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Acupuncture for Managing Cancer-Related Insomnia: A Systematic Review of Randomized Clinical Trials

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Abstract

Background. Insomnia is a prominent complaint of cancer patients that can significantly affect their quality of life and symptoms related to sleep quality. Conventional drug approaches have a low rate of success in alleviating those suffering insomnia. The aim of this systematic review was to assess the efficacy of acupuncture in the management of cancer-related insomnia. *Methods*. A total of 12 databases were searched from their inception through January 2016 without language restriction. Randomized controlled trials (RCTs) and quasi-RCTs were included if acupuncture was used as the sole intervention or as an adjunct to another standard treatment for any cancer-related insomnia. The data extraction and the risk of bias assessments were performed by 2 independent reviewers. *Results*. Of the 90 studies screened, 6 RCTs were included. The risk of bias was generally unclear or low. Three RCTs showed equivalent effects on the Pittsburgh Sleep Quality Index and 2 RCTs showed the similar effects on response rate to those of conventional drugs at the end of treatment. The other RCT showed acupuncture was better than hormone therapy in the numbers of hours slept each night and number of times woken up each night. The 3 weeks of follow-up in 2 RCTs showed superior effects of acupuncture compared with conventional drugs, and a meta-analysis showed significant effects of acupuncture. Two RCTs tested the effects of acupuncture on cancer-related insomnia compared with sham acupuncture. One RCT showed favourable effects, while the other trial failed to do so. *Conclusion*. There is a low level of evidence that acupuncture may be superior to sham acupuncture, drugs or hormones therapy. However, the number of studies and effect size are small for clinical significance. Further clinical trials are warranted.

Keywords

acupuncture, cancer, insomnia, sleep disturbance, systematic review

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Introduction

Sleep disturbance and insomnia, which are prominent complaints of cancer patients, have become a significant problem.[1,2] Up to 80% of patients with cancer will complain of sleep disturbance during diagnosis, treatment, and as far as 10 years into survivorship.[3] Daytime sleepiness and sleep disturbances have been reported to influence perceptions of fatigue.[3,4] A study on cancer survivors showed that 52% reported sleeping difficulties and 58% reported cancer-aggravated sleeping problems.[5] Insomnia in cancer patients is frequent and is severe enough to warrant treatment with pharmacological and psychological therapy. Approximately 25% to 50% of patients with cancer-related insomnia are treated with sedative-hypnotics drugs.[6,7] However, cancer patients often face several problems and limitations from the pharmacological treatments, including dizziness, residual daytime sedation, fatigue, daytime sleepiness, and headache.[8,9] The use of complementary and alternative medicine is common among cancer patients.[10] In particular, clinical research has shown that acupuncture may provide

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clinical benefit in cancer patients compared with related symptom control and supportive care.[11] Acupuncture may help treat specific cancer-related symptoms, including pain, gastrointestinal side effects, hot flushes, fatigue, anxiety, and depression.[12-18]

There are 3 systematic reviews related to the effects of acupuncture on insomnia.[18-20] One review yielded mixed evidence,[19] while the other Cochrane systematic review showed that the acupuncture was not more effective than routine care with noncancer-related insomnia patients.[20] The third review assessed the use of acupuncture in cancer care, including the treatment of insomnia.[18] That review showed favourable effects of acupuncture on sleep quality from 3 trials with a high risk of bias. However, that review included only studies in English, one included trial was not relevant for insomnia[21] and the studies are outdated. There has been no current systematic review that evaluated the clinical evidence of acupuncture for cancer-related insomnia specifically. The aims of this systematic review were to update, complete, and critically evaluate the efficacy of acupuncture in the management of cancer-related insomnia.

Methods

Study Registration

The protocol for this systematic review was registered in the Prospective Register of Systematic Reviews (PROSPERO): CRD42015027385.[22]

Data Sources

The following databases were searched from inception through January 2016: PubMed, EMBASE, AMED, the Cochrane Library, 7 Korean medical databases (Korean Studies Information, DBPIA, Oriental Medicine Advanced Searching Integrated System, Research Information Service System, KoreaMed, The Town Society of Science Technology and the Korean National Assembly Library), and 1 Chinese medical database (China National Knowledge Infrastructure [CNKI]). The search terms included (acupuncture OR electro-acupuncture OR meridian) AND (cancer OR tumour OR neoplasms OR malignancy OR carcinoma) AND (sleep disorder OR sleep disturbance OR insomnia OR wakefulness OR waking) in Korean, Chinese, and English. In addition, the reference lists of all of the obtained studies were searched. Hard copies of all of the articles were obtained and read in full.

Types of Studies

Randomized controlled trials (RCTs) and quasi-RCTs were included in this systematic review. RCTs were included if acupuncture was used as the sole intervention or as an adjunct to another standard treatment for any cancer-related insomnia and if the control group received the same concomitant treatments as the acupuncture group. We excluded case studies, case series, qualitative studies, uncontrolled studies, and controlled trials without randomization methods.

Types of Participants

Participants who were diagnosed with a sleep disorder due to interior-stirring by cancer regardless of gender and age were included.

