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Recording and reporting of adverse events during a randomized controlled trial of cognitive behavioural therapy for insomnia (CBT-I) among cancer survivors

Krista M. Greeley[1†], Rachel M. Lee[1†], Joshua Tulk[1], Scott V. Harding[3], Yanqing Yi[4], Kris Aubrey-Bassler[5] and Sheila N. Garland[1,2*]

Abstract

Background/Aims Sleep disturbances are one of the biggest barriers to resuming normal functioning following cancer treatment. Cognitive behavioral therapy for insomnia (CBT-I) has demonstrated efficacy in cancer survivors but few studies have recorded adverse events (AEs) that occur during treatment. The purpose of this study was to report the prevalence, severity, and attribution of AEs during CBT-I with cancer survivors.

Methods Cancer survivors from Atlantic Canada with insomnia and comorbid cognitive impairment were recruited to participate in a randomized controlled trial of CBT-I. Participants reported the prevalence, severity, and attribution of AEs at mid-treatment (4 weeks) and post-treatment (8 weeks). The likeliness of AEs being related to treatment was also rated by an independent clinician.

Results Of the 122 cancer survivors who completed treatment (M_{age} = 60.3, 77.9% women), 72 reported a total of 197 AEs. At mid-treatment, participants reported 113 AEs, but only 11 were rated as being attributed to the intervention. At post-treatment, participants did not report any AEs attributed to the intervention. An independent rater attributed more AEs to the treatment than the participants at both time points (4 weeks: 16 vs. 11, 8 weeks: 1 vs. 0). Gender (p = .014) and pre-treatment anxiety (p < .001) were associated with reporting an AE.

Discussion CBT-I is a safe treatment that is well-tolerated by cancer survivors. The majority of participants did not experience AEs that could be attributed to the treatment. Clinicians should continue to recommend CBT-I as the first-line treatment for cancer survivors experiencing insomnia symptoms.

Trial registration This study is a secondary analysis of a randomized controlled trial titled 'Addressing Cancer Treatment-Related Insomnia Online in Atlantic Canada (ACTION) study' (https://www.clinicaltrials.gov/search?cond=NCT04026048 identifier: NCT04026048).

Keywords Insomnia, Cognitive behavioural therapy for insomnia, Cancer, Adverse events

[†]Krista M. Greeley and Rachel M. Lee represent co-first authors.

*Correspondence:
Sheila N. Garland
Sheila.garland@mun.ca
Full list of author information is available at the end of the article

Introduction

Disturbed sleep is one of the most prevalent side effects and biggest barriers to resuming normal functioning following treatment for cancer survivors (Ross et al. 2020; Palesh et al. 2010). It is estimated that up to 50% of all cancer survivors experience insomnia symptoms or syndrome at some point during treatment or survivorship (Savard et al. 2011). Insomnia has been associated with detrimental and pervasive impacts on patients' quality of life as well as physical, mental, and cognitive health (Ross et al. 2020; Stepanski et al. 2009). Despite such a high prevalence and negative impact on cancer survivors, insomnia remains underrecognized and undertreated in cancer centres (Induru and Walsh 2014; Reynolds-Cowie and Fleming 2021).

Both pharmacological and psychological interventions can be effective for treating insomnia. In choosing a treatment, an important consideration is the potential for harm or adverse events (AE) associated with treatment. An AE is any negative event that occurs during the treatment, such as the development of new symptoms, an increase in existing symptoms, or deterioration in functioning (Linden 2013; Duggan et al. 2014). AEs are not always directly caused by the treatment; they may be related to a wide variety of factors such as stress or personal circumstances that occur while a patient is undergoing treatment. While there is a requirement to record AEs in clinical trials of pharmacological treatments, there is a lack of attention to AEs that occur during psychological treatments. A systematic review of 115 studies that assessed the reporting of AEs in psychotherapy randomized controlled trials (RCTs) found that only 60% of included studies reported "harmful events" (Klatte et al. 2023). In the AEs that were reported, the majority did not assess the relation of the AE to the treatment. Moreover, a review comparing the way AEs are reported in psychotherapy trials found that the majority (52%) of studies did not define AEs (Papaioannou et al. 2021). Additionally, this review found that serious AEs were mostly defined using terms from psychopharmacotherapy interventions. Overall, the lack of attention to AEs in psychotherapy interventions demonstrates a need for interventions to define and report AEs.

