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Cognitive behavioural therapy monotherapy for insomnia: A meta-analysis of randomized controlled trials

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ABSTRACT

This was a meta-analysis of randomized controlled trials (RCTs) comparing the effects of cognitive behavioural therapy for insomnia (CBTI) as a monotherapy and active control treatments in persons with insomnia who have no major medical conditions or psychiatric comorbidities. PubMed, PsycINFO, EMBASE, Cochrane Library databases, WanFang and CNKI were systematically and independently searched. Standardized mean differences (SMDs) and risk ratio (RR) with their 95% confidence intervals (CIs) were calculated. Nine RCTs with 12 treatment arms comparing CBTI (n = 479) and active control (n = 510) groups were analyzed. Compared to the active control group, the CBTI group showed significantly less improvement in insomnia at post-CBTI assessment in terms of sleep efficiency (SMD: 0.32, 95% CI: 0.00 to 0.63), sleep latency (SMD: -0.33, 95% CI: -0.56 to -0.09), wake after sleep onset (SMD: -0.27, 95% CI: -0.52 to -0.01), the total scores of Pittsburgh Sleep Quality Index (SMD: -0.52, 95% CI: -0.86 to -0.19), the Insomnia Symptom Index (SMD: -0.68, 95% CI: -1.01 to -0.36), the Dysfunctional Attitudes and Beliefs About Sleep Scale (SMD: -0.76, 95% CI: -1.25 to -0.27), and the Athens Insomnia Scale (SMD: -0.66, 95% CI: -1.07 to -0.24). In this meta-analysis, CBTI monotherapy showed no advantage in improving insomnia compared with other standard treatments.

1. Introduction

Insomnia is a common public health problem, which is related to increased risk of physical comorbidities, psychiatric disorders, function impairment (Gong et al., 2016; Li et al., 2015; Ohayon and Bader, 2010) and even all-cause mortality (Araujo et al., 2017). According to different diagnostic criteria, the prevalence of insomnia ranged from 6% to a third of population globally (Ohayon, 2002). Both pharmacotherapy and behavioural interventions, such as cognitive-behavioural therapies for insomnia (CBTIs), are commonly used in treating insomnia. As medications for insomnia are associated with side-effects, dependence, and tolerance (Koffel et al., 2015), psychosocial interventions are employed commonly (Hohagen et al., 1994).

CBTI is frequently used as a first-line choice for chronic insomnia worldwide (Perlis and Smith, 2008a), given its effectiveness (Cheng and Dizon, 2012; Wang et al., 2005). CBTI is a structured sleep

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improvement program, which consists of both cognitive and behavioural components. The cognitive part of CBTI helps to identify and change beliefs or thoughts that lead to insomnia, while the behavioural part helps to develop beneficial sleep habits that improve sleep. Since the NIH State-of-the-Science Conference Statement to use CBTI as a first-line therapy for chronic insomnia, many studies have investigated the effects of CBTI on insomnia (Perlis and Smith, 2008b). The core components of CBTI include sleep hygiene, relaxation training, stimulus control, sleep restriction, cognitive therapy, and cognitive restructuring (Cheng and Dizon, 2012; Edinger and Means, 2005; Okajima et al., 2011; Perlis et al., 2006; van Straten and Cuijpers, 2009).

Several meta-analyses of CBTI assessed the effects of CBTI on insomnia (Cheng and Dizon, 2012; Okajima et al., 2011; Ren et al., 2016). However, there were several common methodological limitations. For example, some studies only focused on a specific type of CBTI, such as computerised CBTI) (Cheng and Dizon, 2012), or group CBTI (Koffel et al., 2015), or self-helped CBTI (Ren et al., 2016), while others included non-active controls, subjects with major medical conditions (i.e. cancer), or did not employ diagnostic criteria for insomnia (Okajima et al., 2011; Trauer et al., 2015). Use of non-active controls could lead to placebo effect and significant bias.

Therefore we conducted this comprehensive meta-analysis of RCTs to examine the effects of CBTIs as a monotherapy for persons with insomnia who have no physical or psychiatric comorbidities.