Types of Intervention

We included studies that evaluated any type of invasive acupuncture. This included studies that used manual acupuncture, electro-acupuncture and auricular (ear) acupuncture. Trials testing other forms acupuncture, such as acupressure, transcutaneous electrical nerve stimulation, point injection, laser irradiation, and cupping were excluded. Trials were included if acupuncture was used as the sole intervention or as an adjunct to another standard treatment for any insomnia in patients with cancer and if the control group received the same concomitant treatments as the acupuncture group. Trials with designs that did not allow the effectiveness of acupuncture to be evaluated (eg, by using a treatment of unproven efficacy in the control group or by comparing 2 different forms of acupuncture) or included comparison treatments/groups that were expected to have similar effects to acupuncture or herbal medicines were excluded.

Types of Outcomes

Primary Outcomes

1. Response rate, defined as the proportion of participants who had significantly improved (judged by primary studies' authors) based on parameters such as prolonged total sleep time, improved sleep efficiency or sleep quality, or symptom relief by the primary studies. These were subjective assessments of overall effectiveness and were reported by the participants themselves.
2. Scales or indices for sleep quality evaluation, for example, the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Athens Insomnia Scale (ASI), were assessed.
3. Sleep efficiency, which is the ratio of total sleep time to time in bed, could be derived using either subjective or objective approaches.

Secondary Outcomes

1. Sleep diary, measured by various subjective approaches. Sleep diary generally has several items for reflecting a subjective assessment of each night's

sleep, including time in bed at night, time woken up in the morning, number of hours slept during the night, number of awakenings, and total time awake during the night, total time spent in bed, sleep efficiency, and sleep quality or satisfaction.
2. Adverse effects, reported in the studies or measured using validated scales.

Selection of Studies and Data Extraction

One author searched the database and screened potentially eligible studies after reading the title and abstract of the identified studies. After the initial screening, which included checking titles and abstracts, a more thorough investigation was performed using the full-text of each article. All articles were read by 2 independent reviewers (TYC and JIK) who extracted data according to predefined criteria. Information such as the participants, interventions, outcomes, and results were obtained from each study. For the extraction of intervention-related information, the revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) items were used to describe the details of the acupuncture treatments used in the study context.[23]

Risk of Bias Assessment

Two authors (TYC and JIK) independently extracted the data from the included trials. The Cochrane risk of bias tool was used to assess the internal validity of each study.[24] The following characteristics were assessed: (1) Was the allocation sequence adequately generated? (2) Was the allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately prevented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were the study reports free of the suggestion of selective outcome reporting? (6) Was the study free of other problems that could introduce a risk of bias? This review used "L," "U," and "H" as keys for these judgements, where "Low" (L) indicated a low risk of bias, "Unclear" (U) indicated that the risk of bias was uncertain, and "High" (H) indicated a high risk of bias. Disagreements were resolved by discussion between all of the authors.

Data Analysis

Relative risk (RR) and 95% confidence intervals were assessed for the effect size of each included study. All statistical analyses were conducted using the Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.3.0 for Windows (Copenhagen, The Nordic Cochrane Center). For studies with insufficient information, we contacted the primary authors to acquire and verify data when possible. Differences between the intervention and control groups were assessed. For dichotomous data, we present the treatment effect as relative risk with 95% confidence intervals (CIs). For continuous data, we used the mean difference (MD) with 95% CIs to measure the treatment effect. In the case of outcome variables with different scales, we used the standardized mean difference (SMD) with 95% CIs. The chi-square test for heterogeneity and the I^2 test were used to evaluate the heterogeneity of the included studies, where I^2 values of 50% or more were considered to be indicators of a substantial level of heterogeneity.[25] The missing data were not imputed from the outcome measures. When possible, we assessed publication bias using a funnel plot. However, the small number of trials prevented the assessment of publication bias.

Results

Description of Studies

Our searches generated 90 hits, and 6 RCTs met our inclusion criteria (Figure 1). The key data from all of the included articles are listed in Table 1.[26-31] A total of 475 patients were included in the analyses. Sample sizes ranged from 45 to 120. Three of the trials originated from China,[28-30] 1 RCT was from Sweden,[31] 1 study was from Denmark,[26] and 1 trial was from the United States.[27] The included patients had various types and stages of cancer. The acupuncture style, number of sessions, and duration of treatment varied across the included studies. Four of the trials used manual acupuncture,[26,28-30] and 2 trials used electroacupuncture.[27,31] The major acupuncture points were GV20 (Baihui), HT7 (Shenmen), SP6 (Sanyinjiao), and PC6 (Neiguan) (Table 2). The total number of treatment sessions ranged from 7 to 30. The backgrounds of the practitioners were reported in 3 of the studies.[26,27,31] The outcome measures included an increase in the PSQI and a reduction in symptoms (insomnia).

Risk of Bias

The details of the risk of bias (ROB) assessment in 6 RCTs are provided in Figure 2. Four[27-29,31] had a low ROB with regard to adequate sequence generation, whereas 2 RCTs[26,28] did not report the method. Only 3 RCTs[26,27,29] had a low ROB with respect to allocation concealment using sealed envelopes. All trials not reported outcome assessor blinding. Only 2 RCTs[26,27] compared acupuncture with sham acupuncture, and another 4 RCTs had a high ROB in participant and personnel blinding because of the nature of the treatment. All 6 RCTs had low ROBs with incomplete outcome data. Only 1 trial[27] had published protocols, and all except 1 RCT was rated unclear in selective reporting of outcomes. All trials reported the patients' baseline characteristics, and all of the RCTs had a low ROB based on other sources of bias.