There are several reasons why AEs in psychotherapy are underreported compared to pharmacological interventions. First, clinicians may be underestimating the potential negative effects that can occur with psychotherapy, believing it to be somehow safer. However, this can lead to the misbelief that there are no AEs in psychotherapy. Thus, it is important that psychotherapy interventions adequately report all AEs so clinicians and patients can make an informed decision about using psychotherapy. Second, in the systematic review by Klatte and colleagues, they found that some researchers defined mental health as the only relevant type of AE in psychotherapy trials (Klatte et al. 2023). This mindset would then ignore any other type of AE that can occur from the intervention, including the onset of symptoms such as headaches or pain, or increased medication use. Overall, when determining an appropriate intervention for a patient with insomnia, the associated AEs should be weighed before recommending the treatment.

Cognitive behavioural therapy for insomnia (CBT-I) is recommended by the American College of Physicians and the American Academy of Sleep Medicine (Edinger et al. 2021; Qaseem et al. 2016) and has repeatedly demonstrated efficacy among cancer survivors (Johnson et al. 2016; Ma et al. 2021; Squires et al. 2022). CBT-I is typically conducted over several weekly sessions with a trained clinician and addresses the perpetuating underlying thoughts, emotions, and behaviours that contribute to insomnia (Williams et al. 2013). It typically includes five key components: stimulus control, sleep restriction, cognitive restructuring, relaxation training, and sleep hygiene (Edinger et al. 2021; Trauer et al. 2015). Despite strong evidence supporting its efficacy for treating insomnia, CBT-I carries a potential for AEs. For example, sleep restriction has been associated with a decreased total sleep time that may cause some patients to feel increased daytime sleepiness, potentially leading to impaired daily functioning (Kyle et al. 2014). A 2021 systematic review of 99 RCTs of CBT-I reported that only one third of studies included reports of AEs experienced during treatment (Condon et al. 2021). The AEs reported included deterioration of comorbid mental health problems, and worsening sleep, fatigue, and cognitive complaints. Further, only 7% of these studies met the criteria for adequately reporting AEs based on the Consolidated standards for reporting trials (CONSORT) guidelines (Ioannidis et al. 2004).

Despite the presence of AEs during CBT-I, there is very little known about AEs during CBT-I within cancer survivors. The present study examined AEs experienced by cancer survivors as part of a randomized controlled trial of CBT-I. We assessed the type and severity of AEs, their attribution to treatment, and whether AEs were associated with study withdrawal. Open ended patient responses about their experience were also collected. The results of this study will provide information on the safety of CBT-I and help inform the treatment decisions of cancer survivors and care providers.

Methods

Study design

The current study is a pre-specified secondary analysis of a recently completed randomized, waitlist-controlled trial called the Addressing Cancer Treatment-Related Insomnia Online in Atlantic Canada (ACTION) study. The purpose of the larger trial was to determine if virtually-delivered CBT-I would improve perceived cognitive impairment symptoms. A protocol describing the trial design and methodology was previously published as well as the primary outcomes (Garland et al. 2021; Garland et al. 2024). Participants reported on AEs via a Qualtrics survey (Qualtrics 2020) at mid- (4 weeks after beginning treatment) and post-treatment (8 weeks after beginning treatment). Participants were randomly assigned to one of nine therapists (made up of clinical psychology doctoral students and a registered clinical psychologist) to deliver the CBT-I intervention. After all responses were collected, an independent physician coder separately rated all AEs on their severity and likelihood of being attributed to the treatment.