2. Methods

2.1. Selection criteria

According to the PICOS acronym, the following inclusion criteria were used: Participants (*P*): persons with insomnia but without major physical conditions and psychiatric comorbidities defined by respective studies; insomnia was diagnosed according to systematic diagnostic criteria, such as the Chinese classification and diagnostic criteria for mental disorders, Third Edition (CCMD-3) (Chen, 2002), the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), DSM-IV-TR (American Psychiatric Association, 2000) or other DSM edition, the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (World Health Organization, 1992), American Academy of Sleep Medicine Criteria (Edinger et al., 2004), the first, second and third editions of the International Classification of Sleep Disorders (ICSD)(American Academy of Sleep Medicine, 2005, 2014; Diagnostic Classification Steering Committee (Thorpy MJ chairman), 1990). Intervention (*I*): CBTIs monotherapy. Comparison (*C*): active control group, i.e., participants in control group received certain type of treatments, such as pharmacotherapy and sleep hygiene education, during the study period. Outcomes (*O*): the primary outcome measure was the improvement of insomnia at post-CBTI assessment as measured by sleep efficacy and/or standardized rating scales, such as the Pittsburgh Sleep Quality Index (PSQI). Sleep efficiency refers to the ratio of total sleep time and time in bed, which has been widely used in other studies (Reed and Sacco, 2016). Key secondary outcome measures included other sleep related data, such as total sleep time, total wake time, sleep quality, and the improvement of insomnia at additional follow up assessment. Study design (*S*): single or double-blind RCTs with accessible and meta-analysable data. Case reports/series, qualitative report, observational trials, non-randomized studies, reviews and meta-analyses were excluded. Studies that used interventions with a specific CBTI component (such as sleep hygiene), or did not clearly define the interventions as CBTI were also excluded.

2.2. Search methods

PubMed, PsycINFO, EMBASE, Cochrane Library databases, WanFang and CNKI databases were systematically and independently searched by two reviewers (YYW and WWR), from their inception date until November 12, 2017. The following search terms were used: insomnia, sleep, early morning awakening, maintenance disorder, dyssomnia, sleepless, cognitive behavioral for insomnia, cognitive behavioural therapy for insomnia, cognitive behavioural treatment for insomnia, cognitive behavioral treatment for insomnia, cognitive behavioral therapy of insomnia, cognitive behavioural therapy of insomnia, CBTI, CBT-I, randomized controlled trials, randomized controlled trial, RCT, and RCTs. Moreover, reference lists of relevant reviews were searched manually in order to avoid any missing studies.

2.3. Data extraction

Four reviewers (LNZ, SFZ, YY, YYW) independently extracted the relevant data. Any inconsistencies arising from the process were discussed to reach an agreement or were resolved by referring to another independent reviewer (YTX). In order to avoid inter-dependence, only actigraphy data were extracted for studies with both actigraphy and sleep dairy data. For studies with 3 treatment arms comparing CBTI with two different control groups (Harvey et al., 2014; Irwin et al., 2014), half of participants in the CBTI group were assigned to each control group to avoid inflating the number of participants in CBTI group. In two studies with more than one follow-up assessment, we included 6 months (Alessi et al., 2016) and 8 months (Wu et al., 2006) assessments to enable comparison with other studies in study duration.

2.4. Quality assessment

Study quality was assessed by the Cochrane risk of bias (Higgins and Green, 2014) and Jaded scale (Jadad et al., 1996). The Cochrane risk of bias was used to assess the aspects of selection bias (random sequence generation and allocation concealment), reporting bias (selective reporting), blinding, attribution bias, and other source of bias, while the Jaded assessed the randomization, blinding, and withdrawals and dropouts of participants. The Jadad total score < 3 was considered as low quality; otherwise, it was considered as high quality (Jadad et al., 1996). The grading of recommendations assessment, development, and evaluation (GRADE) system (Atkins et al., 2004; Balshem et al., 2011) was used to evaluate the evidence level of outcomes.

2.5. Data synthesis and statistical analyses

The Review Manager Version 5.3 (http://www.cochrane.org) and Comprehensive Meta-Analysis V2.0 (www.meta-analysis.com) were used to analyse data. Due to the discrepancy in sampling methods, measurements and demographic characteristics across studies, the random effects model was used in all meta-analytic outcomes because it is more conservative than fixed-effects model (DerSimonian and Laird, 1986). Standardized mean difference (SMD) with 95% confidence intervals (CIs) was used for continuous outcomes, while risk ratio (RR) ± 95% CI was used for dichotomous data. Study heterogeneity was measured using I^2, with I^2 values greater than 50% indicating significant heterogeneity (Higgins et al., 2003). When significant heterogeneity for primary outcome existed, a sensitivity analysis, i.e., one outlying (SMD > 1.5) study (Edinger and Sampson, 2003) was removed to explain the heterogeneity source. Funnel plots and Egger's test (Egger et al., 1997) for primary outcome were conducted to evaluate publication bias. All meta-analytic outcomes were 2 tailed, with significance level set at 0.05.