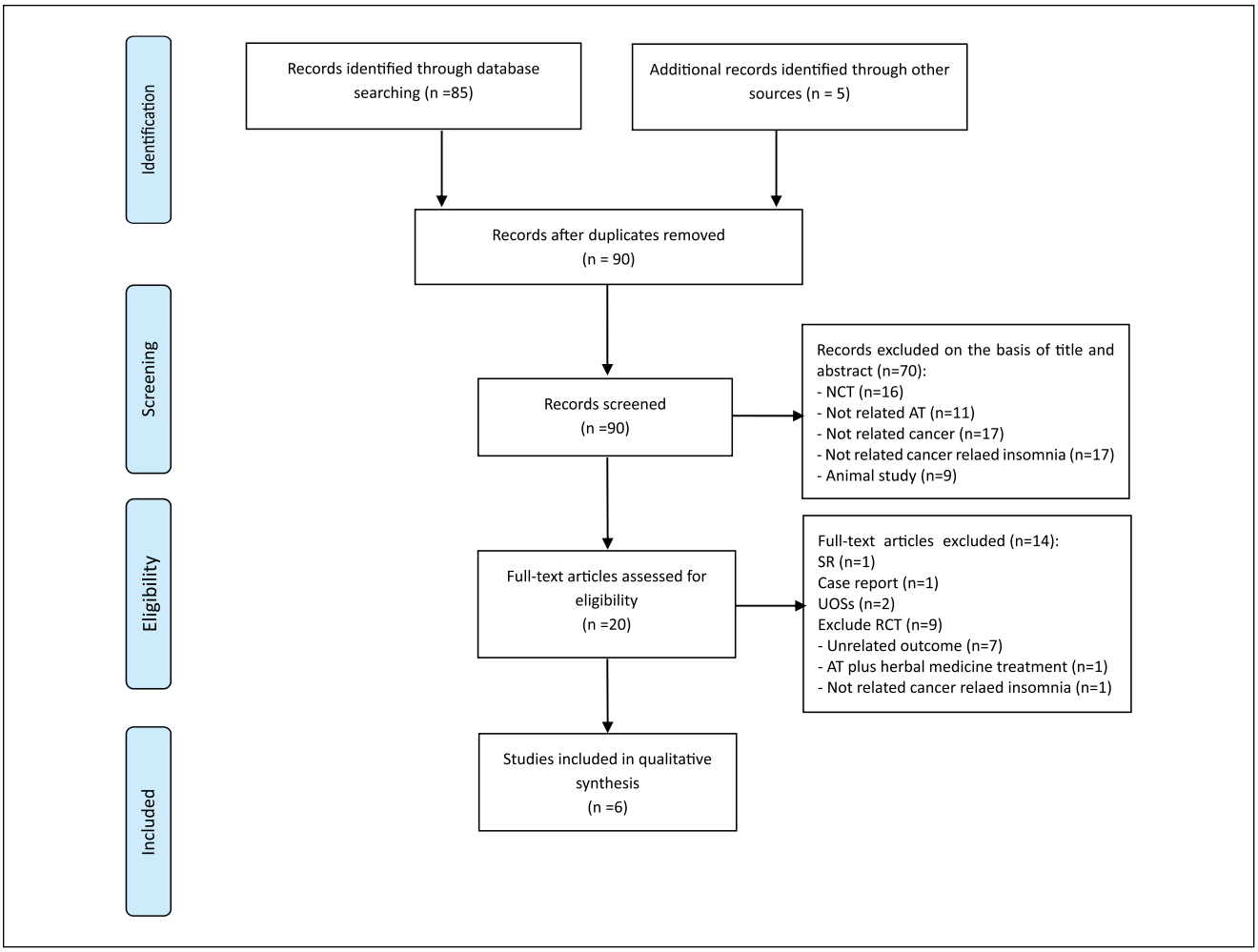

Figure 1. Flowchart of trial selection process. AT, acupuncture; NCT, not clinical trial; RCT, randomized controlled trial; SR, systematic review; UOS, uncontrolled observational study.

Outcomes Measurements

Acupuncture Versus Sham Acupuncture. Two RCTs compared the effects of acupuncture with sham acupuncture and no-treatment or a wait-list group in breast cancer patients (Table 3).[26,27] One RCT that used a logbook for night sleep disturbance[26] showed favorable effects of acupuncture, whereas the other RCT failed to show beneficial effects of electro-acupuncture on sleep quality score based on PSQI.[27]

Acupuncture Versus Conventional Drug. Three RCTs compared the effects of acupuncture to those of conventional drugs based on PSQI and response rate (Table 3).[28-30] Three RCTs compared the effects of acupuncture on PSQI. One RCT showed favorable effects of acupuncture on PSQI after 1 week of treatment (7 daily times) compared with conventional drugs,[29] whereas the other study failed to do so.[28] The meta-analysis showed no significant difference between acupuncture and drug therapy (n = 175, MD, −0.04, 95% CI= −1.28 to 1.21, $P = .95$) with high heterogeneity ($I^2 = 73\%$, Figure 3A). Another RCT showed superior effects of 4 weeks of acupuncture treatment on PSQI compared with conventional drugs.[30] The 3-week follow-up in 2 RCTs[28,29] showed superior effects of acupuncture compared with conventional drugs, and a meta-analysis also showed significant effects of acupuncture (n = 175, MD, −1.67, 95% CI = −2.79 to −0.56, $P = .003$) with high heterogeneity ($I^2 = 73\%$, Figure 3B).