Sample

Participants were recruited from treatment clinics, radio advertisements, posters, referrals from oncologists, and from mailouts to individuals who participated in the Atlantic Partnership for Tomorrow's Health (Atlantic PATH) study (Sweeney et al. 2017). Eligibility screenings were conducted by a trained member of the research team and were based on participants report of their cancer diagnosis and other symptoms. Participants were eligible if they were cancer survivors of any type or stage from Atlantic Canada, had completed their cancer treatment at least 6 months prior to study entry, and were considered in remission or cancer free. Those with hematological malignancies were eligible to participate, as long as their condition and treatment regimen was stable (continued maintenance or hormonal treatments were allowed). Participants had to meet the criteria for insomnia disorder based on the Diagnostic Statistical Manual of Mental Disorders, fifth edition and report perceived cognitive impairment by indicating a response of "quite a lot" or "always" on questions pertaining to concentration and memory on the European Organization for Research and Treatment of Cancer core quality of life questionnaire (Aaronson et al. 1993; American Psychiatric Association 2013). Participants also had to be English speaking with access to the internet and a webcam. Exclusion criteria included having poor performance status (i.e., score greater than 2 on the Eastern Cooperative Oncology Group Performance Status Scale; (Oken et al. 1982)), an untreated psychological or sleep disorder other than insomnia, having received cranial radiation, having a major sensory deficit or other condition that could affect participation or cognitive functioning, or had previous experience with CBT-I. Ethical approval was obtained by the Newfoundland and Labrador Health Research Ethics Board (#20200427). Informed consent was obtained before participation.

Procedure

Participants who were eligible to participate were randomized to either the immediate CBT-I treatment or a waitlist control. Those in the waitlist control group began CBT-I 8 weeks after baseline assessment. The intervention was delivered individually and virtually with weekly, one-hour sessions for a duration of seven weeks via a video conferencing platform. The intervention was delivered by clinical psychology doctoral students who were supervised by a PhD-level clinical psychologist with more than ten years of experience with the intervention. CBT-I included sleep restriction, which increases sleep drive by limiting time-in-bed to the amount of time actually spent sleeping; stimulus control to strengthen the association between the bed with sleeping by limiting potentially stimulating behaviours in bed; cognitive restructuring to address maladaptive or inaccurate beliefs or attitudes about sleep; relaxation training to teach arousal reduction strategies for use throughout the day and at bedtime; and sleep hygiene to ensure the environmental conditions were conducive to sleep (Perlis et al. 2005; Spielman et al. 1987; Bootzin et al. 1991; Morin et al. 2023).

Measures

There is no validated method of reporting AEs in trials of CBT-I in cancer populations. As such, we developed our assessment based on the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and the National Cancer Institute, Cancer Therapy Evaluation Program attribution standards (Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 2017). This approach is consistent with recent developments of a patient-reported outcomes version of the CTCAE (Basch et al. 2014).

AEs were assessed using open- and closed-ended questions (See Appendix A). We followed the CONSORT 2022 guidelines for reporting harms (Junqueira et al. 2023) to ensure that the: (1) AEs were clearly defined with descriptions of anticipated AEs; (2) Measurement of AEs and methodology were clearly stated, including validation of measures and timing of use; (3) AEs were reported with an attribution to the relationship of the intervention (i.e., is the AE actually related to the intervention?); and (4) Severity of each AE was reported. First, participants were asked to describe how the treatment was going to provide context about their perspective on the treatment. Next, participants were asked about five categories of possible AEs: (1) Distress, illness,

or incidents; (2) New development of symptoms; (3) Unplanned medical visits/procedures; (4) Unplanned need to take medication; (5) Any other physical or mental health concern. For each category, participants were asked to indicate whether they had experienced this type of AE, the severity of the AE on a 3-point scale of mild, moderate, or severe, and the likelihood that the AE was attributed to the intervention on a 5-point scale of definitely, probably, possibly, unlikely, and unrelated. Lastly, participants were asked to provide details of the event if they wished to elaborate. This measure was administered at mid-treatment (4 weeks) for participants to report AEs experienced from baseline to mid-treatment, and at post-treatment (8 weeks) for participants to report AEs experienced from mid- to post-treatment.

