Sleep Medicine Reviews 63 (2022) 101615

Contents lists available at ScienceDirect

Sleep Medicine Reviews

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

CLINICAL REVIEW

Systematic review and meta-analysis of cognitive-behavioural therapy for insomnia on subjective and actigraphy-measured sleep and comorbid symptoms in cancer survivors

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ARTICLE INFO

Article history:
Received 9 November 2021
Received in revised form
15 January 2022
Accepted 16 February 2022
Available online 25 February 2022

Keywords:
Cancer
Cognitive-behavioural therapy for insomnia
Insomnia
Meta-analysis

SUMMARY

This systematic review and meta-analysis assessed the efficacy of cognitive-behavioural therapy for insomnia (CBT-I) among cancer survivors and explored its effect on comorbid symptoms. Studies were included if they assessed the efficacy of CBT-I in adults diagnosed with cancer published prior to August 2020. The primary outcome was insomnia severity. The protocol was pre-registered on PROSPERO (CRD42020169986). Twenty-two studies met eligibility criteria. CBT-I significantly improved insomnia severity ($g = 0.78$) with durable benefits at 3- and 6-month follow-up. CBT-I produced significant small to large effects for diary-measured sleep efficiency, wake after sleep onset, total sleep time, sleep onset latency, sleep quality, anxiety, depression, fatigue, and overall quality of life. Subgroup analyses revealed no significant difference between in-person and self-help CBT-I. Overall, CBT-I is a robustly efficacious and durable treatment for insomnia among cancer survivors and can produce concomitant benefits on other symptoms. Implementation efforts are needed to ensure that people with cancer have access to CBT-I as the recommended first-line treatment for insomnia.

Insomnia in cancer survivors

Insomnia is 2–3 times more common in cancer survivors than the general population [1] and has the potential to occur before cancer treatment begins and persist into survivorship despite improvements in other domains [2]. Insomnia in cancer does not appear to be solely associated with one particular cancer type or treatment, although certain cancers and treatments have higher prevalence rates (e.g., breast cancer [3] and chemotherapy [4]). Further, insomnia is present in cancer even after the cancer has been successfully treated and other side effects have been resolved [2]. The consequences of insomnia among cancer survivors can be extensive with greater severity associated with: increased risk of developing infections [5,6]; worsening cognitive impairments and mood disturbances [7,8]; increased severity of physical symptoms; impaired daily functioning; and reduced quality of life [9,10]. Some cancer survivors have reported being more overwhelmed by insomnia and resulting sequelae than from cancer treatment itself [7].

Cognitive-behavioural therapy for insomnia (CBT-I)

Cognitive-behavioural therapy for insomnia (CBT-I) is the recommended first-line treatment for insomnia in the general population [11] and those diagnosed with cancer [12,13] with evidence that it can be delivered effectively via the internet [14,15], videos [16], telemedicine [17], self-help manuals [18], and in groups [19]. CBT-I also reduces other cancer-related symptoms including depression [20], fatigue [21–23], and perceived cognitive impairment [24], while increasing quality of life [25]. The evidence that CBT-I improves sleep and co-occurring conditions makes it a potent cancer survivorship intervention.

Importance of the present review

The present meta-analysis reflects an extension of the one conducted by Johnson and colleagues [13], incorporating all

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https://doi.org/10.1016/j.smrv.2022.101615
1087-0792/

Abbreviations

BPT	behavioural placebo treatment
CBT-I	cognitive-behavioural therapy for insomnia
iCBT-I	internet cognitive-behavioural therapy for insomnia
CMA	comprehensive meta-analysis
ISI	insomnia severity index
M	mean
MBSR	mindfulness-based stress reduction
MBT	mindfulness-based therapy
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PI	prediction interval
PSQI	Pittsburgh sleep quality index
RCT	randomized controlled trial
SD	standard deviation
SE	sleep efficiency
SOL	sleep onset latency
TST	total sleep time
WASO	wake after sleep onset
95% CI	95% confidence interval
95% PI	95% prediction interval

randomized-controlled trials (RCTs) published since that time. Further, the primary outcome of the previous review was sleep efficiency (SE) and not insomnia severity. Assessing insomnia severity captures issues that are directly related to diagnostic criteria for insomnia disorder, such as difficulty falling or staying asleep, dissatisfaction with sleep quality, and impairment in different areas of functioning [26]. Assessing additional trials will let us answer clinically relevant questions regarding the impact of CBT-I on comorbid symptoms like poor sleep quality, fatigue, anxiety, depression, poor quality of life, and pain severity, and whether treatment modality (e.g., in-person, self-help) influences treatment effect.

Objective

The primary objective of our review is to quantify the efficacy and durability of CBT-I compared to other treatments for improving insomnia severity and comorbid symptoms in cancer survivors. Our secondary aims were to quantify the efficacy and durability of CBT-I on these outcomes by treatment modality (face-to-face vs. not) and comparison group (active vs. not).

Methods

Protocol and registration

The protocol for this review was pre-registered on PROSPERO (CRD42020169986) and adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [27].

Eligibility criteria

Study design and participants

Only RCTs were eligible due to their high internal validity and ability to determine causality. Studies were eligible if they enrolled adults (18 years or older) who had been diagnosed with any type or stage of cancer, and presented with clinically-relevant insomnia based on a valid assessment measure (e.g., the insomnia severity index [ISI] [28]).

Interventions and comparisons

Eligible studies assessed the efficacy of CBT-I. To be considered CBT-I, the intervention had to have included sleep restriction, stimulus control, and cognitive restructuring components. We compared CBT-I to any other active (e.g., pharmacotherapy, other psychotherapies, mindfulness-based therapies, exercise, usual care) or non-active treatment (e.g., wait-list, placebo). Studies were excluded if they included other CBT/CBT-I treatments as their only comparison/control intervention.

Outcomes

Eligible studies included at least one empirically validated measure of insomnia severity. Secondary outcomes included sleep diary- and wrist actigraphy-measured sleep parameters [i.e., sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE), and total sleep time (TST)], subjective sleep quality, fatigue, depression and anxiety symptoms, overall quality of life, and pain severity.

Search methods

We searched *PubMed*, *EMBase*, *PsycINFO*, and clinicaltrials.gov and the World Health Organization's (WHO) international clinical trials registry platform via the Cochrane central register of randomized controlled trials (CENTRAL) database for articles published in English up to and including August 2020. *ProQuest* was searched for grey literature. We also scanned the references of each study that met inclusion criteria. The search strategy used for *PubMed* was:

((“Cognitive Therapy” [Mesh]) OR (cognitive or behavio* or therapy)) AND ((“Sleep Initiation and Maintenance Disorders” [Mesh]) OR (insomnia or sleep or sleep disturbance [Title/Abstract])) AND ((“Neoplasms” [Mesh]) OR (cancer or carcinoma or neoplasm*[Title/Abstract])). The *PubMed* RCT filter was then applied to the search results.