Two RCTs tested the effect of acupuncture on response rate. Two RCTs showed the equivalent effects of acupuncture on the cancer-related insomnia response rate after 1 week of treatment. The meta-analysis also showed no significant difference between the 2 groups (n =175, RR = 0.97; 95% CI = 0.88-1.06, $P = .44$, $I^2 = 0\%$, Figure 3C). One RCT showed favorable effects of acupuncture on response rate after 3-week follow-up,[28] whereas the other RCT failed to do so.[29] The meta-analysis showed superior effects of acupuncture on response rate compared with conventional

Table 1. Summary Characteristics of Included Randomized Clinical Studies.

First Author (Year) Country	Sample Size/ Age (Years)	Intervention (regimen) Control (regimen)		Outcomes	Summary of Results	Adverse Events
Bokmand (2013)[26] Denmark	94 breast cancer/ 61 (45-76)	(A) AT (15-20 min, 1 time weekly for 5 weeks, n = 31)	(B) Sham AT (superficial penetrating needles at nonacupuncture points, n = 29) (C) No treatment (n = 34)	Disturbed night sleep (log book, rated "yes" or "no" at the same time points)	A vs B: RR, 0.53 [0.33, 0.88], P = .01 A vs C: RR: 0.53 [0.33, 0.83], P = .005	14 (fatigue, pruritus, nausea, A:5; B: 8; C:1, n.r. in details,)
Mao (2014)[27] United States	76 breast cancer/ 59.7 (41-76)	(A) EA (30 min, twice weekly for 2 weeks, then 1 time weekly for 6 weeks, n = 22)	(B) Sham AT (Streitbergst nonpenetrating needles at nonacupuncture, n = 22) (C) Waitlist (n = 23)	PSQI	A vs B: MD, -0.6 [−2.53, 1.33], NS A vs C: MD, −0.5 [−2.69, 1.69], NS	n.r.
Song (2015)[28] China	120 various cancer (n.r. in details)/ n.r.	(A) AT (30 min, 1 time daily for 7 days, n = 60)	(B) Conventional drug (estazolam tablets 1 mg per day for 7 days, n = 60)	(1). Response rate (2). PSQI	(1). RR, 0.95 [0.84, 1.06], NS (1 week); RR, 1.31 [1.06, 1.62], P = .01 (3-week follow-up) (2). MD, 0.75[−0.51, 2.01], NS (1 week); MD, −2.39 [−3.53, −1.25], P < .0001 (3-week follow-up)	n.r.
Dan (2013)[29] China	60 various cancers (n.r. in details)/ 52.2/51.3	(A) AT (30 min, 1 time daily for 7 days, n = 27)	(B) Conventional drug (estazolam tablets 1 mg per day for 7 days, n = 28)	(1). Response rate (2). PSQI	(1). RR, 1.00 [0.86, 1.16], NS (1 week); RR, 1.19 [0.92, 1.52], NS (3-week follow-up) (2). MD, −0.55 [−0.99, −0.11], P = .01 (1 week); MD, −1.22 [−1.58, 0.86], P < .00001 (3-week follow-up)	Pain (A: 1), bleeding (A:1); AEs from drug (B:2)
Feng (2011)[30] China	80 malignant tumors (30 pulmonary; 16 gastric; 7 breast; 14 colorectal; 4 lymphoma; 2 cervical carcinoma; 4 ovarian)/ 63.8/63.6	(A) AT (20-30 min, 1 time daily for 30 days, n = 40)	(B) Conventional drug (fluoxetione hydrochloride capsule 20 mg per day for 30 days, n = 40)	PSQI	MD, −3.52 [−4.22, −2.82], P < .00001	n.r.
Frisk (2012)[31] Sweden	45 breast cancer/ 54.1/53.4	(A) EA (30 min, 2 times weekly for first 2 weeks, then 1 time weekly for 10 weeks (n = 26)	(B) Hormone therapy (estrogen/ progestogen combination and tamoxifen, n = 18)	Log book (1). Numbers of hours slept / night (2). Times woken up/night	(1). NS (2). NS	None

Abbreviations: AE, adverse event; AT, acupuncture; EA, electro-acupuncture; NCC, National Cancer Center; n.r., not reported; NS, not significant; NSCLC, non–small cell lung cancer; PSQI, Pittsburgh Sleep Quality Index; RR, risk ratio.

Table 2. Details of Acupuncture Procedure Based on the Revised STRICTA Criteria.