3. Results

3.1. Literature search and study characteristics

A total of 250 relevant articles were identified in the initial literature search. As shown in Fig. 1, 9 RCTs with 12 treatment arms were

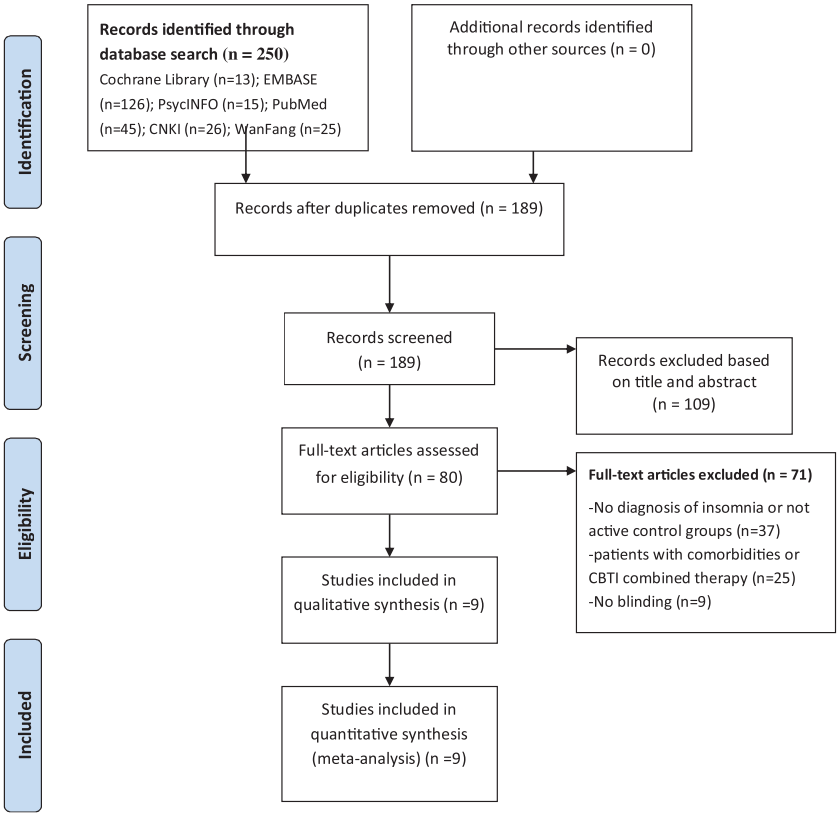

Fig. 1. PRISMA flow diagram.

included in the analyses. In one study (Edinger et al., 2009), the CBTI group included two active arms for two different types of insomnia, hence the two arms were analysed separately. The pooled sample size was 989, with 479 in the CBTI group and 510 in the control group. Study sites included China (1 RCT, n = 39), United States (5 RCTs, n = 433), Sweden (1 RCT, n = 148), and Norway (1 RCT, n = 181), and combined United States and Canada (1 RCT, n = 188) sites. The CBTI treatment duration ranged from 2 to 16 weeks. The diagnostic criteria of insomnia included DSM-IV, DSM-IV-TR, DSM-III-R, International Classification of Sleep Disorders (ICSD), ICSD-2, and American Academy of Sleep Medicine criteria. CBTI treatment frequency varied from 25 min/week with a 2-week interval in between, to 120 min per week (Table 1).

3.2. Assessment quality and quality of evidence

The risk of bias of the included studies is summarized in Supplemental Fig. 1. Three RCTs were double blinded and the rest was single blind. Seven RCTs described the random sequence generation, and two studies mentioned allocation concealment. All studies were rated as low risk in terms of attrition and reporting bias. Jadad total score ranged from 3 to 5 (Table 1). Of the 9 RCTs, all were rated as "high quality". The quality of evidence of 5 outcome measures ranged from "very low" (45%, 9/20), via "low" (40%, 8/20) to "moderate" (15%, 3/20) according to the GRADE approach (Table 3) (Fig. 2).

3.3. Sleep efficiency

Eight RCTS with 10 CBTI treatment arms reported data on sleep efficiency at the post-CBTIs assessment. Compared with active control group, the CBTIs group showed significantly less improvement at post-CBTI assessment (n = 826, SMD: 0.32, 95% CI: 0.00 to 0.63, I^2 = 76%, p = 0.05, Table 2). The significant group difference disappeared after removing one outlying (SMD > 1.5) study (Edinger and Sampson, 2003) (n = 806, SMD: 0.24, 95% CI: -0.06 to 0.54, I^2 = 75%, p = 0.12). Four studies with 4 CBTI arms reported additional follow-up assessments, but no significant group difference was found (n = 281, SMD: 0.26, 95% CI: -0.19 to 0.7, I^2 = 61%, p = 0.25, Table 2).

