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REVIEW ARTICLE

Cognitive Behavioural Therapy for Insomnia Monotherapy in Patients with Medical or Psychiatric Comorbidities: a Meta-Analysis of Randomized Controlled Trials

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Abstract
This is a meta-analysis of randomized controlled trials (RCTs) comparing cognitive behaviour therapy for insomnia (CBT-I) monotherapy with active control treatment for insomnia in patients with medical or psychiatric comorbidities. Both international (PubMed, EMBASE, PsycINFO, Cochrane Library) and Chinese (WanFang, and CNKI) databases were systematically searched. The random effects model was used. Thirteen RCTs comparing CBT-I ($n = 441$) and active controls ($n = 412$) groups were included. CBT-I group showed significant advantage over active controls at post-treatment assessment in terms of Insomnia Severity Index (ISI; SMD = -0.74), sleep onset latency (SMD = -0.36), wake after sleep onset (SMD = -0.21), sleep quality (SMD = 0.56), Pittsburgh sleep quality index total scores (PSQI; SMD = -0.76) and the total score of dysfunctional beliefs and attitudes about sleep scale (DBAS; SMD = -1.09). Subgroup analyses revealed significant improvement in sleep onset latency in patients with psychiatric disorders (SMD = -0.45), while significant reduction of number of wakeup after sleep onset was found in patients with medical conditions (SMD = -0.31). This meta-analysis found that CBT-I monotherapy had greater efficacy than other active control treatment for insomnia in patients with medical or psychiatric comorbidities.

Keywords Cognitive behavioural therapy · Insomnia · Comorbidities · Meta-analysis

Introduction

Insomnia is a common sleep disorder [1] that can lead to negative health outcomes, such as fatigue, increased daytime irritability, cognitive deficits and poor health status [2, 3]. Insomnia often co-exists with major medical conditions, such as diabetes [4], hypertension [5] and

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cancer [6], which increase personal suffering and even the risk of all-cause mortality [7]. In addition, insomnia also occurs in up to 40%–50% of patients with psychiatric disorders [8], such as depression [9], bipolar and anxiety disorder [10], and increases the risk of suicide [11, 12].

There is a complex association between insomnia and major medical/ psychiatric disorders. Medical and psychiatric disorders could precipitate the development of insomnia, while insomnia could increase the risk of medical/ psychiatric conditions. Therefore both insomnia and major medical/ psychiatric disorders need to be treated concurrently [1, 13]. Psychotropic medications, such as benzodiazepines and non-benzodiazepine hypnotics (e.g. Zolpidem), are commonly prescribed, although the long-term use is not encouraged due to the risk of dependency [14, 15].

Psychosocial interventions, such as cognitive behavioural therapy for insomnia (CBT-I), have been increasingly used in treating patients with insomnia disorder [16–19]. The efficacy of CBT-I in primary insomnia has been shown in several meta-analyses [20–26] and CBT-I is recommended for insomnia by the American Academy of Sleep Medicine [17, 27].

Research findings on the efficacy of CBT-I in patients with major medical conditions (e.g. cancer [28]) or psychiatric disorders (e.g. depression (Manber et al., 2008) and posttraumatic stress disorder (Ger-main, Shear, Hall, & Buysse, 2007; Talbot et al., 2014)), have been mixed. One recent meta-analysis [29] examined the efficacy of CBT-I for patients with medical or psychiatric comorbidities. However, the diagnosis of insomnia was based on either patients' complaints or standardized diagnostic scales, such as the insomnia severity index (ISI), and only a proportion of participants in the included studies had comorbid medical and/or psychiatric disorders. Due to the heterogeneity in diagnostic criteria and study samples across studies, the findings could be biased to an uncertain extent.

Thus we conducted this meta-analysis of randomized controlled trials (RCTs) comparing CBT-I monotherapy with active control treatment for insomnia in patients with major medical or psychiatric disorders using stringent diagnostic criteria.