		Needling Details									
First Author (Year)	Acupuncture Rationale	Points Used	No. of Needles Inserted	Depths of Insertion	Responses Elicited[a]	Needle Stimulation[b]	Needle Retention Time	Needle Type (Diameter * Length, manufactory)	Treatment Regimen (Total Sessions)	Other Components of Treatment	Practitioner Background
Bokmand (2013) [26]	TCM theory	Y	HC6 (bilateral), KI3 (bilateral), SP6(bilateral), LR3 (bilateral)	n.r.	n.r.	MA, fixed	15-20 min	n.r.	5 weeks (5 sessions)	NA	Y
Mao (2014) [27]	TCM theory	Y	Chose at least 4 local points around the joint with the most pain. EX) Shoulder: LI15 (bilateral), SI9 (bilateral) Knee: ST34 (bilateral), ST35 (bilateral), SP9 (bilateral), etc	n.r.	De-qi	MA + EA, individualized	30 min	Stainless steel (0.25 * 30 mm, 0.25 * 40 mm, Seirin-America Inc, Weymouth, MA)	8 weeks (10 sessions)	NA	Y
Song (2015) [28]	TCM theory	Y	AT: GV20, GV24, EX-HN3, HT7, ST36 (bilateral), SP6 (bilateral) Moxibustion (box moxibustion): CV8, CV4	n.r.	De-qi	MA, fixed	30 min	Stainless steel (0.30 * 25 mm, 0.30 * 40 mm, n.r.)	7 days (7 sessions)	NA	n.r.
Dan (2013) [29]	TCM theory	Y	AT: GV20, GV24, EX-HN3, HT7, ST36 (bilateral), SP6 (bilateral) Moxibustion (box moxibustion): CV8, CV4	n.r.	De-qi	MA, fixed	30 min	Stainless steel (0.30 * 25 mm, 0.30 * 40 mm, n.r.)	7 days (7 sessions)	NA	n.r.
Feng (2011) [30]	TCM theory	Y	ST40 (bilateral), SP9 (bilateral), SP10 (bilateral), SP6 (bilateral), EX-HN3, GV20, EX-HN1, PC6 (bilateral), HT7	n.r.	De-qi	MA, fixed	20-30 min	n.r.	30 days (30 sessions)	NA	n.r.
Frisk (2012) [31]	TCM theory	Y	BL15 (bilateral), BL23 (bilateral), BL32 (bilateral), GV20, HE7, PC6 (bilateral), LR3, SP6, SP9	5-20 mm	De-qi	MA + EA, fixed	30 min	Stainless steel (0.25 * 15 mm, 0.30 * 30 mm, n.r.)	12 weeks (14 sessions)	NA	Y

Abbreviations: AT, acupuncture; EA, electro-acupuncture; MA, manual acupuncture; NA, not applicable; n.r., not reported; STRICTA, STandards for Reporting Interventions in Clinical Trials of Acupuncture; TCM, traditional Chinese medicine; Y, reported.

[a]De-qi means acupuncture-evoked specific sensations such as soreness, numbness, heaviness, and distention at the site of needle placement, and these sensations may spread to other parts of the body.

[b]Acupuncture method was classified into 3 categories on the basis of the levels of individualization: "fixed" means all patients receive the same treatment at all sessions, "partially individualized" means using a fixed set of points to be combined with a set of points to be used flexibly, and "individualized" means each patient receives a unique and evolving diagnosis and treatment.