3.4. Total sleep time

Seven RCTS with 9 CBTI arms reported data on total sleep time at the post-CBTIs assessment. There was no significant difference between active control group and the CBTIs group at post-CBTI assessment (n = 667, SMD: 0.06, 95% CI: -0.16 to 0.28, I^2 = 42%, p = 0.60, Table 2). Three studies with 3 CBTI arms reported additional follow-up assessments, and there was no significant group difference (n = 122, SMD: 0.24, 95% CI: -0.3 to 0.78, I^2 = 54%, p = 0.38, Table 2).

3.5. Sleep latency

Seven RCTS with 9 CBTI arms reported data on sleep latency at the post-CBTIs assessment. Compared with control group, the CBTIs group showed significantly less improvement at post-CBTI assessment (n = 778, SMD: -0.33, 95% CI: -0.56 to -0.09, I^2 = 56%, p = 0.007, Table 2). Four studies with 4 CBTI arms reported additional follow-up assessments, and again there was no group difference (n = 281, SMD: -0.29, 95% CI: -0.62 to 0.04, I^2 = 32%, p = 0.08, Table 2).

3.6. Wake after sleep onset

Six RCTS with 8 CBTI arms reported data on wake after sleep onset at the post-CBTIs assessment. Compared with active control group, the CBTIs group showed significantly less improvement at post-CBTI assessment (n = 740, SMD: -0.27, 95% CI: -0.52 to -0.01, I^2 = 60%, p = 0.04, Table 2). Three studies with 3 CBTI arms reported additional follow-up assessments with no group differences found (n = 245, SMD: -0.36, 95% CI: -0.79 to 0.07, I^2 = 47%, p = 0.1, Table 2).

Table 1
Characteristics of RCTs included in the meta-analysis.

First Author (year)	References	country	Participants					Intervention					Outcomes (Sleep)	Dropout rate (CBTIs, %)	Jadad score[b]
			n[a]	M (%)[a]	Age mean (y)[a]	Diagnostic criteria	Design: -Setting -Blinding	Type of CBTIs	Duration (wks)[b]	Type of interventions;	Frequency of CBTIs	Follow-up time point			
Alessi, C. (2016)	(Alessi et al., 2016)	US	159	96.9	72.2	ICSD-2	-community-dwelling veterans -double blind	CBTI	6	CBTI (106)vs. sleep education (53)	5 sessions during 6 weeks (60 min per session)	6, 12 month	Sleep diary; actigraphy (SE); scales (PSQI, ISI)	9/106	5
Blom, K. (2016)	(Blom et al., 2016)	Sweden	148	21.62	48	American Academy of Sleep Medicine criteria	-recruited via advertisements and articles -assessors blind	Internet-based CBTI	8	Internet CBTI (73) vs credible insomnia treatment (75)	NR	6, 12, 36 (only 36 month data available)	scales (ISI)	5/73	4
Edinger, J. D. (2001)	(Edinger et al., 2001)	US	50	56	55.2	DSM-III-R	-recruited from ads and face-to-face solicitation -double blind	CBTI	6	CBTI (25) vs muscle relaxation training (25)	6 weekly individual sessions (30- to 60-min per session)	6 month	Sleep diary; PSG (TST, SE); scales (ISQ)	2/25	5
Edinger, J. D. (2003)	(Edinger and Sampson, 2003)	US	20	90	51	DSM-IV	-Outpatient -participant blind	ACBT	2	ACBT (10)sleep hygiene suggestions (10)	2 sessions at 2-wk intervals (25 min per session)	3 month	Sleep diary; scales (SES, ISQ, DBAS)	0/10	3
Edinger, J. D. (2009)	(Edinger et al., 2009)	US	81	86.4	54.2	DSM-IV, SCID, DSISD	-Outpatient -participant blind	CBTI	8	CBTI (41) vs sleep hygiene education (40)	4 biweekly individual sessions, (30- to 60-min per session)	6 month	Sleep diary; actigraphy (TST, SL, WASO, SE); scales (ISQ, PSQI, DBAS)	5/41	4
Hagatun, S. (2017)	(Hagatun et al., 2017)	Norway	181	33	44.9	DSM-IV	-community (recruited by ads) -participant blind	SHUTi	9	CBTI (95) vs online sleep education (86)	NR	6 month	Sleep diary; Scales (ISI, DBAS, BIS)	questionnaire 18/95; sleep diary 27/95;	4
Harvey, A. G. (2014)	(Harvey et al., 2014)	US & Canada	188	37.8	47.4	ICSD,DSM-IV	-recruited via ads & referrals -technicians blind	CBTI	8	1. CBTI (60) vs cognitive therapy (65) 2. CBTI (60) behavior therapy (63)	8 sessions, (75 min per session per week)	6 month	Sleep diary; PSG (TST, SL, WASO, SE); scales (ISI)	1/60	4
Irwin, M. R. (2014)	(Irwin et al., 2014)	US	123	71.5	65.55	DSM-IV-TR & ICSD-2	-Outpatient -assessor blind	CBTI	16	1. CBTI (50) vs Tai Chi Chih (48) 2. CBTI (50) vs Sleep Seminar (25)	4-month weekly group session (120 min per week)	3,12 month (extracted 3 month scale score);	Sleep diary; PSG (TST, SL, WASO, SE); scales (PSQI, AIS)	2/50	4
Wu, R. G. (2006)	(Wu et al., 2006)	China	39	/	/	ICSD,DSM-IV	-recruited through ads and letter to physicians -double blind	CBTI	8	CBTI (19) vs PTC (20)	16 sessions (2 times per week)	8 month	Sleep diary; PSG (TST, SL, SE)	0/19	4

