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


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A R T I C L E   I N F O

Keywords:
Insomnia
Cognitive behavioural therapy for insomnia
Meta-analysis

A B S T R A C T

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 beha-
vioural 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 in-
somnia (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
computerized CBTI (Cheng and Dizon, 2012), or group CBTI (Koffel
et al., 2015), or self-helped CBTI (Ren et al., 2016), while others in-
cluded 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 in-
somnia 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 (Thorp MJ chairman),
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 Pitts-
burgh 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 in-
cluded 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, qualita-
tive 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: in-
somnia, sleep, early morning awakening, maintenance disorder, dys-
omnia, sleepless, cognitive behavioral for insomnia, cognitive beha-
vioural therapy for insomnia, cognitive behavioural treatment for
insomnia, cognitive behavioral treatment for insomnia, cognitive be-
havioural therapy of insomnia, cognitive behaviour therapy of insom-
nia, CBTI, CBT-I, randomized controlled trials, randomized con-
trolled 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 dis-
tussed 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 Jadad 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 re-
porting), blinding, attribution bias, and other source of bias, while the
Jadad 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; Balsbem 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 in-
tervals (CIs) was used for continuous outcomes, while risk ratio
(RR) ± 95% CI was used for dichotomous data. Study heterogeneity
was measured using I², with I² values greater than 50% indicating
significant heterogeneity (Higgins et al., 2003). When significant het-
erogeneity for primary outcome existed, a sensitivity analysis, i.e., one
outlying (SMD > 1.5) study (Edinger and Sampson, 2003) was re-
moved to explain the heterogeneity source. Funnel plots and Egger’s
test (Egger et al., 1997) for primary outcome were conducted to eval-
uate 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 litera-
ture search. As shown in Fig. 1, 9 RCTs with 12 treatment arms were

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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 CBTI group showed significantly less improvement at post-CBTI assessment (n = 826, SMD: 0.32, 95% CI: 0.00 to 0.63, I² = 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, I² = 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, I² = 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 CBTI group at post-CBTI assessment (n = 667, SMD: 0.06, 95% CI: -0.16 to 0.28, I² = 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, I² = 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 CBTI group showed significantly less improvement at post-CBTI assessment (n = 778, SMD: -0.33, 95% CI: -0.56 to -0.09, I² = 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, I² = 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 CBTI group showed significantly less improvement at post-CBTI assessment (n = 740, SMD: -0.27, 95% CI: -0.52 to -0.01, I² = 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, I² = 47%, p = 0.1, Table 2).
<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>References country</th>
<th>Participants</th>
<th>Diagnostic criteria</th>
<th>Design: Setting - Blinding</th>
<th>Intervention Type</th>
<th>Duration (wks)</th>
<th>Type of interventions; Frequency of CBTIs</th>
<th>Follow-up time point</th>
<th>Outcomes (Sleep)</th>
<th>Dropout rate (%)</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alesi, C. (2016)</td>
<td>(Alessi et al., 2016) US 159 96.9 72.2 ICSD-2 -community dwelling veterans -double blind</td>
<td>CBTI 6</td>
<td>CBTI (106) vs. sleep education (53)</td>
<td>5 sessions during 6 weeks (60 min per session) NR</td>
<td>Sleep diary; actigraphy (SE); scales (PSQI, ISI) 9/106</td>
<td>5</td>
<td></td>
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<tr>
<td>Blom, K. (2016)</td>
<td>(Blom et al., 2016) Sweden 148 21.62 48 American Academy of Sleep Medicine criteria</td>
<td>Internet-based CBTI (73) vs credible insomnia treatment (75) Internet-based CBTI</td>
<td>6 weeks individual sessions (30- to 60-min per session)</td>
<td>6 month</td>
<td>Sleep diary; PSG (TST, SE); scales (ISQ) 2/25</td>
<td>5</td>
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<td>Edinger, J. D. (2001)</td>
<td>(Edinger et al., 2001) US 50 56 55.2 DSM-III-R -recruited from ads and face-to-face solicitation -double blind</td>
<td>CBTI 6</td>
<td>CBTI (25) vs muscle relaxation training (25)</td>
<td>6 month</td>
<td>Sleep diary; PSG (TST, SE); scales (ISQ) 5/73</td>
<td>4</td>
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<td>Edinger, J. D. (2003)</td>
<td>(Edinger and Sampson, 2003) US 20 90 51 DSM-IV -Outpatient -participant blind</td>
<td>ACBT 2</td>
<td>ACBT (10) sleep hygiene suggestions (10)</td>
<td>3 month</td>
<td>Sleep diary; scales (SIS, ISQ, DBAS) 0/10</td>
<td>3</td>
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<tr>
<td>Edinger, J. D. (2009)</td>
<td>(Edinger et al., 2009) US 81 86.4 54.2 DSM-IV, SCID, ICSD -Outpatient -participant blind</td>
<td>CBTI 8</td>
<td>CBTI (41) vs sleep hygiene education (40)</td>
<td>6 month</td>
<td>Sleep diary; PSG (TST, SL, WASO, SE); scales (PSQI, DBAS) 5/41</td>
<td>4</td>
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<td>Hagatun, S. (2017)</td>
<td>(Hagatun et al., 2017) Norway 181 33 44.9 DSM-IV -community (recruited by ads)</td>
<td>SHUTi 9</td>
<td>CBTI (95) vs online sleep education (86)</td>
<td>6 month</td>
<td>Sleep diary; Scales (ISI, DBAS, BIS) 18/95, sleep diary 27/95; questionnaire 4</td>
<td>4</td>
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<tr>
<td>Harvey, A. G. (2014)</td>
<td>(Harvey et al., 2014) US &amp; Canada 188 37.8 47.4 ICSD, DSM-IV -recruited via ads &amp; referrals-technicians blind</td>
<td>CBTI 8</td>
<td>1. CBTI (60) vs cognitive therapy (65) 2. CBTI (60)</td>
<td>6 month</td>
<td>Sleep diary; PSG (TST, SL, WASO, SE); scales (ISI) 1/60</td>
<td>4</td>
<td></td>
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<tr>
<td>Irwin, M. R. (2014)</td>
<td>(Irwin et al., 2014) US 123 71.5 65.55 DSM-IV TR &amp; ICSD-2 -Outpatient -assessor blind</td>
<td>CBTI 16</td>
<td>1. CBTI (50) vs Tai Chi Chih (48) 2. CBTI (50) vs Sleep Seminar (25)</td>
<td>4-month weekly group session (120 min per week)</td>
<td>Sleep diary; PSG (TST, SL, WASO, SE); scales (PSQI, AIS) 2/50</td>
<td>4</td>
<td></td>
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<tr>
<td>Wu, R. G. (2006)</td>
<td>(Wu et al., 2006) China 39 / / KSD, DSM IV -recruited through ads and letter to physicians -double blind</td>
<td>CBTI 8</td>
<td>CBTI (19) vs PTC (20)</td>
<td>8 month</td>
<td>Sleep diary; PSG (TST, SL, SE) 0/19</td>
<td>4</td>
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</tbody>
</table>