Methods

Selection Criteria

Following the PICOS acronym [30], the inclusion criteria were as follows: participants (P): patients with a diagnosis of insomnia and major medical or psychiatric comorbidities; insomnia was diagnosed using standardized diagnostic criteria, such as the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [31], the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [32], or the International Classification of Sleep Disorders (ICSD) [33, 34]. Intervention (I): CBT-I monotherapy. Comparison (C): active control group, such as behavioural desensitization and sleep hygiene education. Outcomes (O): the primary outcome measure was the improvement of insomnia symptoms as assessed with standardized scales, such as the Insomnia Severity Index (ISI). Secondary outcome measures included the Pittsburgh Sleep Quality Index (PSQI), dysfunctional attitudes and beliefs about sleep scale (DBAS) and sleep parameters based on polysomnography, actigraphy or sleep diaries, such as sleep efficiency, total sleep time, sleep latency, wake after sleep onset, time in bed, sleep quality and number of awakenings. Study

design (S): Randomized controlled trials (RCTs). Studies that did not specifically mention CBT-I were excluded, although certain components of CBT-I were used.

Search Methods

Literature search was independently conducted by three authors (FCZ and YY) in PubMed, EMBASE, PsycINFO, Cochrane Library, WanFang, and CNKI databases from the inception date until November 12, 2017, using the following terms: CBTI, CBT-I, cognitive behavioural therapy for insomnia, cognitive behavioural for insomnia, cognitive behavioural treatment for insomnia, cognitive behavioural treatment for insomnia, cognitive behavioural therapy of insomnia, cognitive behavioural therapy of insomnia, insomnia, sleep, maintenance disorder, dyssomnia, sleepless, early morning awakening, Randomized controlled trials, Randomized controlled trial, RCT, and RCTs. In addition, we manually reviewed the reference list of relevant reviews for additional studies.

Data Extraction

Relevant data were independently extracted by two authors (FCZ and YY). Any discrepancies were resolved by consensus or a discussion with the third author (YTX). If both polysomnography or actigraphy and rating scales were used, polysomnography and actigraphy were preferred as they are more objective than scales. Several studies had several follow-up assessments. In order to reduce heterogeneity caused by study periods, only the data at 3 months follow-up were extracted and analyzed.

Quality Assessment

The study quality was assessed using the Cochrane risk of bias [35] and the Jadad scale [36, 37]. The total score of the Jadad scale ranges from 1 to 5, with a higher score indicating higher quality. Studies with a Jadad total score of <3 was considered as low-quality; otherwise they were considered as high-quality [36]. The system grading of recommendations assessment, development, and evaluation (GRADE) was used in evaluating the evidence level of outcomes [38, 39].

Data Synthesis and Statistical Analyses

Due to the discrepancy in sampling methods, measurements and demographic and clinical characteristics between studies, the random effects model was used for meta-analytic outcomes [40]. Compared to fixed-effects model, the random-effects model is more conservative [40]. Intention-to-treat (ITT) analyses were preferred if available in included studies [41–43]. The heterogeneity across included studies was assessed using I^2 index [44], with I^2 of 25%, 50% and 75% indicating mild, moderate, and high heterogeneity between studies, respectively. The standardized mean difference (SMD) with 95% confidence intervals (CIs) was used for continuous outcome variables. Funnel plots and Egger's test were performed [45] for publication bias of primary outcome. A significance level of 0.05 was set for all meta-analytic outcomes (two-sided). Review Manager Version 5.3 (http://www.cochrane.org) and

Comprehensive Meta-Analysis V2.0 (www.meta-analysis.com) were used for all analyses.

Results

Literature Search and Study Characteristics

A total of 250 relevant articles were initially identified in the literature search. Finally, 13 RCTs with 27 treatment arms were included in the analyses (Fig. 1). One study [46] included three arms (e.g., an internet CBT-I, an in-person CBT-I and a control group), and so data from both CBT-I groups were combined for analyses. Eight hundred and fifty-three participants were included in this meta-analysis, with 441 patients in the CBT-I group and 412 in the active control group. The included studies were carried out in the United States (7 RCTs, $n = 481$), Sweden (1 RCT, $n = 64$), Canada (2 RCTs, $n = 183$), and Spain (3 RCTs, $n = 125$). The diagnosis of insomnia was established using DSM-IV, DSM-IV-TR, DSM-III-R, International Classification of Sleep Disorders (ICSD), ICSD-

