wang, M.S. Chow, C.W. Lam, Herb-herb combination for therapeutic enhancement and advancement: theory, practice and future perspectives, Molecules 18 (5) (2013) 5125–5141.
[53] C. Dou, J. Rebane, S. Bardal, Interventions to improve benzodiazepine tapering success in the elderly: a systematic review, Aging Ment. Health (2018) 1–6.
[54] S. Gu, J. Pei, Chinese herbal medicine meets biological networks of complex diseases: a computational perspective, Evid. Complement. Alternat. Med. 2017 (2017) 7198645.
[55] T.B. Agbabiaka, N.H. Spencer, S. Khanom, C. Goodman, Prevalence of drug-herb and drug-supplement interactions in older adults: a cross-sectional survey, Br. J. Gen. Pract. 68 (675) (2018) e711–e717.
[56] D. Dookeeram, S. Bidaisee, J.F. Paul, P. Nunes, P. Robertson, V.R. Maharaj, I. Sammy, Polypharmacy and potential drug-drug interactions in emergency department patients in the Caribbean, Int. J. Clin. Pharm. 39 (5) (2017) 1119–1127.
[57] K.H. Pitkälä, M.H. Suominen, J.S. Bell, T.E. Strandberg, Herbal medications and other dietary supplements. A clinical review for physicians caring for older people, Ann. Med. 48 (8) (2016) 586–602.
[58] K.A. Cappuzzo, Herbal product use in a patient with polypharmacy, Consult. Pharm. 21 (11) (2006) 911–915.
[59] L.W. Kibathi, S. Bae, S.R. Penzak, P. Kumar, Potential influence of centrally acting herbal drugs on transporters at the blood-cerebrospinal fluid barrier and blood-brain barrier, Eur. J. Drug Metab. Pharmacokinet. 43 (December (6)) (2018) 619–635, https://doi.org/10.1007/s13318-018-0486-6.