Data collection and analysis

Study selection

Two reviewers independently screened titles and abstracts of the studies exported to Rayyan [29]. Following independent screenings, the reviewers met to discuss their selections to ensure concordance. Any discrepancies were resolved by the senior author. Those that met inclusion criteria proceeded to full-text review. The same process was used to perform the quality assessment for included studies.

Data extraction

Reviewers extracted: sample characteristics; intervention characteristics; comparison treatment characteristics; outcomes; and data pertaining to means and standard deviations (SDs) of outcomes of interest at pre- and post-treatment and follow-up. Study authors were contacted when data were missing. One article and its corresponding secondary analysis utilized a three-arm design (in-person CBT-I vs. video-based CBT-I vs. control) [23,30]. The CBT-I interventions were compared to the same control group, violating the assumption of independence. Excluding this effect did not impact the overall effect size for the primary outcome.

Risk of bias assessment and quality assessment

Risk of bias and quality assessments were performed [31]. The overall score ranged from 0 to 35 and consists of a treatment quality subscale ranging from 0 to 9, and a quality of study design and methods subscale ranging from 0 to 26 [31]. Small sample effects (often thought to be indicative of publication bias [32]) were assessed using funnel plots and Begg's test [33].

Summary measures

All analyses were conducted using comprehensive meta-analysis (CMA) software. CBT-I was compared to control interventions using Hedges' *g* [34], which was calculated using raw means and SDs for pre- and post-treatment scores. In cases where standard error (SE) values or 95% confidence intervals (CIs) were reported instead of SDs, the following calculations were used to calculate SD: $SD = SE^* \sqrt{N}$ when given SE, and $SD = \sqrt{N}^*$[(upper limit − lower limit)/(2*$t_{critical}$)] when given 95% CIs. Study authors were contacted when SDs were otherwise unobtainable.

Assessment of heterogeneity

Heterogeneity was assessed using I^2 and prediction intervals. I^2 represents the proportion of overall variability attributable to variation in the magnitude of the "true" effect between studies (as opposed to sampling error). Although often criticized [35], I^2 and its 95% CIs [36] were calculated to guide the application of our meta-regression analyses. Prediction intervals (PIs) are also reported to characterize variation in between-study variation more directly, and reflect the range of effects expected if one decided to conduct a new, well-powered study with methods similar to those included in the model [35].

Additional analyses

Subgroup analyses were planned a priori to assess the potential effects of control group (active vs. non-active) and CBT-I treatment modality (in-person vs. self-help CBT-I). Meta-regressions were also performed for outcomes with $I^2 > 50\%$ with planned moderators of mean participant age, participant sex, and overall treatment quality score.

Estimation of practical significance

Estimating practical significance is important due to the arbitrary nature of null hypothesis statistical testing. Practical significance was estimated by: 1) comparing pooled effect sizes to the approximate benchmark of $g = 0.42$ provided by Ferguson [37]; and 2) calculating mean differences from pre-to post-treatment and post-treatment to follow-up to assess the size of the outcomes of interest. These values were compared to values reported in the literature that are indicative of clinically-significant change.

Results

Study identification

Searches returned 606 unique citations. As shown in Fig. 1, 48 articles underwent full-text review, with 22 fulfilling inclusion criteria, including the nine articles analyzed by Johnson and colleagues [13,19,21,23,38–43]. Fifteen articles were original reports with those remaining reporting on secondary analyses. Articles that utilized the same dataset were represented by their parent article if they provide no new information.

Study characteristics

Table 1 outlines the study characteristics. In total, 1461 participants were included, with samples ranging from 21 to 255. Seven studies exclusively assessed women with breast cancer [15,23,38,40,42,44,45], while those remaining assessed men and women diagnosed with various cancers [19,21,41,46–50]. Of the 15 original reports, seven used individual in-person CBT-I [21,38,40,42,45,48,50]; three used internet-delivered CBT-I (iCBT-I) [15,41,46]; two used self-help CBT-I [47,49]; two used group CBT-I [19,44]; and one used both individual in-person and video-based CBT-I [23]. The duration of CBT-I ranged from 6 to 12 weeks, generally with one 30–120 min session per week. CBT-I interventions were compared to active and non-active treatments: three were compared to treatment-as-usual (TAU) [21,46,47], four to a wait-list control [15,39,41,42], two to no treatment [23,50], one to sleep education [38], one to acupuncture [48], one to mindfulness-based stress reduction (MBSR) [19], one to Tai Chi Chih (TCC) [44], one to a behavioural placebo treatment (BPT) [40], and one to an at-home aerobic exercise program [49]. One of the included studies and three out of four of its secondary analyses originally presented with four groups: CBT-I with armodafinil, CBT-I with a placebo, armodafinil alone, and a placebo alone [22,25,50,51]. These groups were aggregated into CBT-I or no CBT-I because armodafinil (alone and with CBT-I) did not significantly impact any of the outcomes assessed. Eleven of the included primary studies performed a follow-up assessment [15,19,21,30,40,42,44,47–50]: one 15-weeks (which was included as 3-months follow-up for the purposes of data analysis) [15], seven 3-months [15,30,40,42,47,49,50], two 5-months (included as 6-months follow-up for the purposed of data analysis) [19,48], and seven 6-months [21,30,40,42,44,47,49]. Only one trial assessed pain severity as an outcome [48], precluding the use of meta-analysis.

Risk of bias assessment and quality assessment

Quality assessment of the included 15 primary studies are presented in Table S1. Scores ranged from 22 to 34 (out of a possible 35) with a mean of 27.93 (*SD* = 3.60). The means and SDs obtained in the validity testing of the Yates scale are: 'excellent' = 22.7 (*SD* = 1.95); 'average' = 18.71 (*SD* = 2.25); 'poor' = 12.10 (*SD* = 3.17) [31]. Therefore, the average overall quality score of included studies would be considered excellent. Based on these scores, none of the included studies were of poor quality.

Publication bias

For the primary outcome of insomnia severity, Begg's test for asymmetry was not statistically significant, Kendall's tau = 0.029, $p = .441$. While visual inspections of funnel plots for certain secondary outcomes (i.e., objective sleep outcomes, subjective sleep quality, depression symptoms, overall quality of life) indicated varying degrees of asymmetry, Begg's test was only statistically significant for actigraphy-measured SOL, Kendall's tau = −0.733, $p = .019$. All other secondary outcome p-values for Begg's test ranged from 0.070 to 0.480.

Meta-analysis

Primary outcome. CBT-I resulted in significant improvements in insomnia severity, corresponding to a 7.81-point reduction in mean (ISI) score, with a large effect size when pooled across studies (Table 2 and Fig. 2), $g = 0.78$ [95% CI: 0.57, 0.98]. However, this effect was characterized by substantial heterogeneity.