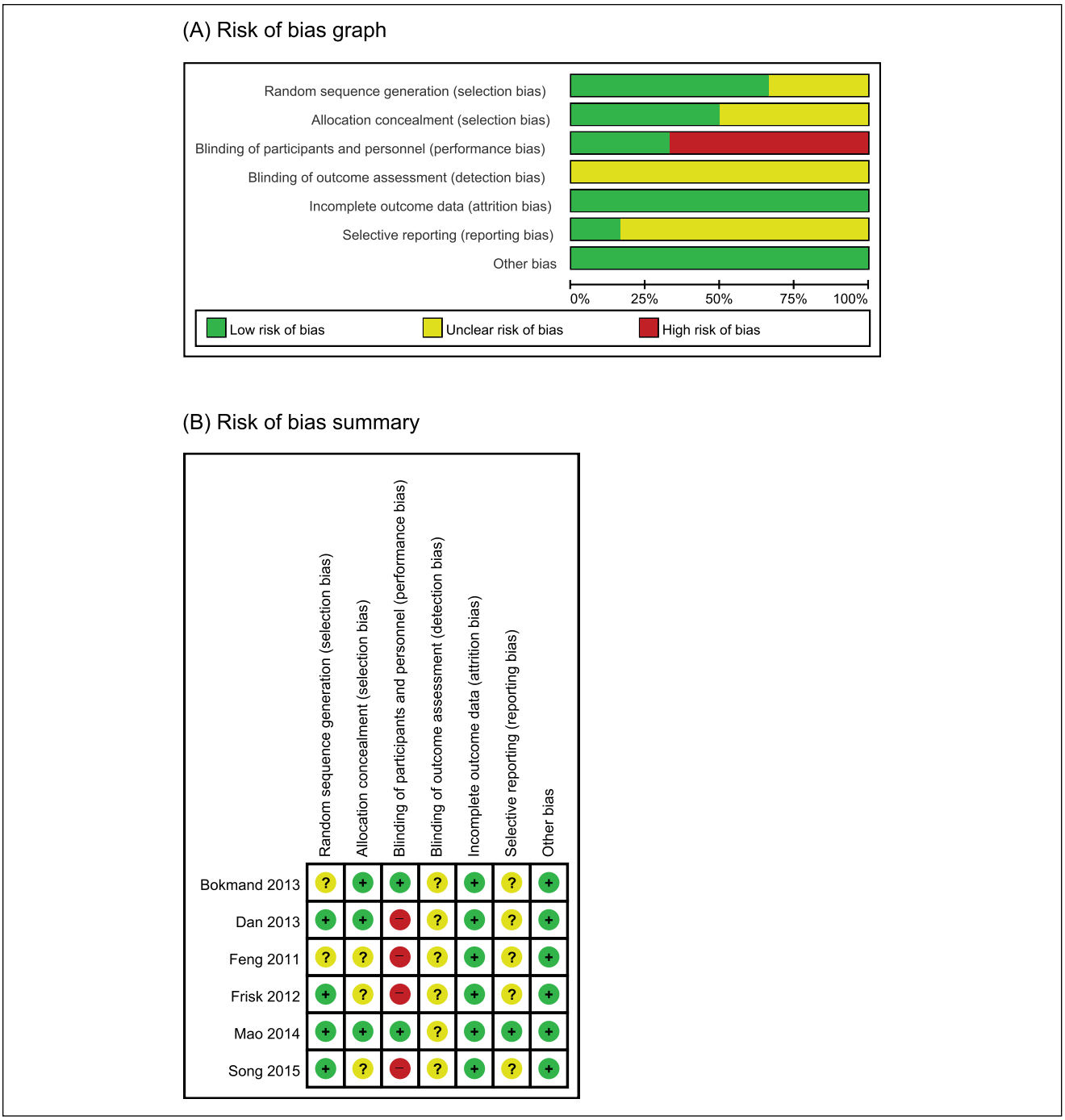

Figure 2. (A) Risk of bias graph: review authors' judgments about each item's risk of bias item presented as percentage across all included studies. (B) Risk of bias summary: review authors' judgments about each item's risk of bias for each included study. +, low risk of bias; −, high risk of bias; ?, unclear.

medication (n = 175, RR, 1.25; 95% CI = 1.07-1.48, P = .006, I^2 = 0%, Figure 3D).

Acupuncture Versus Hormone Therapy. One RCT tested the effects of acupuncture on cancer-related insomnia compared with hormone therapy.[31] That trial demonstrated a significant improvement in the numbers of hours slept each night and number of times woken up each night.

Adverse Events. Three RCTs investigated adverse events, whereas other trials did not. One RCT reported mild or moderate adverse events, including fatigue, pruritus, and nausea in

Table 3. Summary of Findings for Acupuncture for Cancer-Related Insomnia.

Acupuncture compared with sham acupuncture for cancer-related fatigue						
Patient or population: Breast cancer patients with cancer-related fatigue Intervention: Acupuncture Comparison: Sham acupuncture						
	Illustrative Comparative Risks[a] (95% CI)					
	Assumed Risk	Corresponding Risk				
Outcomes	Sham Acupuncture	Acupuncture	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE[b])	Comments
Sleep quality (PSQI)	The mean sleep quality in the control groups was −0.8	The mean sleep quality in the intervention groups was 0.6 lower (2.53 lower to 1.33 higher)		45 (1 study)	⊕⊕⊕⊖ moderate[c]	Mao (2014)[27]
Sleep disturbance Follow-up: mean 4 weeks	724 per 1000	384 per 1000 (239 to 637)	RR 0.53 (0.33 to 0.88)	60 (1 study)	⊕⊕⊖⊖ low[c,d]	Bokmand (2013)[26]
Acupuncture compared with conventional drug for cancer-related insomnia						
Patient or population: Various cancer patients with cancer-related insomnia Intervention: Acupuncture Comparison: Conventional drug						
	Illustrative Comparative Risks[a] (95% CI)					
	Assumed Risk	Corresponding Risk				
Outcomes	Conventional Drug	Acupuncture	Relative Effect (95% CI)	No of Participants (Studies)	Quality of the Evidence (GRADE[b])	Comments
Response rate	Study population 932 per 1000 Moderate	904 per 1000 (820-988)	RR 0.97 (0.88-1.06)	175 (2 studies)	⊕⊕⊖⊖ low[d,e]	Dan (2013)[29] Song (2015)[28]
Response rate follow-up: mean 3 weeks	Study population 682 per 1000 Moderate	852 per 1000 (730-1000)	RR 1.25 (1.07-1.48)	175 (2 studies)	⊕⊕⊖⊖ low[d,e]	Dan (2013)[29] Song (2015)[28]
PSQI 1 week		The mean PSQI in the intervention groups was 0.04 lower (1.28 lower to 1.21 higher)		175 (2 studies)	⊕⊕⊖⊖ low[d,e]	Dan (2013)[29] Song (2015)[28]
PSQI 4 weeks		The mean PSQI in the intervention groups was 3.52 lower (4.22 lower to 2.82 lower)		80 (1 study)	⊕⊕⊖⊖ low[d,e]	Feng (2011)[30]
PSQI follow-up:mean 3 weeks		The mean PSQI 3weeks in the intervention groups was 1.67 lower (2.79 to 0.56 lower)		175 (2 studies)	⊕⊕⊖⊖ low[d,e]	Dan (2013)[29] Song (2015)[28]

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; RR, risk ratio.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]GRADE Working Group grades of evidence: High quality—Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality—We are very uncertain about the estimate.

[c]Small sample size.

[d]No report on random sequence generation.

[e]High heterogeneity.