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.

* 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.
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, I² = 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, I² = 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, I² = 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, 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, I² = 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, I² = 66%, p = 0.1, Table 2).

3.8.3. Insomnia Symptom Questionnaire (ISQ)

Three RCTs with 4 CBTI arms reported data on insomnia assessed by the ISQ at post-CBTIs assessment. Compared with active control group, the CBTIs group showed significantly less improvement at post-assessment (n = 139; SMD: -0.46, 95% CI: -0.95, 0.02, p = 0.06, Table 2). Three studies with 4 CBTI arms reported additional follow-up assessments, and no group difference was found (n = 86; SMD: -0.75, 95% CI: -1.76, 0.26, p = 0.15, Table 2).

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

Three RCTs with 4 CBTI arms reported data on insomnia assessed by the DBAS at post-CBTIs assessment. Compared with active control group, the CBTIs group showed significantly less improvement at post-assessment (n = 270; SMD: -0.76, 95% CI: -1.25, -0.27, p = 0.002, Table 2). Three studies with 4 CBTI arms reported additional follow-up assessments, and no group difference was found (n = 86; SMD: -0.90, 95% CI: -2.07, 0.27, p = 0.13, Table 2).

3.8.5. Athens Insomnia Scale (AIS)

Two RCTs with 2 CBTI arms reported data on insomnia assessed by the AIS at post-CBTIs assessment. Compared with active control group, the CBTIs group showed significantly less improvement at post-assessment (n = 123; SMD: -0.50, 95% CI: -0.89, -0.11, p = 0.01, Table 2). Three studies with 4 CBTI arms reported additional follow-up assessments, and no group difference was found (n = 123; SMD: -0.66, 95% CI: -1.07, -0.24, p = 0.002, Table 2).

Discontinuation due to any reason

In Hagatun et al’s study, rate of discontinuation regarding sleep diary were extracted and analyzed.