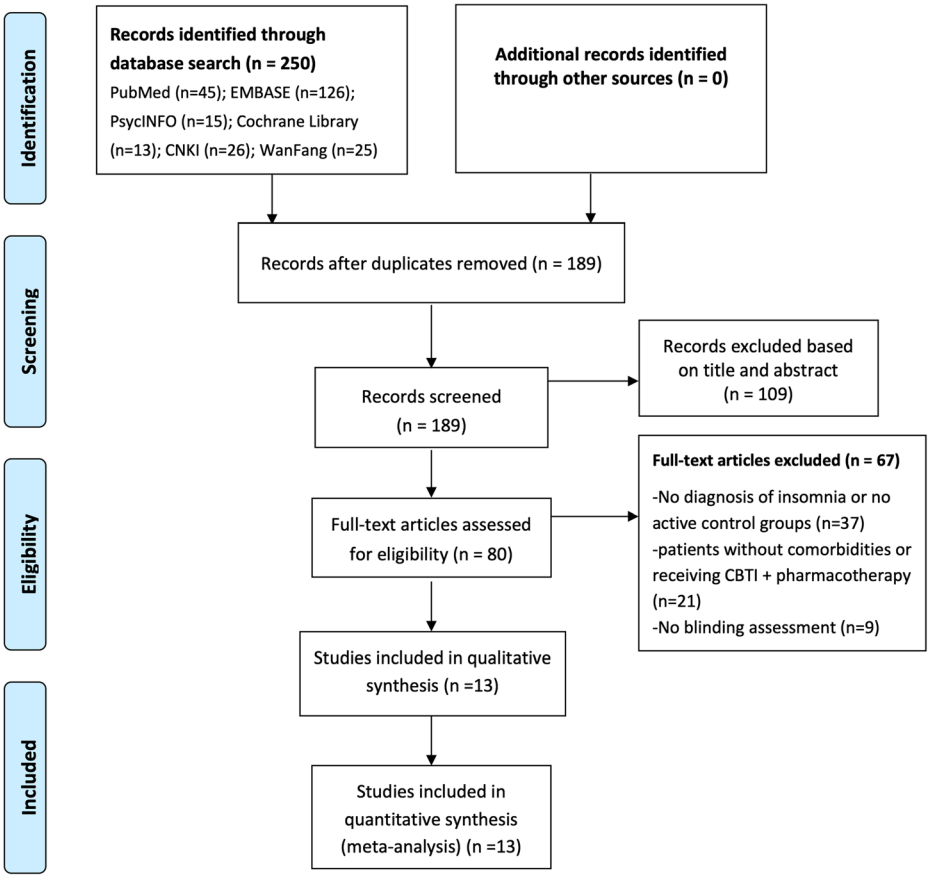

Fig. 1 PRISAMA flowchart

Table 1 Characteristics of studies included in this meta-analysis

First Author (references)	Year	country	Participants					
			n [a]	M (%)	Age M (SD)	Diagnostic criteria	Design: -setting -blinding	Comorbidity
Taylor [39]	2017	US	67	83.33	31.81 (7.33)	DSM-5	-outpatients/army -NR	anxiety, depression, etc.
Irwin [41]	2017	US	90	0	59.8 (8.58)	DSM-IV, ICSD	-outpatients -Partial blind	breast cancer
Smitherman [42]	2016	US	31	9.67	30.81 (12.9)	ICSD-3	-outpatients -Single blind	chronic migraine
Smith [43]	2015	US	100	21	59.4 (9.5)	American Academy of Sleep Medicine	-NR -Double blind	knee osteoarthritis
Norell-Clarke [44]	2015	Sweden	64	23.44	51.5 (12.55)	DSISD	-NR Assessor blind	depressive symptomatology
Lee [45]	2015	US	30	43.33	38.37 (11.92)	DSM-IV-TR	-outpatients -NR	bipolar disorder
Harvey [46]	2015	US	58	37.93	36.64 (10.97)	DSM-IV-TR, ICSD, DSISD	-mix -Double blind	bipolar disorder type I
Garland [47]	2015	Canada	72	27.78	59.44 (11.22)	DSM-IV-TR, SCID	-NR -Patient blind	cancer
Martinez [48]	2014	Spain	59	0	47.58 (6.82)	DSM-IV-TR	-NR -Researcher blind	fibromyalgia
Garland [49]	2014	Canada	111	27.93	58.89 (11.08)	ICSD, American Academy of Sleep Medicine	-NR -Partial blind	cancer
Sánchez [50]	2012	Spain	26	0	46.79 (5.15)	DSM-IV-TR	-NR -NR	fibromyalgia
Miro [51]	2011	Spain	40	0	NR	DSM	-NR -Examiner blind	fibromyalgia
Dirksen [52]	2008	US	72	0	58.3 (10.3)	DSM, ICSD	-NR -NR	breast cancer