Analysis

Frequencies of the characteristics of the AEs (occurrence, severity, and attribution to treatment) at mid and post-treatment were analyzed. The number and reason for study withdrawal was systematically tracked by the research team. Reasons for study withdrawal were provided by participants. A physician coder (who was aware of CBT-I as a recommended treatment for insomnia but not trained as a provider) was blinded to patient ratings and independently rated all AEs on their severity and likelihood of being attributed to the treatment using the Common Terminology Criteria for Adverse Events (CTCAE). AEs determined to be unrelated included stress related to family conflict and other personal relationships and COVID-19 infection in self or others. Kappa was calculated to determine inter-rater reliability of AE attribution between participants and the independent rater for each category of AE. A series of Fishers exact tests were performed to explore whether age, gender, cancer type, CBT-I provider, anxiety, depression, or treatment group (immediate vs. delayed) had any influence on experiences of AEs attributed to treatment as rated by the participants. Fisher's exact tests were used due to a small expected cell count and small sample size. Patient experiences with the intervention were collected from open-ended questions at mid- and post-treatment.

Results

Participants

The mean age of participants was 60.3 ± 11.31 years (range: 28–85 years). Most participants (77.9%) were women, White (91.8%), and in a committed relationship (77.9%) with a high level of education (average 15.92 ± 3.03 years). Breast cancer was the most common diagnosis (45.1%). Complete demographic and clinical characteristics of the sample are presented in Table 1.

Adverse events

Overall, 72/122 (59.0%) participants reported at least one valid AE at some point during their participation in CBT-I. Thirty-three AEs were assessed as invalid by the study team for either being a false report (i.e., a participant said "yes" to experiencing an AE but then reported they did not have an AE), reporting something besides an AE (e.g., improved sleep), or not providing any detail about the reported AE. Participants reported a total of 197 valid AEs. Of these, 113 were reported during treatment and 84 were reported at treatment completion.

Participants attributed fewer AEs to treatment than the independent rater. Of the 113 valid AEs at mid-treatment, only 11 (9.8%) were self-rated by eight participants (M_{age} = 66.6, 87.5% women, 50% breast cancer) as being probably or definitely attributed to treatment. In contrast, 16 (14.3%) of the 113 AEs experienced by 13 participants were rated by the independent rater as being probably or definitely attributed to treatment. Of the 84 valid AEs at post-treatment, none were rated by participants as being probably or definitely attributed to treatment and one was rated by the independent rater as being probably or definitely attributed to treatment. The AEs self-reported as being attributed to treatment were increased medication for headaches, strange dreams, anxiety, and increased tiredness/fatigue and associated distress. Inter-rater reliability ranged from no (mid-treatment unplanned medical visits: $\kappa = -0.06$) to moderate agreement (mid-treatment medication use: $\kappa = 0.41$). More adverse events were attributed to CBT-I at mid-treatment than post-treatment by both participants (11 vs 0) and the independent rater (16 vs 1). See Fig. 1 for all adverse event attributions rated by participants and the independent rater.

Severity of adverse events

Most AEs were mild (57 AEs; 36 mid-treatment, 21 post-treatment) or moderate (108 AEs; 55 mid-treatment, 53 post-treatment) in severity. Participants reported a total of 27 serious AEs, which required medical attention (19 mid-treatment, 8 post-treatment), however no participants reported a serious AE that they believed was probably or definitely related to treatment. Severity ratings were missing for 5 AEs. Table 2 shows the type and severity of AEs rated as being probably or definitely attributed to treatment by both participants and the independent rater.