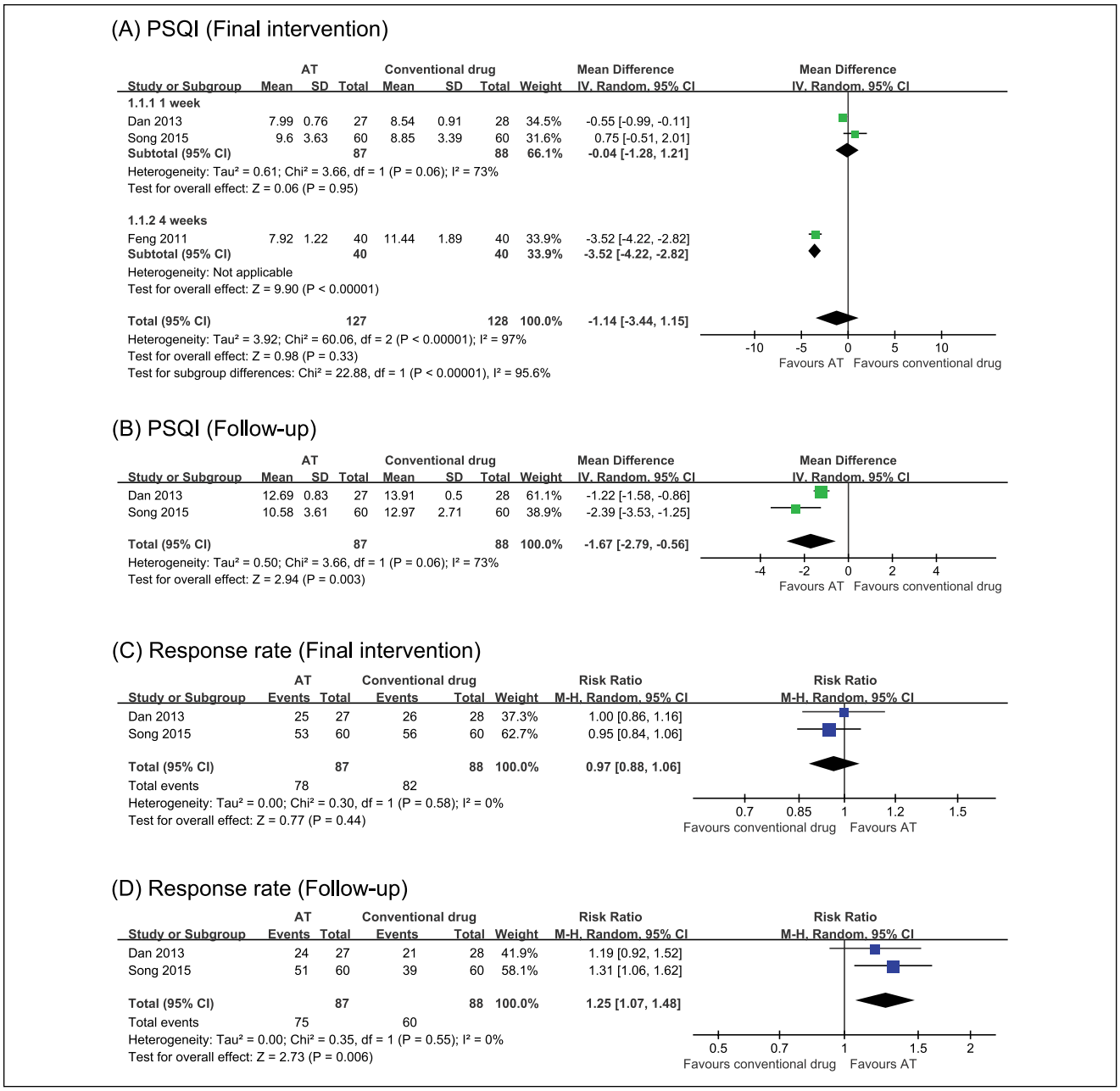

Figure 3. Forest plot of acupuncture compared with conventional drugs on (A) PSQI after final intervention; (B) PSQI at 3 weeks follow-up; (C) Response rate after final intervention; (D) Response rate at 3 weeks follow-up. AT: acupuncture; PSQI: Pittsburgh sleep quality index.

acupuncture (n = 5), sham acupuncture (n = 8), and no treatment (n = 1).[26] The other RCT reported 2 mild adverse events, including pain and bleeding in the acupuncture group and 2 in the drug group,[29] whereas 1 RCT showed no adverse events.[31]

Discussion

Few rigorous trials have tested the effects of acupuncture for managing cancer-related insomnia. The totality of the evidence from acupuncture RCTs for managing cancer-related insomnia is mixed according to the type of cancer and the acupuncture and treatment regimens. Our review suggested some possible positive or equivalent benefits of acupuncture compared with conventional drug therapy or hormone therapy. Compared with sham acupuncture, one trial showed specific effects of acupuncture, whereas another trial failed to do so. The level of evidence was low in general. Furthermore, the number of trials and total

sample size included in our analysis were not sufficient to draw firm conclusions.

Our review has several important limitations. First, our study cannot avoid publication bias or location bias. The distorting effects of these biases on systematic reviews are well documented.[32,33] Second, we searched a large number of databases without publication language restrictions. We are confident that our search strategies located all relevant data, although some degree of uncertainty remains. Half of the included RCTs were from China, and the generalization of the results to other countries might be limited. Further limitations include the paucity and the often suboptimal methodological quality of the primary data. Finally, the nature of all reported outcome are subjective measures and these prone to be potential bias of measurement. In total, these facts considerably limit the conclusiveness of this systematic review.