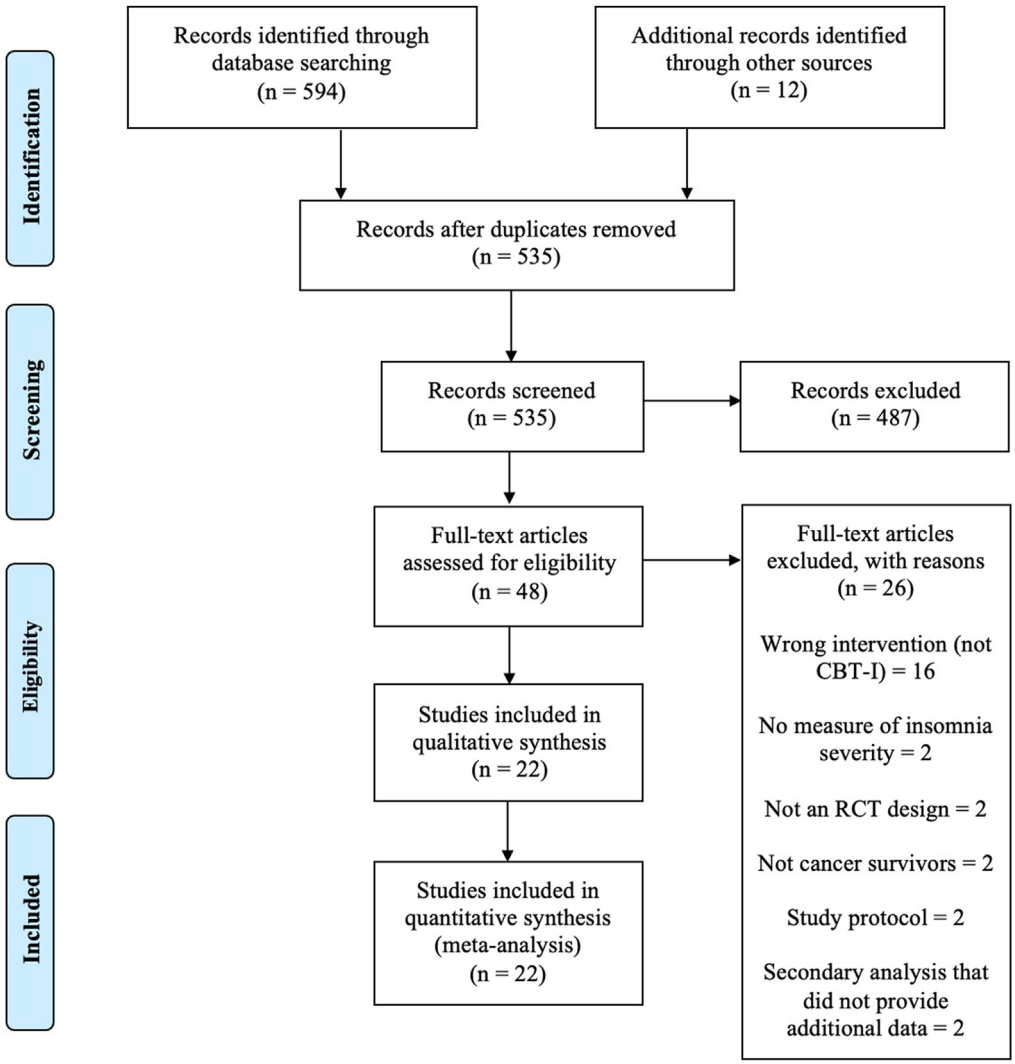

Fig. 1. PRISMA flow diagram of studies included and excluded at each stage of systematic review

Secondary sleep and symptom outcomes. Table 2 presents the treatment effects on secondary sleep outcomes. CBT-I resulted in large effects for sleep quality ($g = 0.70$) corresponding to a 4.62-point reduction in mean Pittsburgh sleep quality index (PSQI) score. As measured by sleep diaries, CBT-I resulted in small to large effects corresponding to a 20.58-min reduction in SOL ($g = 0.65$), a 26.24-min reduction in WASO ($g = 0.60$), a 30.12-min increase in TST ($g = 0.21$), and a 12.32% increase in SE ($g = 0.71$). As measured by actigraphy, CBT-I resulted in small-to-medium effects corresponding to a 3.40-min reduction in SOL ($g = 0.29$), a 10.61-min reduction in WASO ($g = 0.21$), and a 23.29-min reduction in TST ($g = 0.30$). CBT-I did not result in statistically significant improvements in actigraphy-measured SE from pre-to post-treatment. CBT-I resulted in small but significant improvements in fatigue ($g = 0.35$), depression ($g = 0.31$), anxiety ($g = 0.28$), and quality of life ($g = 0.31$).

Durability of treatment effects. Tables 3 and 4 present the durability of treatment effects on insomnia severity, sleep, and secondary outcomes at 3- and 6-month follow up. Improvements in insomnia severity remained significant, with small-to-medium effect sizes (3-month: $g = 0.42$; 6-month: $g = 0.33$). Improvements in sleep quality did not remain statistically significant at 3-months, but significant small effects were observed at 6-months ($g = 0.28$). Reductions in diary-measured SOL remained significant with small pooled effect sizes at 3 ($g = 0.31$) and 6 ($g = 0.29$) months. Similar effects were observed for reductions in diary-measured WASO (3-month: $g = 0.38$; 6-month: $g = 0.38$), improvements in TST (3-month: $g = 0.26$; 6-month: $g = 0.18$), and improvements in SE (3-month: $g = 0.43$; 6-month: $g = 0.38$). A meta-analysis could not be conducted for actigraphy-measured SOL, WASO, TST, and SE at 3-months follow-up because one study reported results at this time point. Only reductions in actigraphy-measured SOL were maintained at 6-months follow-up with a small effect size, $g = 0.25$, with non-significant effects observed for WASO ($g = 0.11$), TST ($g = 0.15$), and SE ($g = 0.12$). Small but statistically significant improvements from pre-treatment to post-treatment were observed for fatigue ($g = 0.16$) and quality of life ($g = 0.20$) at 3-months but not 6-months ($g = 0.11$ and $g = 0.16$, respectively), whereas significant effects on depression ($g = 0.17$) and quality of life ($g = 0.20$) were observed only at 6-months. Significant effects were not observed for anxiety at 3- and 6-months follow-up.

Subgroup analyses. Type of Control Treatment. Table S2 presents the results of subgroup analyses comparing studies using active and non-active control treatments. Studies that utilized wait-list

Table 1
Characteristics of included studies.