Abbreviations: CBTI, Cognitive Behavioural Therapy for Insomnia; ACBT, Abbreviated Cognitive-Behavioral Insomnia Therapy; SHUTi, Sleep Healthy Using the Internet; PTC, pharmacological therapy; DSM-IV, Diagnostic Statistical Manual of Mental Disorders, Fourth Edition; DSM-III-R, Diagnostic Statistical Manual of Mental Disorders, Revised Third Edition; DSM-IV-TR, Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ICSD, International Classification of Sleep Disorders; SCID, Structured Interview for Psychiatric Disorders; DSISD, Duke Structured Interview for Sleep Disorders M, male; min, minute; wk, week; d, day; n, number of patients; NR, not report.

PSQI, Pittsburgh Sleep Quality Index; ISQ, Insomnia Symptom Questionnaire; ISI, Insomnia Severity Index; SES, Self-Efficacy Scale; DBAS, Dysfunctional Beliefs and Attitudes About Sleep Scale; BIS, Bergen Insomnia Scale; AIS, Athens Insomnia Scale; PSG, Polysomnography, SE, Sleep Efficiency; TST, Total Sleep Time; SL, Sleep Latency, WASO; Wake After Sleep Onset.

[a] The sample size was derived at the randomization assessment; gender proportion and age were derived from extractable information.

[b] Jadad total score < 3 was rated as low quality; otherwise, it was considered as high quality.

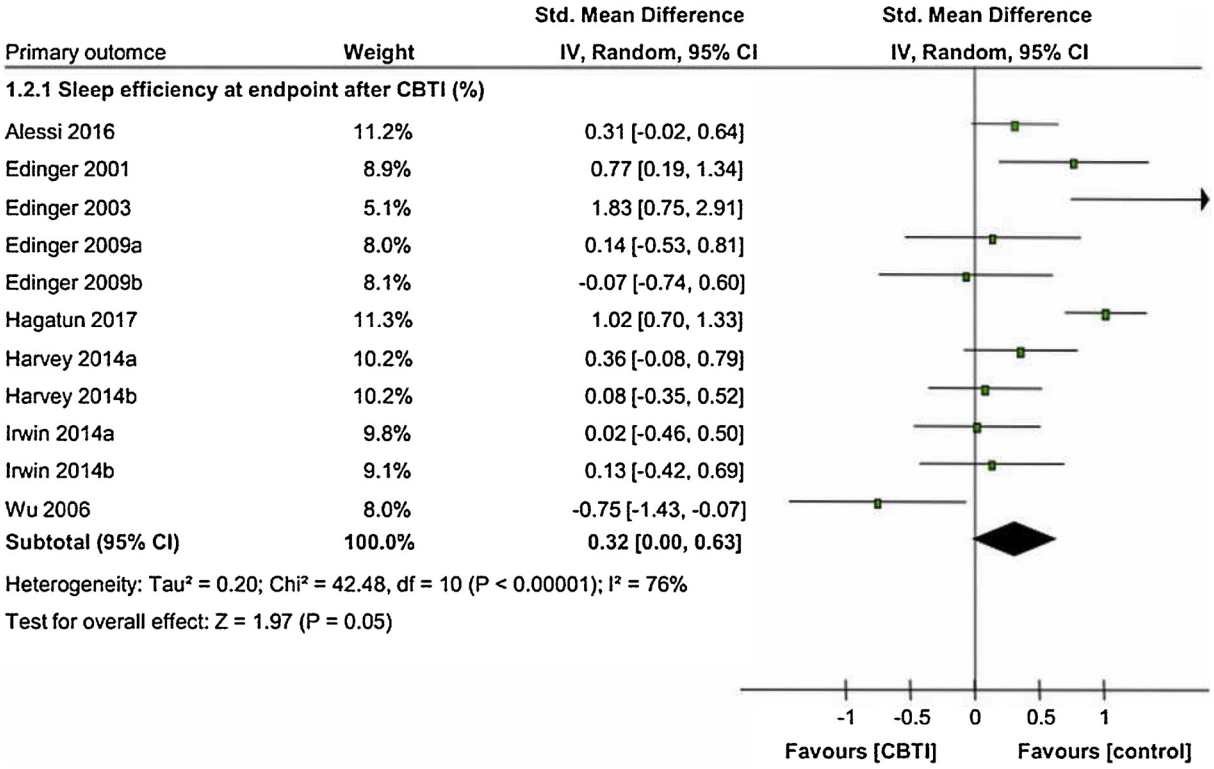

Fig. 2. Effect of CBTIs on sleep efficiency at post-CBTIs assessment.