Study withdrawals related to adverse events

Of the 132 participants who enrolled in the study, nearly all completed the treatment phase (n = 122, 92.4%). Three participants assigned to the waitlist control group did not begin treatment sessions. Three participants from the waitlist control group and four from the immediate

Table 1 Descriptive statistics for demographic and clinical variables in CBT-I participants ($N=122$)

Demographic and Clinical Variables	N (%)	Mean (SD)
Age		60.3 (11.31)
20–29	2 (2)	
30–39	4 (3)	
40–49	15 (12)	
50–59	29 (24)	
60–69	47 (39)	
70–79	20 (16)	
80–89	5 (4)	
Gender		
Women	95 (77.9)	
Men	27 (22.1)	
Race		
White	112 (91.8)	
Indigenous	5 (4.1)	
Black	1 (.8)	
West Indian	1 (.8)	
Multiracial	2 (1.7)	
Unspecified	1 (.8)	
Years of education		15.92 (3.03)
Cancer type		
Breast	55 (45.1)	
Colon/Rectal	4 (3.3)	
Head/Neck	4 (3.3)	
Prostate	9 (7.3)	
Hematological	17 (13.9)	
Uterine	7 (5.7)	
Skin	9 (7.3)	
Other†	17 (13.9)	
Multiple types	21 (17.2)	
Anxiety**		
Pre-treatment		
No anxiety	41 (34)	
Borderline	33 (39)	
Anxiety	48 (39)	
Mid-treatment		
No anxiety	67 (55)	
Borderline	27 (22)	
Anxiety	28 (23)	
Post-treatment		
No anxiety	73 (61)	
Borderline	24 (20)	
Anxiety	23 (19)	
Depression**		
Pre-treatment		
No depression	69 (57)	
Borderline	29 (24)	
Depression	24 (20)	
Mid-treatment		
No depression	96 (79)	
Borderline	18 (15)	
Depression	8 (7)	
Post-treatment		
No depression	104 (87)	
Borderline	14 (12)	
Depression	2 (2)	

†Other cancers indicated by participants included carcinoma, appendix, neuroendocrine tumor, blastoma on liver, tongue, thyroid, bladder, kidney, lymphatic, and ovarian cancers

** Measured by the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983)

group did not complete all treatment sessions. Of all study withdrawals ($n=10$), only one was attributed to a treatment-related AE (treatment related distress). Reasons for withdrawal not attributed to treatment included losing contact with participants ($n=2$), unrelated health concerns ($n=2$), a cancer recurrence ($n=2$), family emergencies ($n=2$), or being too busy ($n=1$).

Factors associated with adverse events

A series of Fishers exact tests were performed to explore whether age, gender, cancer type, CBT-I provider, anxiety, depression, or treatment group (immediate vs. delayed) were related to reports of AEs either at mid- or post-treatment, as rated by participants. Gender ($p=0.014$) and anxiety symptoms ($p<0.001$) were the only factors significantly associated with having an AE at any time during treatment, such that women were more likely to experience an AE than men and greater anxiety was more associated with experiencing an AE. See Table 3 for all associations.

Patient experience

Participants who experienced AEs, were invited to report on their experience of CBT-I. Participants commented on the amount of effort that treatment required, particularly at the beginning. One participant noted:

> *The first week of the sleep restriction therapy was challenging. I was extremely tired during the day and almost felt like giving up. I couldn't understand why I was actually getting more sleep than before I started the study but felt more tired, however, I really felt that it was all part of the process and I believed by the end of the therapy I would truly be able to sleep much better. After that week, it got a lit-*