First Author (references)	Intervention				Outcomes (Sleep)	Dropout (CBT-I)	Jadad score[b]
	Type of CBT-Is	Duration (wks)	Type of intervention	FUT (m)			
Taylor [39]	In-person CBT-I	6	a brief check-in call	6	Sleep Dairy, PSG (TST, SE, SQ, SL, WASO, NOA), ISI, DBAS, ESS	33/67	3
Irwin [41]	CBT-I	12	Tai Chi Chih	3	Sleep Dairy, PSG (TST, SE, SL, WASO), PSQI, AISI	3/45	3

Table 1 (continued)

First Author (references)	Intervention				Outcomes (Sleep)	Dropout (CBT-I)	Jadad score[b]
	Type of CBT-Is	Duration (wks)	Type of intervention	FUT (m)			
Smitherman [42]	CBT-I	6	mix (lifestyle modification etc.)	1.5	PSG (TST, SE), PSQI, ESS	2/16	4
Smith [43]	CBT-I	NR	behavioral desensitization	3	Sleep Dairy, PSG (TST, SE, SL, WASO), ISI	7/50	4
Norell-Clarke [44]	Group CBT-I	8	relaxation training	6	PSG (TST, SQ, SL, WASO, EMA), ISI	2/32	4
Lee [45]	CBT-I	8	psychoeducation	NR	PSQI, ISI, PROMIS-Sleep, QoL-Sleep,	1/17	3
Harvey [46]	Bipolar disorder-specific modification CBT-I	NR	psychoeducation	6	PSG (TST, SE, SL, WASO, TWT, TIB), PSQI, ISI, SDS-sleep, PROMIS-Sleep, PROMIS-SRI	6/30	4
Garland [47]	CBT-I	8	mindfulness-based cancer recovery	3	DBAS	0/40	3
Martinez [48]	CBT-I	6	sleep hygiene	3	PSQI	2/32	4
Garland [49]	CBT-I	8	mindfulness-based stress reduction	3	PSG (TST, SE, SL, WASO), PSQI, ISI, DBAS	7/47	4
Sánchez [50]	CBT-I	6	sleep hygiene	NR	PSG (TST, SE, WASO, TIB, NOA)	0/13	3
Miro [51]	Group CBT-I	6	sleep hygiene	NR	PSQI	2/22	4
Dirksen [52]	CBT-I	6	sleep education and hygiene	NR	ISI	6/40	3

Abbreviations: *CBT-I* Cognitive Behavioural Therapy for Insomnia; M, male; min, minute; wks, weeks; n, number of patients; NR, not report; FUT, Follow up Timepoint; DSM-IV, Diagnostic Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-5, Diagnostic Statistical Manual of Mental Disorders, version 5; ICSD, International Classification of Sleep Disorders; DSISD, Duke Structured Interview for Sleep Disorders; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; DBAS, Dysfunctional Beliefs and Attitudes About Sleep Scale; ESS, Epworth Sleepiness Scale; PROMIS-Sleep, Patient-Reported Outcomes Measurement Information System-Sleep Disturbance; PROMIS-SRI, Patient-Reported Outcomes Measurement Information System-Sleep Related Impairment instrument; SDS-sleep, The Sleep Disorders Specialty-sleep; QoL-Sleep, Quality of Life-sleep; PSG, Polysomnography; SE, Sleep Efficiency; TST, Total Sleep Time; TWT, Total Wake Time; SL, Sleep Latency; WASO, Wake After Sleep Onset; EMA, Early Morning Awakening; TIB, Time in Bed; NOA, Number of Awakenings