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Arms (subjects)</th>
<th>SMD or RR (95%CI)</th>
<th>I² (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time at endpoint after CBTI (min)</td>
<td>10 (667)</td>
<td>0.06 [-0.16, 0.28]</td>
<td>42</td>
<td>0.60</td>
</tr>
<tr>
<td>Total sleep time at additional follow-up (min)</td>
<td>4 (122)</td>
<td>0.24 [-0.30, 0.78]</td>
<td>54</td>
<td>0.38</td>
</tr>
<tr>
<td>Sleep efficiency at endpoint after CBTI (%)</td>
<td>11 (826)</td>
<td>0.32 [0.00, 0.63]</td>
<td>76</td>
<td>0.05</td>
</tr>
<tr>
<td>Sleep efficiency at additional follow-up (%)</td>
<td>5 (369)</td>
<td>0.26 [-0.19, 0.70]</td>
<td>61</td>
<td>0.25</td>
</tr>
<tr>
<td>Sleep latency at endpoint after CBTI (min)</td>
<td>10 (778)</td>
<td>-0.33 [-0.56, -0.09]</td>
<td>56</td>
<td>0.007</td>
</tr>
<tr>
<td>Sleep latency at additional follow-up (min)</td>
<td>5 (281)</td>
<td>-0.29 [-0.62, 0.04]</td>
<td>32</td>
<td>0.08</td>
</tr>
<tr>
<td>Wake after sleep onset at endpoint after CBTI (min)</td>
<td>9 (740)</td>
<td>-0.27 [-0.52, -0.01]</td>
<td>60</td>
<td>0.04</td>
</tr>
<tr>
<td>Wake after sleep onset at additional follow-up (min)</td>
<td>4 (245)</td>
<td>-0.36 [-0.79, 0.07]</td>
<td>47</td>
<td>0.10</td>
</tr>
<tr>
<td>Time in bed at endpoint after CBTI (min)</td>
<td>3 (369)</td>
<td>-0.40 [-0.87, 0.06]</td>
<td>77</td>
<td>0.09</td>
</tr>
<tr>
<td>PSQI total score at endpoint after CBTI</td>
<td>5 (351)</td>
<td>-0.52 [-0.86, -0.19]</td>
<td>50</td>
<td>0.002</td>
</tr>
<tr>
<td>PSQI total score at additional follow-up</td>
<td>5 (348)</td>
<td>-0.34 [-0.76, 0.07]</td>
<td>66</td>
<td>0.10</td>
</tr>
<tr>
<td>ISI total score at endpoint after CBTI</td>
<td>5 (676)</td>
<td>-0.68 [-1.01, -0.36]</td>
<td>75</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ISI total score at additional follow-up</td>
<td>4 (495)</td>
<td>-0.27 [-0.45, -0.08]</td>
<td>0</td>
<td>0.005</td>
</tr>
<tr>
<td>ISIQ total score at endpoint after CBTI</td>
<td>4 (139)</td>
<td>-0.46 [-0.95, 0.02]</td>
<td>46</td>
<td>0.06</td>
</tr>
<tr>
<td>ISIQ total score at additional follow-up</td>
<td>3 (86)</td>
<td>-0.75 [-1.76, 0.26]</td>
<td>79</td>
<td>0.15</td>
</tr>
<tr>
<td>DBAS total score at endpoint after CBTI</td>
<td>4 (270)</td>
<td>-0.76 [-1.25, -0.27]</td>
<td>60</td>
<td>0.002</td>
</tr>
<tr>
<td>DBAS total score at additional follow-up</td>
<td>3 (86)</td>
<td>-0.90 [-2.07, 0.27]</td>
<td>83</td>
<td>0.13</td>
</tr>
<tr>
<td>AIS total score at endpoint after CBTI</td>
<td>2 (123)</td>
<td>-0.66 [-1.07, -0.24]</td>
<td>18</td>
<td>0.002</td>
</tr>
<tr>
<td>AIS total score at additional follow-up</td>
<td>2 (123)</td>
<td>-0.50 [-0.89, -0.11]</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>Discontinuation due to any reason</td>
<td>12 (1099)</td>
<td>0.62 [0.42, 0.92]</td>
<td>6</td>
<td>0.02</td>
</tr>
</tbody>
</table>

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

* In Hagatun et al’s study, rate of discontinuation regarding sleep diary were extracted and analyzed.
Table 3
GRADE analyses.

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

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 a more 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-CBTI assessment. No significant difference was found between active control group and CBTI group at post-CBTI assessment (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-CBTI assessment. Compared with control groups, CBTI group showed significantly less improvement at post-CBTI assessment (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: -0.76, 95% CI: -0.98 to 0.02, I\(^2\) = 0%, p = 0.005, Table 2).

3.8.5. Athens Insomnia Scale (AIS)
One study 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-CBTI assessment (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: -0.59, 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 CBTI 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 CBTI group showed significantly less improvement in insomnia at post-CBTI 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 CBTI 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) revealed that CBTI was more effective than control interventions in treating insomnia, with moderate to large effect sizes reported. This current meta-analysis further confirms the efficacy of CBTI in treating insomnia, with a significant improvement in all outcomes assessed.

Future research should focus on investigating the long-term effects of CBTI, as well as exploring the mechanisms underlying its therapeutic effects. Further research is also needed to identify predictors of response to CBTI, which could help in tailoring treatment to individual needs.
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 additional side effects of sleeping pills (Koffel et al., 2015; Kuppili et al., 2019). Apart from sleeping pills, it is helpful to incorporate psychosocial interventions, 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.ajip.2019.10.008.

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