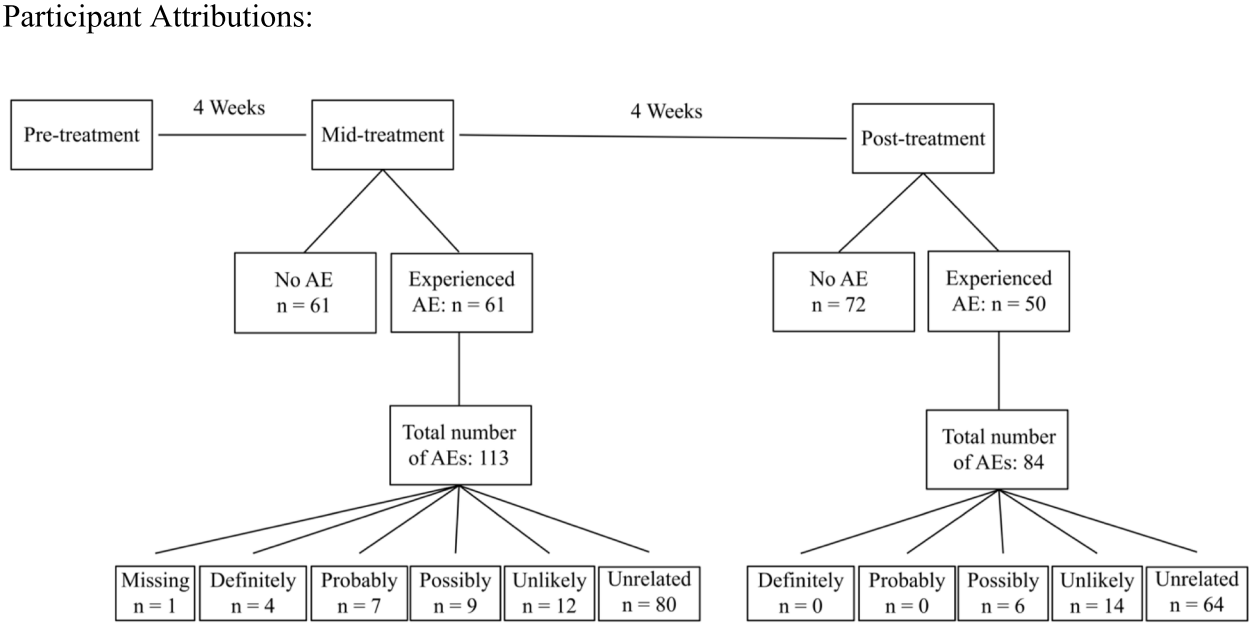

Fig. 1 Adverse event attributions

tle easier and I could feel a positive difference as the weeks went on. It was exciting to have an extra 30 minutes added. That really gave me the motivation to stick with it. I learned much more about myself than I ever imagined. The awareness of my thought process and other patterns was key to understanding how it all related to my insomnia (woman, 52, appendiceal cancer, post-treatment).

Another participant commented that CBT-I was "without a doubt, one of the hardest things I've ever tried to do but it is starting to work." (woman, 67, basal cell carcinoma, 4 weeks). Some noted initial struggles that led to improvements: "It was hard at first but once I saw the difference in my ability to get a good night's sleep, I was motivated to follow the instructions. The therapist was very supportive, and I'm so pleased with the results!"

Table 2 Adverse events attributed to treatment

	Number and Severity of Adverse Events probably or definitely attributed to treatment			
	By Participants		By Independent Rater	
	4 weeks	8 weeks	4 weeks	8 weeks
Distress, illness, or incidents	4 mild 1 moderate	0	4 mild 1 moderate 1 missing	0
Development of new symptoms	1 moderate	0	2 mild 2 moderate	1 mild
Unplanned medical visits, procedures, or accidents	0	0	0	0
Unplanned need to take medications	1 moderate	0	1 moderate 1 missing	0
Other physical or mental health concerns	4 mild	0	3 mild 1 moderate	0

Table 3 Fisher's exact test of factors associated with experiencing mid- and post-treatment AEs