First author (Date)	Country	Sample characteristics	Allocation	Screening tool	Treatment components	Length/number of sessions	Follow-up	Outcome measures
Agyemang (2016) [46]	U.S.A.	Men & women, any diagnosis, stage 0-III	iCBT-I = 16 TAU = 15	DSM-IV	SR, SC, SH, CR	One Core/week for 6 wks; 45–60 min to complete	N/A	ISI, sleep diary, PHQ-9, GAD-7, FACT-G
Casault et al. (2015) [47]	Canada	Men & women, any diagnosis, stage 0-III	mCBT-I = 20 No treatment = 18	IIS and ISI	SC, SR, CR, SH	One 10–15 page booklet/wk for 6 wks; 1 phone consult every 2 wks for max 30 min	3- & 6-mo	ISI, sleep diary, HADS, MFI, EROTC-QOL, DBAS-Brief, SBQ
[a]Epstein & Dirksen (2007) [38]	U.S.A.	Women stage I-III BCa	CBT-I = 40 Sleep education = 41	Sleep diaries	SC, SR, SH	6 sessions, 1/wk: session 1 = 2 h; session 2–4 = ~1 h; sessions 5–6 15–30 min phone consults	N/A	Sleep diary, actigraphy
[a,b]Dirksen & Epstein (2007) [43]								ISI, POMS/F, STAI-S, STAI-T, CESD, FACT-B
[a]Espie et al. (2008) [21]	U.K.	Men & women, any diagnosis, stage 0-III	CBT-I = 100 TAU = 50	PSQI	SC, SR, CR	5 sessions: 50 min/wk for 5 wks	6-mo	PSQI, ESS, HADS, FSI, FACT-G, sleep diary, actigraphy
[a]Fiorentino (2008) [45]	U.S.A	Women who were BCa survivors	CBT-I = 11 WLC = 10	DSM-IV	SC, SR, SH, CR	6 sessions: 1 h/wk for 6 wks	N/A	Actigraphy, ISI, PSQI, sleep diary, MOS-SF 36, FOSQ, CESD, BSI, MFSI-SF, GCS
[a,c]Fiorentino et al. (2010) [39]								Actigraphy, ISI, PSQI, sleep diary
[a]Garland et al. (2014) [19]	Canada	Men & women, any diagnosis, stage 0-III	Group CBT-I = 47 MBCR = 64	DSM-IV	SC, SR, CR, RT	8 sessions: 90 min/wk for 8 wks	5-mo	ISI, PSQI, CSSI, POMS-SF, DBAS, sleep diary, actigraphy
Garland et al. (2019) [48]	U.S.A.	Men & women, any stage or diagnosis	CBT-I = 80 Acupuncture = 80	ISI and DSM-V	SR, SC, CR, RT, SH	7 sessions for 8 wks: session 1 = 1 h; sessions 2–5 = 30 min/wk; sessions 6 and 7 = 30 min/biweekly	5-mo	ISI, PSQI, sleep diary, BPI, MFSI-SF, HADS, PROMIS-Global
Irwin et al. (2017) [44]	U.S.A.	Women, BCa	Group CBT-I = 45 Tai Chi Chih = 45	DSM-IV-TR, ICD	CR, SC, SR, SH, RT	8 sessions: 2 h/wk for 8 wks; followed by 4 wks of skill consolidation	6- & 15-mo	PSQI, AISI, sleep diary, MFI, ESS, IDSC
[a]Matthews et al. (2014) [40]	U.S.A.	Women finished treatment for stage I-III BCa	CBT-I = 32 BPT = 28	IIS	SR, SC, CR	6 sessions, 1/wk: sessions 1–3 and 6 in-person, 30–45 min; sessions 4 and 5 over phone 15–20 min	3- & 6-mo	ISI, EORTC-QLQ-C30, AFI, PFS, HADS, DBAS-16, PKT, sleep diary
Mercier et al. (2018) [49]	Canada	Men & women, any diagnosis, stage 0-III	Self-help CBT-I = 21 Aerobic exercise = 20	ISI	SC, SR, CR, SH	1 video segment (5–20 min each) and 1 booklet/wk for 6 wks	3- & 6-mo	ISI, PSQI, sleep diary, EX diary, GLTEQ
[a]Ritterband et al. (2012) [41]	U.S.A.	Men & women, any stage or diagnosis	SHUTi = 14 WLC = 14	DSM-IV-TR	SR, SC, SH, CR	6 Cores: 45–60 min each, available for 9 wks	N/A	ISI, sleep diary, MFSI-SF, HADS, SF-12
Roscoe et al. (2015) [50]	U.S.A.	Men & women, finished treatment for any cancer at any stage or diagnosis	CBT-I = 47 no CBT-I = 49	DSM-IV	SC, SR, CR, SH	7 sessions: 1, 2, & 4 in-person (30–60 min); 3, 5, & 6 by phone (15–30 min)	3-mo	ISI, PSQI
[d]Garland et al. (2016) [51]								Sleep diary
[d]Heckler et al. (2016) [22]								BFI, FACIT-F
[d]Peoples et al. (2017) [25]								FACT-G
[d]Peoples et al. (2019) [20]								PHQ-9
[a]Savard et al. (2005) [42]	Canada	Women finished treatment for stage I-III BCa	CBT-I = 28 WLC = 30	ICSD, DSM-IV	SC, SR, CR, SH	8 sessions: 90 min/wk for 8 wks	3-, 6-, & 12-mo	IIS, sleep diary, PSG, ISI, HADS, MFI, EORTC QLQ-C30
[a]Savard et al. (2014) [23]	Canada	Women, stage 0-III BCa	PCBT-I = 81 VCBT-I = 80 no CBT-I = 80	ISI	SC, SR, CR, SH	PCBT-I: 6 sessions, 50 min/wk for 6 wks VCBT-I: 1 video (5–20 min) & 1 booklet/wk for 6 wks	N/A	ISI, sleep diary, IIS, MFI, HADS, EORTC QLQ-C30, DBAS, actigraphy
[e]Savard et al. (2016) [30]							3-, 6-, & 12-mo	
Zachariae et al. (2018) [15]	Denmark	Women, stage 0-III BCa	iCBT-I = 133 WLC = 122	PSQI	SR, SC, CR, SH	6 Cores: 45–60 min each, available for 9 wks	15 wk	ISI, PSQI, sleep diary, FACIT-F