3.7. Time in bed

Two RCTS with 3 CBTI arms reported data on time in bed at the post-CBTIs assessment. No significant group difference was found (n = 369, SMD: -0.4, 95% CI: -0.87 to 0.06, I^2 = 77%, p = 0.09, Table 2).

3.8. Insomnia assessed by scales

3.8.1. Pittsburgh Sleep Quality Index (PSQI)

Three RCTs with 4 CBTI arms reported data on insomnia assessed by the PSQI at post-CBTIs assessment. Compared to the active control group, the CBTIs group showed significantly less improvement at post-assessment (n = 351; SMD: -0.52, 95% CI: -0.86 to -0.19, I^2 = 50%, p = 0.002, Table 2). Three studies with 4 CBTI arms reported additional follow-up assessments, and no group difference was found (n = 348, SMD: -0.34, 95% CI: -0.76 to 0.07, I^2 = 66%, p = 0.1, Table 2).

3.8.2. Insomnia Severity Index (ISI)

Four studies with 5 CBTI arms reported data on insomnia assessed by ISI at post-CBTIs assessment. Compared with active control group,

Table 2
Sleep data at post-CBTIs assessment.

Variables	Arms (subjects)	SMD or RR (95%CI)	I^2 (%)	*P*-value
Total sleep time at endpoint after CBTI (min)	10 (667)	0.06 [−0.16, 0.28]	42	0.60
Total sleep time at additional follow-up (min)	4 (122)	0.24 [−0.30, 0.78]	54	0.38
Sleep efficiency at endpoint after CBTI (%)	11 (826)	0.32 [0.00, 0.63]	76	**0.05**
Sleep efficiency at additional follow-up (%)	5 (281)	0.26 [−0.19, 0.70]	61	0.25
Sleep latency at endpoint after CBTI (min)	10 (778)	−0.33 [−0.56, −0.09]	56	**0.007**
Sleep Latency at additional follow-up (min)	5 (281)	−0.29 [−0.62, 0.04]	32	0.08
Wake after sleep onset at endpoint after CBTI (min)	9 (740)	−0.27 [−0.52, −0.01]	60	0.04
Wake after sleep onset at additional follow-up (min)	4 (245)	−0.36 [−0.79, 0.07]	47	0.10
Time in bed at endpoint after CBTI (min)	3 (369)	−0.40 [−0.87, 0.06]	77	0.09
PSQI total score at endpoint after CBTI	5 (351)	−0.52 [−0.86, −0.19]	50	**0.002**
PSQI total score at additional follow-up	5 (348)	−0.34 [−0.76, 0.07]	66	0.10
ISI total score at endpoint after CBTI	5 (676)	−0.68 [−1.01, −0.36]	75	< **0.0001**
ISI total score at additional follow-up	4 (495)	−0.27 [−0.45, −0.08]	0	**0.005**
ISQ total score at endpoint after CBTI	4 (139)	−0.46 [−0.95, 0.02]	46	0.06
ISQ total score at additional follow-up	3 (86)	−0.75 [−1.76, 0.26]	79	0.15
DBAS total score at endpoint after CBTI	4 (270)	−0.76 [−1.25, −0.27]	60	0.002
DBAS total score at additional follow-up	3 (86)	−0.90 [−2.07, 0.27]	83	0.13
AIS total score at endpoint after CBTI	2 (123)	−0.66 [−1.07, −0.24]	18	**0.002**
AIS total score at additional follow-up	2 (123)	−0.50 [−0.89, −0.11]	9	**0.01**
Discontinuation due to any reason[a]	12 (1099)	0.62 [0.42, 0.92]	6	**0.02**

Abbreviations: AISAthens Insomnia Scale; DBASDysfunctional Attitudes and Beliefs About Sleep Scale; PSQIPittsburgh Sleep Quality Index; ISIInsomnia Severity Index; ISQInsomnia Symptom Questionnaire.

[a] In Hagatun et al's study, rate of discontinuation regarding sleep diary were extracted and analyzed.

Table 3
GRADE analyses.