	Valid AEs reported by participants at mid- and post-treatment	
	df (N)	*p*
Age	6 (122)	.769
Cancer Type	6 (122)	.264
CBT-I provider	8 (122)	.468
Gender	1 (122)	.014*
Anxiety at pre-treatment†	2 (122)	< .001*
Anxiety during treatment†	2 (122)	.151
Anxiety after treatment†	2 (120)	.130
Depression at pre-treatment†	2 (122)	.429
Depression during treatment†	2 (122)	.661
Depression after treatment†	2 (120)	.327
Treatment group	1 (122)	.465

†Assessed by the Hospital Anxiety and Depression Scale (Zigmond et al. 1983)

* Indicates statistical significance ($p < .05$)

(woman, 64, kidney cancer, post-treatment). Participants also expressed frustration with the required effort, but admitted it was what led to the improvement. "It is a bit annoying to have to stick to a schedule but it's working!" (woman, 64, kidney cancer, mid-treatment). One participant commented: "It just goes to show if you put in the time, work, and effort, you will definitely see results, and FAST!" (woman, 41, breast cancer, mid-treatment).

Other participants reported they were pleased at their increased sleep self-efficacy and felt like they had more tools and knowledge to improve their sleep.

> *"Some of my own trial and error attempts at better sleep were actually conflicting with each other. The CBT-I was very logical and the changes I made, made clear sense. Having a plan instead of desperate random attempts gave almost instant consistency." (woman, 43, cervical cancer, mid-treatment).*

Another participant noted "Amazing [how] much insight I have been able to gain on why my sleep patterns were affected as much as they were. I can now see that there were many more factors contributing to insomnia that I am now able to start working on with the tools I have gained." (woman, 42, melanoma, mid-treatment). Participants reported that the effort they put into CBT-I ultimately led to feelings of empowerment and accomplishment: "I put the effort in so I was able to get positive results." (woman, 50, thyroid cancer, post-treatment). Another participant commented that CBT-I was "wonderful, empowering and informative so I can take better control of my sleeping." (woman, 49, breast cancer, post-treatment).

Discussion

The present study examined the occurrence, severity, and attribution of AEs during CBT-I in cancer survivors. Cancer survivors experienced very few AEs that could be attributed to CBT-I [11 of 197 (5.6%) as rated by participants; 16 of 197 (8.1%) as rated by an independent physician rater]. This supports that CBT-I is a safe and well-tolerated treatment. The independent rater attributed more AEs to the treatment than the participants, which may be because the rater is a physician and is trained to have a low threshold for identifying the complications of treatment.

Existing research on psychological interventions seldom report AEs experienced during treatment, especially research on CBT-I (Condon et al. 2021). In those that do include AEs, most report that there were no AEs reported

during the study (e.g., (Freeman et al. 2017)). In a trial of 1,711 adults receiving either sleep hygiene education or digital, app- and internet-based CBT-I, the most common AEs experienced for those receiving CBT-I were increased fatigue, headaches, sleepiness, and reduced motivation. In that study, none of the AEs attributed to treatment were rated as serious (Espie et al. 2019). This is consistent with the present study. All AEs attributed to treatment were mild or moderate, including increased headaches, strange dreams, anxiety, and fatigue. AEs in the present study that were severe were rated as being unlikely attributed to the intervention. A core component of CBT-I is initially restricting time-in-bed to match sleep ability, and the removal of compensatory behaviors designed to lessen the impact of poor sleep, such as napping (Edinger et al. 2021). As such, it is expected that this phase of the treatment would be associated with increased fatigue and subsequently increased headaches, anxiety, or motivation. These side effects are expected to subside as treatment progresses (Edinger et al. 2021). Differences in the frequency, attribution, and severity of AEs during CBT-I across studies could be due to differences in samples (i.e., cancer survivors vs. general population), and measurement. Therefore, it is recommended that future RCTs examining CBT-I consistently report AEs using the CONSORT guidelines in different populations to determine if certain groups are more likely to experience AEs during CBT-I than others (Junqueira et al. 2023).