[a] Sample size analyzed; 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

Table 2 Sleep data at post-CBT-I assessment

Variables	Arms (subjects)	SMD or RR [95%CI]	I^2 (%)	*P* value
Total sleep time at endpoint after CBT-I (min)	8 (531)	-0.15 [−0.30, 0.04]	45	0.14
Total sleep time at additional follow-up (min)	3 (235)	-0.20 [−0.47, 0.07]	15	0.14
Sleep efficiency at endpoint after CBT-I (%)	7 (498)	0.18 [0.003, 0.36]	36	0.05
Sleep efficiency at additional follow-up (%)	3 (234)	0.31 [0.04, 0.58]	0	0.03
Sleep latency at endpoint after CBT-I (min)	6 (505)	-0.36[−0.62, −0.10]	51	0.007
Sleep Latency at additional follow-up (min)	3 (234)	-0.13 [−0.40, 0.14]	32	0.33
Wake after sleep onset at endpoint after CBT-I (min)	7 (531)	-0.21 [−0.38, −0.04]	34	0.02
Wake after sleep onset at additional follow-up (min)	3 (250)	-0.30 [−0.56, −0.05]	47	0.02
Time in bed	2 (84)	-0.09 [−0.72, 0.90]	67	0.82
Sleep quality	2 (164)	0.56 [0.23, 0.88]	0	<0.001
Number of awakenings	2 (126)	0.20 [−0.16, 0.57]	0	0.28
PSQI total score at endpoint after CBT-I	7 (417)	-0.76 [−1.09, −0.42]	61	<0.001
PSQI total score at additional follow-up	3 (215)	-0.56 [−1.01, −0.12]	55	0.01
ISI total score at endpoint after CBT-I	7 (527)	-0.74 [−0.92, −0.56]	39	<0.0001
ISI total score at additional follow-up	2 (168)	-0.33 [−0.64, −0.01]	0	0.04
DBAS total score at endpoint after CBT-I	3 (283)	−1.09 [−1.48, −0.71]	60	<0.001
DBAS total score at additional follow-up	3 (251)	−0.80 [−1.35, −0.25]	76	0.004
Discontinuation due to any reason	11 (776)	0.81 [0.44, 1.47]	60	0.49

Abbreviations: CBT-I: Cognitive Behavioural Therapy for Insomnia; DBAS: Dysfunctional Attitudes and Beliefs About Sleep Scale; PSQI: Pittsburgh Sleep Quality Index; ISI: Insomnia Severity Index; min: minute

2, or American Academy of Sleep Medicine criteria. Treatment frequency varied from weekly to biweekly, and the number of sessions of CBT-I treatment ranged from 3 to 12 (Table 1).

Assessment Quality and Quality of Evidence

The risk of bias in the 13 RCTs is shown in Table S1. Five studies were double blinded, 8 studies were single blinded or partial blinded, and the rest did not provide any information of blinding. All the included RCTs described the random sequence generation, and 5 mentioned allocation concealment. All studies were rated as "low risk" in terms of attrition and reporting bias. Jadad total score ranged from 3 to 4 (Table 1). All included RCTs were rated as "high quality". The quality of evidence of outcome measures were evaluated as "very low" (5.9%, 1/17), "low" (29.4%, 5/17), and "moderate" (64.7%, 11/17) according to the GRADE approach (Table 3).

Publication Bias

As the number of studies was less than 10 for analyses on efficacy measures, publication bias could not be evaluated [47].

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 after treatment (min)	8 (531)	Serious [b]	No	No	No	Not suspected [e]	No	+/+/± /; Moderate
Total sleep time after follow-up (min)	3 (235)	No	No	No	Serious [d]	Not suspected [e]	No	+/+/± /; Moderate
Sleep efficiency after treatment (%)	7 (498)	Serious [b]	No	No	No	Not suspected [e]	No	+/+/± /; Moderate
Sleep efficiency after follow-up (%)	3 (234)	No	No	No	Serious [d]	Not suspected [e]	No	+/+/± /; Moderate
Sleep latency after treatment (min)	6 (505)	Serious [b]	Serious [c]	No	No	Not suspected [e]	No	+/± /−/; Low
Sleep latency after follow-up (min)	3 (234)	No	No	No	Serious [d]	Not suspected [e]	No	+/+/± /; Moderate
Wake after sleep onset after treatment (min)	7 (531)	Serious [b]	No	No	No	Not suspected [e]	No	+/+/± /; Moderate
Wake after sleep onset after follow-up (min)	3 (250)	No	No	No	Serious [d]	Not suspected [e]	No	+/+/± /; Moderate
Time in bed after treatment (min)	2 (84)	Serious [b]	Serious [c]	No	Serious [d]	Not suspected [e]	No	+/−/−/−/; Very low
Sleep quality after treatment (min)	2 (164)	Serious [b]	No	No	Serious [d]	Not suspected [e]	No	+/± /−/; Low
Number of awakenings after treatment	2 (126)	Serious [b]	No	No	Serious [d]	Not suspected [e]	No	+/± /−/; Low
PSQI total score after treatment	7 (417)	No	Serious [c]	No	No	Not suspected [e]	No	+/+/± /; Moderate
PSQI total score after follow-up	3 (215)	No	Serious [c]	No	Serious [d]	Not suspected [e]	No	+/± /−/; Low
ISI total score after treatment	7 (527)	Serious [b]	No	No	No	Not suspected [e]	No	+/+/± /; Moderate
ISI total score after follow-up	2 (168)	No	No	No	Serious [d]	Not suspected [e]	No	+/+/± /; Moderate
DBAS total score after treatment	3 (283)	Serious [b]	Serious [c]	No	Serious [d]	Not suspected [e]	Yes	+/± /−/; Low
DBAS total score after follow-up	3 (251)	No	Serious [c]	No	Serious [d]	Not suspected [e]	Yes	+/+/± /; 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, $N < 300$