Abbreviations. AFI = attentional function index; AISI = Athens insomnia scale; BFI = brief fatigue inventory; BPI = brief pain inventory; BPT = behavioral placebo treatment; BSI = brief symptom inventory; CBT-I = cognitive-behavioural therapy for insomnia; iCBT-I = internet cognitive-behavioural therapy for insomnia; CES-D = Center for Epidemiologic Studies–depression scale; CR = cognitive restructuring; CSSI = Calgary symptoms of stress inventory; DBAS-Brief = dysfunctional beliefs and attitudes about sleep scale – brief; DSM-IV = diagnostic and statistical manual of mental disorders 4th edition; DSM-V = diagnostic and statistical manual of mental disorders 5th edition; EORTC-QOL = European Organization for Research and Treatment of Cancer quality of life; ESS = Epworth sleepiness scale; EX diary = exercise diary; FSI = fatigue symptom inventory; FACT-B = functional

assessment of cancer therapy-breast; FACT-G = functional assessment of cancer therapy-general; FACIT-F = functional assessment of chronic illness therapy-fatigue; FOSQ = functional outcomes of sleep questionnaire; FSI = fatigue symptom inventory; GCS = Greene climacteric scale; GLTEQ = Godin leisure-time exercise; ICSD = International Classification of Sleep Disorders; IDSC = inventory for depressive symptomology – clinician; IIS = insomnia interview schedule; ISI = insomnia severity index; MBCR = mindfulness-based cancer recovery; MFI = multidimensional fatigue inventory; MFSI-SF = multidimensional fatigue symptom inventory – short form; PFS = Piper fatigue scale; PHQ-9 = patient health questionnaire; PKT = patient knowledge test; POMS-SF = profile of mood states – short form; PROMIS-Global = patient-reported outcomes measurement information system; PSG = polysomnography; RT = relaxation training; SC = stimulus control; SF-12 = medical outcomes study short form 12 health survey; SF-36 = medical outcomes study short form 36 health survey; SH = sleep hygiene; SR = sleep restriction; STAI = state-trait anxiety inventory.

[a] Denotes articles included in the previous systematic review and meta-analysis by Johnson and colleagues [13].

[b] Denotes articles that are secondary studies of Epstein and Dirksen [38].

[c] Denotes articles that are secondary studies of Fiorentino [45].

[d] Denotes articles that are secondary studies of Roscoe and colleagues [50].

[e] Denotes articles that are secondary studies of Savard and colleagues [23].

controls or no treatment were coded as 'non-active', and those that utilized non-CBT-I treatments (e.g., acupuncture [48], Tai Chi Chih [44], BPT [40], TAU) were coded as 'active'. The effect of CBT-I on insomnia severity was significantly greater for studies that utilized non-active control treatments, $Q = 7.96$, $p = .005$. While all but actigraphy-measured WASO and SE remained statistically significant with a wide range of effect sizes (0.21–1.02), the difference between studies that utilized active and non-active controls was not statistically significant for any of the secondary outcomes.

Mode of CBT-I Intervention. Table S3 presents the results of subgroup analyses comparing studies that used in-person vs. self-help CBT-I. Trials that utilized CBT-I interventions involving in-person contact with a therapist were categorized as 'in-person', and those that utilized CBT-I interventions that were conducted independently by participants (e.g., web-based programs, booklets, etc.) were categorized as 'self-help'. Sleep diary-measured SOL was the only outcome that presented a statistically significant difference, with in-person CBT-I producing a larger effect ($g = 0.80$), than those using self-help CBT-I ($g = 0.37$).

Meta-regression. Due to significant heterogeneity for insomnia severity, and diary-measured SOL and WASO, meta-regressions were conducted. There was significant evidence of heterogeneity for sleep quality, however a meta-regression was not conducted because there were less than 10 comparisons [52]. The following were assessed as potential moderators: mean participant age; percentage of male participants; and total quality assessment score (assessed using the total Yates quality assessment score for each study). A summary of moderator analyses is displayed in Table S4. Studies with a higher mean participant age reported lower effect sizes for insomnia severity and SOL, but not WASO. Studies with a greater proportion of male participants reported greater effect sizes in SOL, but not insomnia severity or WASO. Higher-quality studies reported lower effect sizes for insomnia severity but not SOL or WASO.

Discussion

Our results demonstrate the robust efficacy of CBT-I among cancer survivors. The effect size observed for insomnia severity was $g = 0.78$, which is comparable to the effect size of $d = 0.78$ reported by Johnson and colleagues [13]. CBT-I also significantly improved sleep quality post treatment; however, the durability of this effect was inconsistent. This may be because sleep quality (as measured by the PSQI) encompasses aspects other than insomnia symptoms which can vary naturally (e.g., feel too hot/cold, have bad dreams) and be unimpacted by CBT-I. As the only study to comprehensively describe the effect of CBT-I on comorbid symptoms in cancer survivors, we observed that CBT-I contributed to small but statistically significant improvements in fatigue, depression and anxiety symptoms, and quality of life at post-treatment. These findings are of particular importance as many cancer survivors experience comorbid mood disturbances, decreased quality of life, and increased fatigue [9,53,54]. CBT-I was also efficacious for improving insomnia severity at 3- and 6-months follow-up with mean ISI scores remaining below 8. While this finding is promising, it is important to note that our effect size observed at 6-months follow-up ($g = 0.33$) does not meet the benchmark for practical significance outlined by Ferguson ($g = 0.42$) [37]. This discrepancy may be due to fewer studies conducting longer-term follow-up assessments, which may have impacted our pooled effect size at six-months follow-up.

This is also the first study to comprehensively assess sleep diary- and actigraphy-measured sleep in cancer survivors after receiving

Table 2
Between-group meta-analysis statistics from pre-to post-treatment.