Compared with a previous review,[18] we identified 4 new RCTs[26-29] and successfully updated the evidence. The previous review reported positive outcomes of included trials with concern about a high risk of bias. The newly added trials suggest more positive effects of acupuncture on cancer-related insomnia than the previous review. The results of systematic review of acupuncture for cancer-related insomnia are different from those of noncancer-related insomnia. Two previous systematic reviews for noncancer-related insomnia showed mixed effects according to type of acupuncture and control groups, including high risk of bias studies.[19,20] Our review showed that the effects of acupuncture are equivalent with conventional drugs at the end of treatment, but superior effects at 3 weeks' follow-up in both PSQI and response rate.[28,29] This might suggest that the effects of acupuncture are sustainable, while the effects of conventional drugs decline immediately after treatment. Then acupuncture could obtain a better outcome during treatment follow-up than immediately after treatment compared with conventional drug therapies.

Most of the included studies had an unclear or low risk of bias across the domains. Two RCTs did not report the random sequence generation methods.[26,30] Only 3 used allocation concealment,[26,27,29] and only 2 employed patient blinding.[26,27] Because of the nature of the intervention, practitioner blinding cannot be achieved. Trials with inadequate blinding or inadequate allocation concealment may be subject to selection bias and would therefore be likely to generate exaggerated treatment effects. Failure to follow reporting guidelines, including the CONSORT (Consolidated Standards of Reporting Trials)[34] or STRICTA guidelines[23] prevented the reader from properly evaluating the trials. Collective efforts for increasing adherence to the CONSORT statement and STRICTA guidelines during the design, implementation, and reporting of clinical trials are needed to improve the completeness of reporting in acupuncture RCTs.

Two sham acupuncture methods were used for testing the efficacy of acupuncture for cancer-related insomnia, including superficial penetrating needles at nonacupuncture points and nonpenetrating needles at nonacupuncture points. One trial showed favorable effects of manual acupuncture compared with penetrating needling at nonacupuncture points for cancer-related insomnia,[26] but another trial failed to show superior effects of electro-acupuncture compared with the use of nonpenetrating needles at nonacupuncture points.[27] This finding may suggest the possibility of noninertness of sham acupuncture, which is different from placebo effects of conventional drugs. However, the superiority of acupuncture compared with conventional drugs allows the possible interpretation of specific effects of acupuncture for this condition.

There are several possible interpretations of the results of this systematic review. The treatment might not have been administered optimally in the included trials. The studies may have been inadequately designed or the acupuncture treatments might exhibit nonspecific effects. For instance, the number of treatment sessions could have been too small to generate a significant effect, treatment could have been suboptimal, or the protocol applied in the acupuncture group might not have been suitable for treating cancer-related insomnia. In the included trials, the effects were more positive in the trials with more frequent treatment times (total or time duration).[30] There was also the possibility of revealing the effects of acupuncture in the follow-up stages than in the final treatment.[28,29] Both the optimum dose and the ideal time or type of acupuncture for various cancer patients are currently unknown. No clinical trials investigating dosages and treatment regimens have yet been published.

There are also other issues regarding the use of acupuncture for cancer-related insomnia that should be discussed further. Because cancer-related insomnia may develop in the setting of a highly heterogeneous cancer with a different etiology and severity, acupuncture is likely to have different effects on different subgroups of patients. Therefore, future clinical trials should be focused on a particular subgroup and should include a very large sample size to delineate the effects of acupuncture on patients with different cancer types. Some of the included RCTs showed equivalent or superior effects of acupuncture compared with conventional drugs or hormone therapy.[28-31] The effect size of the included trials was not large enough to be clinically meaningful. The treatment duration of the included trials might not have been sufficiently long to demonstrate complete effects on sleep quality improvement because although acupuncture is effective, the effects can be quite slow to develop. If the treatment period is sufficient, it is possible to obtain different results.

Although acupuncture in general appears to be safe, one important question is the safety of acupuncture for cancer

patients. Adverse events were noted in three of the included trials but they were negligible compared with drug-related adverse events.[26,29,31] Further studies (prospective and retrospective) on the safety of acupuncture for cancer patients are required.

One could question the minimum clinical trial guide for future research in this area. Future acupuncture RCTs on cancer-related insomnia should adhere to accepted standards of trial methodology. Trials should have sufficiently large study populations based on power calculations from appropriate pilot studies and should also perform the following actions: consider the optimal doses, including intervention duration and frequency; describe all aspects of the methodology in full detail to ensure reproducibility; use validated primary outcome measures, including subjective and objective outcome (actigraphy or polysomnography); and employ adequate statistical tests. Trials should also evaluate the quality of sleep and the effects on quality of life and should also report the number of participants who withdraw from the intervention in each arm and their reasons for doing so.

In conclusion, the current trials showed that acupuncture may be superior to sham acupuncture, conventional drug therapy and hormone therapy for the management of cancer-related insomnia. However, the level of evidence is low, the small effect size reduces clinical significance and the small number of rigorous studies prevents us from drawing firm conclusions. Future well-conducted RCTs are needed to determine whether acupuncture can be a viable option for the treatment of cancer-related insomnia.

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