[e] As the number of studies was less than 10, publication bias could not be evaluated

Primary Outcome

Insomnia Severity Index (ISI)

Seven studies reported insomnia data assessed by ISI at post-treatment assessment. Compared with the control group, the CBT-I group showed more significant improvement at post-treatment ($n = 527$; SMD: -0.74, 95% CI: −0.92 to −0.56, $I^2 = 39\%$, $p < 0.0001$, Table 2, Fig. S1.1). Subgroup analyses found superiority of CBT-I over active control group in patients with major medical conditions at post-treatment ($N = 3$, $n = 275$, SMD: -0.58, 95% CI: −0.82 to −0.34, $I^2 = 33\%$, $p < 0.001$), as well as in those with psychiatric disorders at post-treatment ($N = 4$, $n = 252$, SMD: -0.93, 95% CI: −1.20 to −0.66, $I^2 = 7\%$, $p < 0.001$) (Fig. S1.2). Additional follow-up data were only available in 2 studies, which also found superiority of CBT-I group over active control group at 3-month follow-up ($n = 168$, SMD: -0.33, 95% CI: −0.64 to −0.01, $I^2 = 0\%$, $p = 0.04$, Table 2, Fig. S1.3).

Secondary Outcomes

Sleep Efficiency

Data on sleep efficiency were available in 7 RCTs ($n = 498$). Compared with control group, CBT-I was associated with small but significant improvement at post-treatment assessment (n = 498, SMD: 0.18, 95% CI: 0.00 to 0.36, $I^2 = 36\%$, $p = 0.05$, Table 2, Fig. S2.1). Compared with the control group, CBT-I did not show significant benefits in patients with psychiatric disorders at post-treatment assessment (2 RCTs, $n = 158$, SMD: 0.13, 95% CI: −0.19 to 0.46, $I^2 = 2\%$, $p = 0.42$, Table 2). There were also non-significant findings in patients with medical conditions at post-treatment assessment (5 RCTs, $n = 340$, SMD: 0.14, 95% CI: −0.19 to 0.47, $I^2 = 52\%$, $p = 0.40$)(Fig. S2.2). Three studies reported additional follow-up assessments and found a significant improvement of sleep efficiency in CBT-I group that persisted at 3 months ($n = 234$, SMD: 0.31, 95% CI: 0.04 to 0.58, $I^2 = 0\%$, $p = 0.03$, Table 2, Fig. S2.3).

Total Sleep Time

Eight RCTS reported data on total sleep time. There was no significant group difference at post-treatment assessment ($n = 531$, SMD: -0.13, 95% CI: −0.30 to 0.04, $I^2 = 45\%$, $p = 0.14$, Table 2, Fig. S3.1). In the subgroup analyses, neither patients with major medical conditions nor those with psychiatric disorders showed any significant improvement in CBT-I group at post-treatment assessment (major medical conditions: 5 RCTs, $n = 309$, SMD: -0.15, 95% CI: −0.49 to 0.18, $I^2 = 51\%$, $p = 0.37$; psychiatric disorders: 3 RCTs, $n = 222$, SMD: -0.04, 95% CI: −0.44 to 0.35, $I^2 = 51\%$, $p = 0.83$, Fig. S3.2). Three studies reported additional follow-up data at 3 months, but there was no significant group difference ($n = 235$, SMD: -0.20, 95% CI: −0.47 to 0.07, $I^2 = 15\%$, p = 0.14, Table 2, Fig. S3.3).

Sleep Onset Latency

Data were available from 6 RCTs on sleep latency. Compared with control group, the CBT-I group showed significant improvement at post-treatment assessment ($n = 505$, SMD: -0.36, 95% CI: −0.62 to −0.10, $I^2 = 51\%$, $p = 0.007$, Table 2, Fig. S4.1). No group difference was found in patients with major medical conditions at post-treatment assessment (3 RCTs, $n = 283$, SMD: -0.27, 95% CI: −0.78 to 0.24, $I^2 = 78\%$, $p = 0.30$). Nevertheless, subgroup analyses revealed a significant group difference in patients with psychiatric disorders at post-treatment assessment (3 RCTs, $n = 222$, SMD: -0.45, 95% CI: −0.73 to 0.18, $I^2 = 0\%$, $p = 0.001$, Fig. S4.2). Three studies reported data in additional follow-up assessment, but no group difference was found ($n = 234$, SMD: -0.13, 95% CI: −0.40 to 0.14, $I^2 = 32\%$, $p = 0.33$, Table 2, Fig. S4.3).