Outcomes	Pre	Post	M diff	*k*	ES (*g*)	95% CI	95% PI	Statistical heterogeneity		
	M(SD)	M(SD)						I^2	*Q*	95% CI
[a]Insomnia				15	0.78	0.57, 0.98	0.066, 1.48	64.69%	39.64***	38.70%, 79.66%
CBT-I	16.15 (4.34)	8.34 (4.92)	−7.81							
Control	16.32 (4.57)	12.86 (5.16)	−3.46							
SOL (act)				6	0.29	0.095, 0.49	0.014, 0.57	0%	3.47	0%, 74.35%
CBT-I	15.23 (11.91)	11.83 (13.74)	−3.40							
Control	17.98 (19.49)	15.33 (15.56)	−2.65							
SOL (diary)				15	0.65	0.44, 0.86	−0.11, 1.41	69.90%	46.51***	47.74%, 82.66%
CBT-I	39.73 (29.90)	19.15 (17.80)	−20.58							
Control	39.70 (30.97)	31.75 (25.40)	−7.95							
WASO (act)				7	0.21	0.022, 0.41	−0.039, 0.47	0%	1.78	0%, 70.90%
CBT-I	68.66 (36.22)	58.05 (27.37)	−10.61							
Control	76.52 (34.90)	69.74 (32.58)	−6.78							
WASO (diary)				15	0.60	0.42, 0.78	−0.0077, 1.20	59.32%	34.42**	28.06%, 77.00%
CBT-I	52.23 (34.66)	25.99 (23.09)	−26.24							
Control	54.45 (34.69)	41.45 (30.19)	−13.00							
TST (act)				7	0.30	0.11, 0.50	0.051, 0.56	0%	3.27	0%, 70.90%
CBT-I	423.63 (68.68)	400.34 (67.86)	−23.63							
Control	427.25 (61.04)	426.59 (51.24)	−0.66							
TST (diary)				15	0.21	0.10, 0.32	0.093, 0.33	0%	10.45	0%, 53.66%
CBT-I	382.33 (73.37)	412.45 (61.74)	30.12							
Control	375.27 (72.71)	398.84 (69.93)	23.57							
SE (act)				7	0.18	−0.008, 0.38	−0.068, 0.44	0%	2.03	0%, 70.90%
CBT-I	82.35 (8.36)	84.05 (7.56)	1.70							
Control	81.17 (8.03)	82.53 (7.55)	1.36							
SE (diary)				14	0.71	0.55, 0.86	0.29, 1.12	39.02%	21.32	0%, 67.69%
CBT-I	74.18 (11.79)	86.50 (8.49)	12.32							
Control	73.96 (12.25)	79.10 (11.58)	5.14							
[b]Sleep quality				8	0.70	0.38, 1.03	−0.39, 1.79	77.49%	31.09***	0%, 88.60%
CBT-I	11.51 (2.97)	6.89 (3.05)	−4.62							
Control	11.96 (3.00)	9.72 (3.41)	−2.24							
Fatigue	–	–	–	13	0.35	0.21, 0.50	−0.018, 0.73	33.42%	18.02	0%, 65.64%
Depression	–	–	–	14	0.31	0.20, 0.43	0.18, 0.44	0%	9.82	0%, 55.12%
Anxiety	–	–	–	11	0.28	0.15, 0.41	0.13, 0.42	0%	4.61	0%, 37.53%
Quality of life	–	–	–	10	0.31	0.17, 0.45	0.14, 0.48	0%	3.99	0%, 62.47%

Abbreviations. CBT-I = cognitive-behavioural therapy for insomnia; M = mean; M diff = mean difference; SD = standard deviation; SE (act) = actigraphy-measured sleep efficiency; SE (diary) = sleep diary-measured sleep efficiency; SOL (act) = actigraphy-measured sleep onset latency; SOL (diary) = sleep diary-measured sleep onset latency; TST (act) = actigraphy-measured total sleep time; TST (diary) = sleep diary-measured total sleep time; WASO (act) = actigraphy-measured wake after sleep onset; WASO (diary) = sleep diary-measured wake after sleep onset; 95% CI = 95% confidence interval; 95% PI = 95% prediction interval.
Note. Mean values could not be calculated for fatigue, depression, anxiety, and quality of life because several different measures were used to assess these outcomes.
k = number of comparisons.
[a] Insomnia values from Irwin and colleagues [44] were excluded from mean calculations of insomnia severity because the ISI was not used.
[b] Sleep quality values from Epstein and Dirksen [38] were excluded from mean calculations of sleep quality because the PSQI was not used.

CBT-I. There were notable effect size discrepancies between subjective and objective sleep outcomes. For example, CBT-I contributed to a 4-min reduction in actigraphy-measured SOL, while the reduction for diary-measured SOL was approximately 20 min. The only sleep outcome in which pre-to post-treatment effect sizes were similar between sleep diary and actigraphy (0.21 and 0.30, respectively) was TST. There were also differences in durability between sleep diary- and actigraphy-measured sleep outcomes: while diary-measured outcomes (except TST) remained durable at 3- and 6-months follow-up, actigraphy-measured outcomes largely did not. CBT-I was also found to reduce actigraphy-measured TST, indicated by a moderate negative effect size [55].

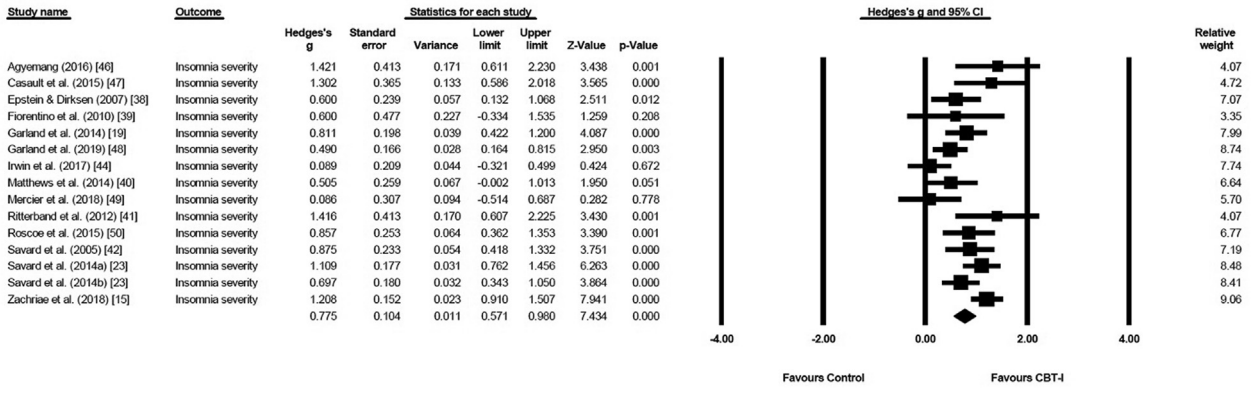

Fig. 2. Improvement of insomnia severity from pre- to post treatment by study and overall. *Abbreviations.* CBT-I=cognitive-behavioural therapy for insomnia. *Note.* Savard (2014a) denotes in-person CBT-I vs. control; Savard (2014b) denotes video-based CBT-I vs. control

Table 3
Between-group meta-analysis statistics from post-treatment to 3-months follow-up.