Primary/secondary outcome	Active arms (N)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Overall quality of evidence[a]
Total sleep time at endpoint after CBTI (min)	10 (667)	Serious[b]	No	No	No	No	No	+/+/+/-/; Moderate
Total sleep time after follow-up (min)	4 (122)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
Sleep efficiency at endpoint after CBTI (%)	11 (826)	Serious[b]	Serious[c]	No	No	No	No	+/+/-/-/; Low
Sleep efficiency after follow-up (%)	5 (281)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
Sleep latency at endpoint after CBTI (min)	10 (778)	Serious[b]	Serious[c]	No	No	No	No	+/+/-/-/; Low
Sleep Latency after follow-up (min)	5 (281)	Serious[b]	No	No	No	Serious[d]	No	+/+/-/-/; Low
Wake after sleep onset after CBTI (min)	9 (740)	Serious[b]	Serious[c]	No	No	No	No	+/+/-/-/; Low
Wake after sleep onset after follow-up (min)	4 (245)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
Time in bed at endpoint after CBTI (min)	3 (369)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
PSQI total score at endpoint after CBTI	5 (351)	*Serious*[b]	*Serious*[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
PSQI total score after follow-up	5 (348)	*Serious*[b]	*Serious*[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
ISI total score at endpoint after CBTI	5 (676)	Serious[b]	Serious[c]	No	No	No	No	+/+/-/-/; Low
ISI total score after follow-up	4 (495)	Serious[b]	No	No	No	No	No	+/+/+/-/; Moderate
ISQ total score at endpoint after CBTI	4 (139)	Serious[b]	No	No	No	Serious[d]	No	+/+/-/-/; Low
ISQ total score after follow-up	3 (86)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
DBAS total score at endpoint after CBTI	4 (270)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
DBAS total score after follow-up	3 (86)	Serious[b]	Serious[c]	No	No	Serious[d]	No	+/-/-/-/; Very Low
AIS total score at endpoint after CBTI	2 (123)	Serious[b]	No	No	No	Serious[c]	No	+/+/-/-/; Low
AIS total score after follow-up	2 (123)	Serious[b]	No	No	No	Serious[c]	No	+/+/-/-/; Low
Discontinuation due to any reason	12 (1099)	Serious[b]	No	No	No	No	No	+/+/+/-/; Moderate

Abbreviations: AIS = Athens Insomnia Scale; DBAS = Dysfunctional Attitudes and Beliefs About Sleep Scale; GRADE = grading of recommendations assessment, development, and evaluation; PSQI = Pittsburgh Sleep Quality Index; ISI = Insomnia Severity Index; ISQ = Insomnia Symptom Questionnaire.

[a] 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.

[b] Meta-analytic studies (more than 50%) were open label or single blind studies.

[c] Meta-analytic results presented a serious inconsistency when I^2 values were greater than 50% or $P < 0.1$ in the Q statistics.

[d] For continuous outcomes, $N < 400$. For dichotomous outcomes, $N < 300$.

the CBTIs group showed significantly less improvement at post-CBTIs (n = 676; SMD: -0.68, 95% CI: -1.01 to -0.36, I^2 = 75%, $p < 0.0001$, Table 2). Three studies with 4 CBTI arms reported additional follow-up assessments. Compared with active control group, the CBTIs group showed significantly less improvement (n = 495, SMD: -0.27, 95% CI: -0.45 to -0.08, I^2 = 0%, p = 0.005, Table 2).

3.8.3. Insomnia Symptom Questionnaire (ISQ)

Three studies with 3 CBTI arms reported data on insomnia assessed by the ISQ at post-CBTIs assessment. No significant difference was found between active control group and CBTIs group at post-CBTIs (n = 139; SMD: -0.46, 95% CI: -0.95 to 0.02, I^2 = 46%, p = 0.06, Table 2). Two studies with 2 CBTI arms reported additional follow-up assessments but no group difference was found (n = 86; SMD: -0.75, 95% CI: -1.76 to 0.26, I^2 = 79%, p = 0.15, Table 2).

3.8.4. Dysfunctional Attitudes and Beliefs about Sleep Scale (DBAS)

Three studies with 3 CBTI arms reported data on insomnia assessed by the DBAS at post-CBTIs assessment. Compared with control groups, CBTIs group showed significantly less improvement at post-CBTIs (n = 270; SMD: -0.76, 95% CI: -1.25 to -0.27, I^2 = 60%, p = 0.002, Table 2). Two studies with 2 CBTI arms reported additional follow-up assessments, with no significant group differences found (n = 86; SMD: -0.9, 95% CI: -2.07 to 0.27, I^2 = 83%, p = 0.13, Table 2).