Wake after Sleep Onset

Data were available from 7 RCTS on wake after sleep onset at the post-treatment assessment. The CBT-I group showed significant improvement compared with active control group ($n = 531$, SMD: -0.21, 95% CI: −0.38 to −0.04, $I^2 = 34\%$, $p = 0.02$, Table 2, Fig. S5.1). Significant group difference was found in patients with major medical conditions (4 RCTs, $n = 309$, SMD: -0.31, 95% CI: −0.54 to −0.09, $I^2 = 0\%$, $p = 0.006$). However, in patients with psychiatric disorders, no significant group difference was found (3 RCTs, $n = 222$, SMD: -0.08, 95% CI: −0.51 to 0.35, $I^2 = 59\%$, $p = 0.72$, Fig. S5.2). In the three studies which reported additional 3 months follow-up, and the superiority of CBT-I group was found ($n = 250$, SMD: -0.30, 95% CI: −0.56 to 0.05, $I^2 = 47\%$, $p = 0.02$, Table 2, Fig. S5.3).

Time in Bed

Two RCTs reported data on time in bed between CBT-I group and active control group at post-treatment assessment, but no significant group difference was found ($n = 84$, SMD: -0.09, 95% CI: −0.72 to 0.90, $I^2 = 67\%$, $p = 0.83$, Table 2, Fig. S6).

Sleep Quality

Data were available in 2 RCTS on sleep quality at the post-treatment assessment, and the CBT-I group showed significant improvement ($n = 164$, SMD: 0.56, 95% CI: 0.23 to 0.88, $I^2 = 0\%$, $p < 0.001$, Table 2, Fig. S7).

Number of Awakenings

Data were available from 2 RCTs on number of awakenings at the post-treatment assessment, but no significant group difference was found ($n = 126$, SMD: 0.20, 95% CI: −0.16 to 0.57, $I^2 = 0\%$, $p = 0.28$, Table 2, Fig. S8).

Pittsburgh Sleep Quality Index (PSQI)

Seven RCTs reported the changes of PSQI total score at post-treatment assessments. CBT-I group showed significant improvement ($n = 417$; SMD: -0.76, 95% CI: −1.09 to −0.42, $I^2 = 61\%$, $p < 0.001$, Table 2, Fig. S9.1). Subgroup analyses revealed a significant advantage of CBT-I for patients with major medical conditions (5 RCTs, $n = 329$, SMD: -0.76, 95% CI: −1.22 to −0.30, $I^2 = 74\%$, $p = 0.001$) and for those with psychiatric disorders (2 RCTs, $n = 88$, SMD: -0.76, 95% CI: −1.19 to −0.32, $I^2 = 0\%$, $p = 0.006$, Fig. S9.2). Follow-up assessments were reported in 3 RCTs, and the superiority of CBT-I persisted for three months ($n = 215$, SMD: -0.56, 95% CI: −1.01 to −0.12, $I^2 = 55\%$, $p = 0.01$, Table 2, Fig. S9.3).

Dysfunctional Attitudes and Beliefs about Sleep Scale (DBAS)

The DBAS total scores were available in 3 RCTs at post-treatment assessment. CBT-I group had significant improvement at post-treatment assessment ($n = 283$; SMD: -1.09, 95% CI: −1.48 to −0.71, $I^2 = 60\%$, $p < 0.001$, Table 2, Fig. S10.1). Three studies reported data at additional follow-up, but there were no significant group difference ($n = 251$; SMD: -0.8, 95% CI: −1.35 to −0.25, $I^2 = 76\%$, $p = 0.004$, Table 2, Fig. S10.2).

All Cause Discontinuation

Eleven studies reported discontinuation rates at post-treatment assessments, but no significant group difference was found ($n = 773$, RR = 0.81, 95% CI: 0.44 to 1.47, $I^2 = 60\%$, $p = 0.49$, Fig. S11).

Discussion

This was the first meta-analysis of RCTs specifically comparing CBT-I monotherapy with active control treatment for insomnia in patients with medical or psychiatric comorbidities.