Outcomes	Post	3-months	M diff	*k*	ES (*g*)	95% CI	95% PI	Statistical heterogeneity		
	M(SD)	M(SD)						I^2	Q	95% CI
Insomnia				7	0.42	0.16, 0.68	−0.33, 1.17	60.80%	15.31*	10.07%, 82.91%
CBT-I	7.03 (4.44)	7.33 (4.77)	0.30							
Control	11.91 (5.55)	9.91 (5.74)	−2.00							
SOL (diary)				6	0.31	0.090, 0.53	−0.21, 0.83	29.14%	7.06	0%, 71.04%
CBT-I	17.59 (15.05)	17.89 (13.99)	0.30							
Control	31.52 (21.96)	28.44 (24.06)	−3.08							
WASO (diary)				6	0.38	0.12, 0.64	−0.0034, 1.20	48.84%	9.77	0%, 79.75%
CBT-I	25.16 (19.97)	26.28 (21.89)	1.12							
Control	47.26 (33.74)	36.71 (32.02)	−10.55							
TST (diary)				7	0.26	0.089, 0.43	0.093, 0.33	0%	3.25	0%, 70.90%
CBT-I	421.09 (55.21)	430.75 (56.54)	9.66							
Control	417.97 (65.74)	421.78 (71.66)	3.81							
SE (diary)				5	0.43	0.14, 0.72	−0.29, 1.12	49.80%	7.97	0%, 81.64%
CBT-I	86.71 (7.41)	86.27 (8.11)	−0.44							
Control	79.16 (10.82)	82.55 (11.10)	3.39							
Sleep quality				3	0.090	−0.14, 0.32	−1.38, 1.56	0%	1.39	0%, 89.66%
CBT-I	6.36 (2.85)	6.36 (2.87)	0							
Control	9.38 (3.63)	9.13 (3.92)	−0.25							
Fatigue	–	–	–	7	0.16	0.011, 0.31	−0.018, 0.73	0%	0.66	0%, 70.90%
Depression	–	–	–	6	0.14	−0.037, 0.32	−0.18, 0.44	0%	2.54	0%, 74.71%
Anxiety	–	–	–	5	0.11	−0.082, 0.30	−0.13, 0.42	0%	0.59	0%, 79.29%
Quality of life	–	–	–	6	0.20	0.027, 0.38	−0.14, 0.48	0%	2.79	0%, 74.71%

Abbreviations. CBT-I = cognitive-behavioural therapy for insomnia; M = mean; M diff = mean difference; SD = standard deviation; SE (diary) = sleep diary-measured sleep efficiency; SOL (diary) = sleep diary-measured sleep onset latency; TST (diary) = sleep diary-measured total sleep time; WASO (diary) = sleep diary-measured wake after sleep onset; 95% CI = 95% confidence interval; 95% PI = 95% prediction interval.
Note. Mean values could not be calculated for fatigue depression, anxiety, and quality of life because several different measures were used to assess these outcomes.
k = number of comparisons.

The discrepancy between subjective and objective outcomes is consistent with a meta-analysis by Mitchell and colleagues, in which CBT-I contributed to moderate-to-large effects in diary-measured SOL, WASO, and SE in adults with insomnia, but only small effects in actigraphy-measured SOL [55]. Correlations between actigraphy- and diary-measured sleep have been found to be low [56], and actigraphy can underestimate certain sleep parameters such as TST and SE [57], which also could have influenced our findings. As such, firm conclusions cannot be made about the practical significance of CBT-I for actigraphy-measured sleep outcomes based on our review alone.

The effect of CBT-I was significantly greater among studies that used non-active control treatments compared to those that used active treatments. This finding is consistent with a meta-analysis by Ma and colleagues [58], in which effect sizes were greater for studies that used non-active control treatments compared to those that used active treatments ($g = -0.85$ compared to -0.66, respectively). In our analysis, active controls were pooled into one group, meaning we cannot strongly conclude that CBT-I is efficacious compared to specific treatments. While CBT-I is the gold-standard non-pharmacological treatment for insomnia and produces larger effect sizes than other active treatments in general, individual patients may have personal preferences that lead them to choose another treatment. Indeed, this would be more reflective of real-world practice where an individual would choose a treatment that is in line with their preferences and values and may impact the outcomes of the trial [59].

Lack of providers and other barriers such as high costs and lack of insurance coverage makes CBT-I inaccessible to a large portion of people diagnosed with cancer [60]. Along with system-level barriers, practical barriers such as travel time can impact access [61]. Given the need to improve access, there has been an increased effort to evaluate alternative delivery models to the traditional face-to-face. In line with previous research [62], we found that treatment modality (in-person vs. self-help) did not significantly impact efficacy. This finding in particular has important implications to accessibility of CBT-I and treatment adherence more broadly, as people with insomnia view efforts to increase access to CBT-I via digital means favourably [63]. Self-help CBT-I may be an answer to accessibility issues by providing patients with lower-cost treatment comparable in effectiveness to in-person treatment that can be accessed from home. The effectiveness of these interventions may be due in part to their increased accessibility, which may improve adherence [62].

To our knowledge, our meta-analysis is the first to present results on the efficacy of CBT-I based on participant age and sex in cancer survivors. We observed that greater participant age was related to smaller effects of CBT-I on insomnia severity and larger effects of CBT-I on diary-measured SOL. Because older adults experience age-related changes to sleep continuity [64], they may see greater benefits as a result of CBT-I in areas of sleep continuity rather than insomnia severity. Future research is required to expand on these relationships. We also found that the percentage of male participants was related to greater effects of CBT-I on SOL. It is possible that male participants accrued more benefits from CBT-I related to diary-reported SOL compared to female participants; however, female participants may have presented with higher SOL values due to premature menopause as a result of treatment for sex-specific cancers. Investigation into the prevalence and reasons for potential sex/gender differences in treatment response is an area ripe for future research.

Limitations

The present review was not without limitations. Not all included studies assessed the efficacy of CBT-I at 3- and 6-months follow-up, limiting our ability to capture its durability over time. There was also a very large proportion of female participants in the included studies, ranging from 56.9% to 100%. This may limit the generalizability of our findings given the potential for sex/gender differences

Table 4
Between-group meta-analysis statistics from post-treatment to 6-months follow-up.