3.8.5. Athens Insomnia Scale (AIS)

One studies with 2 CBTI arms reported data on insomnia assessed by the AIS. Compared with the control group, CBTI group showed significantly less improvement at post-CBTIs (n = 123; SMD: -0.66, 95% CI: -1.07 to -0.24, I^2 = 18%, p = 0.002, Table 2) and at additional follow-up assessments (n = 123; SMD: -0.5, 95% CI: -0.89 to -0.11, I^2 = 9%, p = 0.01, Table 2).

3.8.6. All cause discontinuation

There was no significant group difference in discontinuation rate (n = 1,099, RR = 0.62, 95% CI: 0.42 to 0.92, I^2 = 6%, p = 0.02). Compared with control group, the CBTIs group has significant lower drop-off rate. Only 7 RCTs with 9 treatment arms were included for primary outcomes, thus we could not assess publication bias by performing a funnel plot or Egger's test (at least 10 studies are needed) (Egger et al., 1997).

3.8.7. Publication bias

Publication bias for primary outcome could not be evaluated using a funnel plot graph or the Egger's test because the number of included RCTs was less than 10 (Sterne et al., 2011).

4. Discussion

This was the first meta-analysis of RCTs that compared the effects of CBTIs monotherapy with active control groups in treating insomnia without comorbid major physical or psychiatric comorbidities. Compared with active control group, the CBTIs group showed significantly less improvement in insomnia at post-CBTIs assessment in terms of sleep efficiency, sleep latency, wake after sleep onset, the PSQI, the ISI, and the AIS. In addition, the significant group difference persisted at additional follow-up assessment as measured by the ISI and the AIS. Discontinuation rate was significantly lower in the CBTIs groups, which indicates better adherence to CBTIs.

Previous meta-analyses on computerised CBTI (Cheng and Dizon, 2012), group CBTI (Koffel et al., 2015), self-helped CBTI (Ren et al., 2016) and CBTI without specific types (Okajima et al., 2011; Trauer

et al., 2015) have found significant positive effects on insomnia. However, the common limitations included the presence of adjunctive pharmacotherapy and physical comorbidities, the lack of active controls and use of international diagnostic criteria for insomnia, all of which could increase the heterogeneity of studies and cause significant bias. In this meta-analysis, we only included RCTs using well-defined insomnia, CBTI monotherapy, persons with insomnia who had no major physical and psychiatric comorbidities, inclusion of active control groups and RCTs with blinding assessments. We believed that these attributes would significantly improve the study homogeneity. In addition, we synthesized actigraphy data instead of using sleep diary, which increased the validity of sleep data. Furthermore, several recently published RCTs (Alessi et al., 2016; Blom et al., 2016; Hagatun et al., 2017) were included, which increased the power of this meta-analysis. Unlike previous findings, we found that CBTI did not significantly outperformed control group in the treatment of insomnia in all post-CBTI assessments; moreover, the inferior results of CBTI persisted at the additional follow-up assessment as measured by the ISI and AIS. These results suggest that CBTI a monotherapy has no advantage for improving insomnia compared to active control interventions. The discrepancy between this and previous meta-analyses is probably due to the exclusion of the potentially confounding factors as mentioned above. Of note, CBTI may still have a beneficial role when considering the side effects of sleeping pills (Koffel et al., 2015; Kuppili et al., 2019). Apart from sleeping pills, it is helpful to incorporate psychosocial inventions, such as CBTI, in the treatment of insomnia (Kuppili et al., 2019).

The validity of the results is supported by the improved study homogeneity and high quality the RCTs. There were also several limitations. First, the duration and frequency of CBTI varied across studies, hence the dose-response effect of CBTI could not be examined. Second, the control active treatment groups were heterogeneous, including sleep education, credible insomnia treatment, muscle relaxation, sleep hygiene education, online sleep education, cognitive therapy, behaviour therapy, Tai Chi, Sleep seminar and pharmacological therapy. This could increase the heterogeneity of the study outcomes. Third, only one study was conducted in Asia, while most studies focused on white Caucasian group, which precludes generalizations of the findings.

In conclusion, the results of this meta-analysis found that CBTI monotherapy had no advantage in improving insomnia compared with other standard treatments. However, this meta-analysis does not negate the well-proved effectiveness of CBTI in the treatment of insomnia. Probably CBTI works well when it is combined with other treatments, such as pharmacotherapy. Further double-blind RCTs with larger samples are required to confirm the findings.

Statement

This manuscript does not report a clinical trial. All co-authors have seen and approved the manuscript.

Off-label or investigational use

Not applicable.

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Declaration of Competing Interest

The authors had no conflicts of interest in conducting this study or preparing the manuscript.

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.ajp.2019.10.008.

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