CBT-I usually contains five core components [27]: stimulus control, sleep restriction, sleep hygiene, relaxation training and cognitive restructuring. Of the included studies, 4 studies used all the five components [46, 48–50], 8 studies used four components [51–58] and 1 study used two components [59]. Of the five core components, stimulus control was used in all studies. Four studies also used an additional component (relapse prevention for insomnia) [50, 52, 56, 57], and psycho-education about the association between sleep and fibromyalgia was used in 3 studies [50, 56, 57]. This meta-analysis consistently found superiority of CBT-I over active control group in treating insomnia in patients with major medical or psychiatric comorbidities. The effect size was medium as measured by the primary outcome measure (SMD = −0.74). In addition, the advantage of the CBT-I group remained in most secondary outcome measures, such as sleep onset latency (SMD = -0.36), wake after sleep onset (SMD = -0.21), sleep quality (SMD = 0.56), PSQI total scores (SMD = -0.76) and DBAS total scores (SMD = -1.09). However, no group difference was found in total sleep time, time in bed, number of awakening and sleep quality. This meta-analysis also found that the superiority of CBT-I persisted at 3 months in the following measures: the wake after sleep onset (SMD = -0.30), PSQI (SMD = -0.56) and ISI (SMD = −0.33). The effect sizes in these measures were generally larger than

those reported in the Geiger-Brown et al.'s study [29], in which the benefits in the CBT-I group were less pronounced (effect size: −0.17 to 0.10) at 3 months follow-up.

As for the primary outcome measure, the effect size between CBT-I and active control treatment in this meta-analysis (SMD = -0.74) was smaller compared to the Geiger-Brown et al. study (2015) (effect size = 1.22), which could be due to different proportion of comorbidities between study samples. In the 2015 study [29] the majority of the participants suffered from chronic pain syndrome and mixed medical and/or psychiatric conditions. CBT-I was associated with an effect size of 1.00 in patients with medical conditions and with an effect size of 1.51 in those with psychiatric disorders [29]. Subgroup analyses of this meta-analyses revealed similar findings, which suggests that CBT-I appears to be more effective in treating insomnia patients with psychiatric disorders. The present study revealed that CBT-I was associated with a greater improvement in patients with psychiatric comorbidities (SMD: −0.93) than those with medical comorbidities (SMD: −0.58) as measured by the ISI total score.

In this meta-analysis CBT-I showed superiority over control group in several secondary outcome measures, such as sleep onset latency, wake after sleep onset, sleep quality, PSQI and DBAS total scores. The effect sizes were generally smaller than most findings published in previous meta-analyses regarding CBT-I [20, 22, 25, 26]. Moreover, this meta-analysis did not find any advantage of CBT-I in the following domains: total sleep time, time in bed, and number of awakening. These inconsistent findings may be due to different proportion of comorbidities between study samples.

Subgroup analyses revealed that CBT-I had an advantage on sleep onset latency only in patients with psychiatric disorders, while CBT-I had an advantage regarding number of wakeup after sleep onset only in those with medical conditions. This finding was not reported previously. This meta-analysis also found that the advantage of CBT-I persisted at 3-month follow-up in the following measures: wake after sleep onset, PSQI, and ISI. However, the effect sizes appeared to decrease over time.

The strengths of this meta-analysis include the use of stringent diagnostic criteria for insomnia, inclusion of insomnia patients with major medical conditions or psychiatric disorders, and administration of a variety of secondary outcome measures. However, several limitations need to be addressed. First, there was a discrepancy in study designs, participant characteristics, insomnia definition, and outcome measures between studies, although the random effects model and subgroup analyses have been performed. Second, some relevant factors, such as prescriptions of medications and severity of major medical conditions and psychiatric disorders, were not analysed due to insufficient data. Third, the long-term effect of CBT-I could not be examined due to lack of data. Finally, only English and Chinese databases were searched.

Conclusion

This meta-analysis found that CBT-I monotherapy generally had greater efficacy than other active control treatment for insomnia in patients with medical or psychiatric comorbidities. CBT-I was more efficacious in improving sleep onset latency in patients with mental disorders, while it also has an advantage in reducing number of wakeup after sleep onset in patients with medical conditions. However, the advantage of CBT-I was only maintained in some measurements at 3-month assessment, with decreased effect sizes over time.

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Data Availability Data will be provided by the corresponding author upon reasonable request.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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