Outcomes	Post	6-months	M diff	*k*	ES (*g*)	95% CI	95% PI	Statistical heterogeneity		
	M(SD)	M(SD)						I^2	Q	95% CI
[a]Insomnia				9	0.33	0.12, 0.54	−0.27, 0.94	54.04%	17.41*	2.36%, 78.37%
CBT-I	7.80 (4.69)	7.75 (4.72)	−0.05							
Control	11.53 (5.41)	9.46 (5.59)	−2.07							
SOL (act)				5	0.25	0.032, 0.47	−0.10, 0.60	0%	3.60	0%, 79.29%
CBT-I	11.52 (12.41)	14.19 (20.76)	2.67							
Control	14.42 (14.69)	14.04 (20.45)	−0.38							
SOL (diary)				9	0.29	0.14, 0.44	0.026, 0.56	12.91%	9.19	0%, 54.89%
CBT-I	18.80 (17.64)	18.57 (18.05)	−0.23							
Control	30.21 (22.18)	24.22 (22.94)	−5.99							
WASO (act)				5	0.11	−0.10, 0.33	−0.24, 0.47	0%	1.18	0%, 79.29%
CBT-I	63.13 (32.71)	62.01 (36.13)	−1.12							
Control	69.57 (35.30)	68.22 (34.41)	−1.35							
WASO (diary)				9	0.38	0.20, 0.55	−0.039, 0.79	33.24%	11.98	0%, 69.29%
CBT-I	28.19 (23.89)	29.03 (25.41)	0.84							
Control	48.44 (36.01)	37.02 (34.85)	−11.42							
TST (act)				5	0.15	−0.065, 0.37	−0.20, 0.51	0%	1.41	0%, 79.29%
CBT-I	399.02 (63.95)	404.41 (67.39)	5.39							
Control	429.36 (54.05)	426.10 (67.46)	−3.26							
TST (diary)				9	0.18	0.040, 0.32	0.012, 0.34	0%	2.48	0%, 64.89%
CBT-I	412.42 (57.04)	427.15 (57.63)	14.73							
Control	411.72 (68.17)	426.62 (65.99)	14.90							
SE (act)				5	0.12	−0.099, 0.34	−0.23, 0.47	0%	1.34	0%, 79.29%
CBT-I	82.68 (8.88)	82.51 (9.72)	−0.17							
Control	82.30 (7.94)	81.30 (10.85)	−1.00							
SE (diary)				9	0.38	0.21, 0.55	−0.020, 0.78	30.86%	11.57	0%, 68.10%
CBT-I	86.89 (8.07)	86.99 (8.23)	0.10							
Control	80.19 (10.59)	83.44 (10.47)	3.25							
Sleep quality				4	0.28	0.001, 0.57	−0.75, 1.32	46.09%	5.57	0%, 82.12%
CBT-I	7.17 (2.86)	7.41 (3.13)	0.24							
Control	9.05 (3.28)	8.02 (3.62)	−1.03							
Fatigue	–	–	–	8	0.11	−0.036, 0.25	−0.071, 0.28	0%	1.11	0%, 67.67%
Depression	–	–	–	9	0.17	0.033, 0.30	0.0067 0.33	0%	5.99	0%, 64.89%
Anxiety	–	–	–	8	0.10	−0.039, 0.24	−0.073, 0.28	0%	1.00	0%, 67.67%
Quality of life	–	–	–	6	0.16	−0.014, 0.33	−0.084, 0.40	0%	2.68	0%, 74.71%

Abbreviations. CBT-I = cognitive-behavioural therapy for insomnia; M = mean; M diff = mean difference; SD = standard deviation; SE (act) = actigraphy-measured sleep efficiency; SE (diary) = sleep diary-measured sleep efficiency; SOL (act) = actigraphy-measured sleep onset latency; SOL (diary) = sleep diary-measured sleep onset latency; TST (act) = actigraphy-measured total sleep time; TST (diary) = sleep diary-measured total sleep time; WASO (act) = actigraphy-measured wake after sleep onset; WASO (diary) = sleep diary-measured wake after sleep onset; 95% CI = 95% confidence interval; 95% PI = 95% prediction interval.
*Note.*Mean values could not be calculated for fatigue, depression, and quality of life because several different measures were used to assess these outcomes.
k = number of comparisons.
[a] Insomnia values from Irwin and colleagues [44] were excluded from mean calculations of insomnia severity because the ISI was not used.

in cancer experiences, treatment adherence, etc. More studies focusing on the effects of CBT-I in males with cancer specifically and sex/gender differences in responses to CBT-I would be beneficial. Further, all included studies were conducted in upper-income countries, and all but one was conducted in a predominantly English-speaking country. This may bias our findings to favour upper-income countries, which does not account for potential differences in efficacy in lower-middle-income countries. Unfortunately, we were unable to assess all secondary symptoms that may be influenced by CBT-I or affect treatment outcome because of insufficient data (e.g., pain, cognitive function). As more research becomes available, these are areas that should be examined. The included studies were not consistent in how they handled the use of sleeping medications with some excluding participants taking sedative-hypnotics and others tracking this as an outcome. As such, the true effect of CBT-I may not be clear in all studies. Finally, the included studies did not report whether participants' onset of insomnia symptoms predated or followed their cancer diagnosis. As demonstrated above, there is still much to understand about insomnia in those diagnosed with cancer and how CBT-I effects may be modified by patient-level characteristics.

We recommend further research to identify demographic or clinical characteristics of cancer survivors who are more likely to respond to CBT-I treatment, characteristics of non-responders, and viable alternatives for non-responders. This can be completed by conducting meta-analyses with individual patient data. Upon identifying reasons for non-response, it is necessary to investigate ways to improve CBT-I to increase adherence and response in cancer survivors. Previous research has found that combining CBT-I with other treatments such as mindfulness-based therapy (MBT) [65] improves insomnia severity for adults diagnosed with insomnia. We recommend future researchers assess the potential benefits of combination therapies for improving insomnia severity in cancer survivors to give clinicians the tools to meet patients where they are rather than applying one type of CBT-I to all patients.

Conclusion

CBT-I remains an efficacious treatment for insomnia in cancer survivors while also contributing to improvements in other symptoms that can present throughout cancer diagnosis, treatment, and beyond. Therefore, CBT-I should continue to be recommended as a first-line treatment for insomnia in cancer survivors. Self-help CBT-I is also recommended for those who cannot access in-person treatment. Further research is needed to assess sex/

gender differences in efficacy to determine what works best and for whom, and more longitudinal studies must be conducted to determine the long-term efficacy of CBT-I. In addition, more research is needed to assess the efficacy of self-help CBT-I compared to in-person CBT-I to combat accessibility and treatment adherence issues.

Practice points

1. Cognitive-behavioural therapy for insomnia remains efficacious in those diagnosed with cancer, and also produces concomitant benefits in sleep outcomes and comorbid conditions such as fatigue, anxiety, and depression from pre-to post-treatment.
2. The effects of cognitive-behavioural therapy for insomnia on insomnia severity remain durable at 3- and 6-months follow-up.
3. Self-help cognitive-behavioural therapy for insomnia interventions produced effects comparable to those of in-person interventions, meaning that self-help CBT-I may be a viable alternative to in-person treatment.

Research agenda

1. Future research should focus on the accessibility of in-person and self-help treatments and how these modalities impact treatment adherence.
2. Increased focus on longitudinal studies to assess the durability of cognitive-behavioural therapy for insomnia treatment over longer periods of time, and whether booster sessions at follow-up improve durability.
3. Focus on investigating the characteristics that can impact adherence to cognitive-behavioural therapy for insomnia, such as participant age, sex, and gender.
4. Future research should use individual patient data to conduct meta-analyses for specific cancer types and treatments
5. Future research should assess objective sleep outcomes (i.e., through actigraphy and polysomnography) in addition to subjective outcomes through sleep diary to provide further evidence on the efficacy of CBT-I for improving objective outcomes.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Acknowledgements

Lauren R. Squires was funded by a Social Sciences and Humanities Research Council (SSHRC) Canada Graduate Scholarship - Masters. Sheila N. Garland is supported by a Canadian Cancer Society Emerging Scholar Award (Survivorship) (Grant #707146).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101615.

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