Under the Food and Drug Act and Regulations, clinical trial sponsors are legally required to monitor and report AEs experienced while testing a medication (Government of Canada 2023). As such, studies examining sleep medications (e.g., orexin receptor antagonists, melatonin receptor agonists, and benzodiazepine receptor agonists) report AEs more frequently than studies on CBT-I. Some of the AEs reported from these medications are unpleasant taste, drowsiness, nausea, psychological dependence, and residual daytime sedation (Schroeck et al. 2016). These vary in frequency and severity. Other minor side effects such as headaches and fatigue overlap between sleep medications and CBT-I. Although AEs are reported less frequently in studies of CBT-I than those of sleep medications, CBT-I studies that do report AEs seem to report a relatively small number (e.g., (Espie et al. 2019)). Additionally, the AEs associated with sleep medications may be experienced for a longer duration than those associated with CBT-I. A meta-analysis that assessed 69 medications for insomnia found evidence that AEs may be experienced long-term (Yue et al. 2023). In contrast, in the current study, there were fewer AEs attributed to CBT-I at post-treatment compared to mid-treatment. This suggests that most treatment-related AEs subside by the time treatment is finished.

Several clinical and demographic factors were assessed to examine whether there were factors that were associated with experiencing an AE during CBT-I. Gender and experiencing anxiety before the intervention were the only significant associations with experiencing AEs at any time during treatment. Women more likely to experience an AE than men and greater levels of anxiety were associated with experiencing an AE. Of the 95 women in our study, 62 reported an AE (65.3%). In contrast, of the 27 men who participated, 10 reported an AE (37.0%). While a similar pattern has been found in drug studies (Unger et al. 2022), there is no research reporting gender differences for AEs during CBT-I, specifically in cancer survivors. As such, it is unknown what contributes to this finding in the present study. One possible reason is that on average, women have a higher total sleep time than men (Ohayon et al. 2004). Furthermore, women cancer survivors experience anxiety and depression (Gotze et al. 2020), stress (Hagedoorn et al. 2008), and fatigue (Ma et al. 2020), at a higher rate than men. With all of this together, perhaps the sleep restriction required as a part of CBT-I had a greater negative impact on the women participants, making them more likely to experience AEs or exacerbate any ongoing conditions they may have had. Alternatively, women may have an increased likelihood both to perceive symptoms and to report symptoms to others (van Wijk and Kolk 1997). If this was the case, perhaps women did not experience more AEs during CBT-I but rather were more likely to report the AEs they did experience. Additionally, anxiety symptoms at pre-treatment were significantly associated with reporting an AE. Perhaps those who with higher anxiety were more likely to experience an AE as the sleep-restriction may have exacerbated their existing anxiety or anxiety-related concerns (e.g., headaches). Alternatively, those with higher anxiety may have been more aware of changes in their body and to their regular routines and thus may have been more likely to report a symptom as an AE to the study team. No other factors (age, cancer type, treatment group, CBT-I provider, anxiety, and depression) impacted whether a patient had an AE during treatment; however, this study may have been underpowered to detect significant differences in some of these smaller subgroups. Future research should investigate whether there are factors that increase the likelihood of experiencing an AE during CBT-I to help clinicians and patients make informed recommendations and decisions.

This study adds to the limited literature about AEs in CBT-I, specifically in oncology populations. Still, there were limitations to this research. First, the sample did not have an equal distribution of genders, ethnicity, or cancer types. Therefore, the AEs experienced in this sample is not representative of the total oncology population. Additionally, self-selection bias may be present considering participants were recruited based on their own interest in receiving

CBT-I. Moreover, the independent physician rater was not trained in CBT-I. Although familiar with the intervention, it is possible that some attributions to treatment could have been false, and some AEs may have been unrecognized by the physician to be attributed to CBT-I. Future studies should use an independent coder who is trained in CBT-I. Another limitation is that there is currently no psychometrically valid instrument for measuring AEs in CBT-I. Despite the lack of standardization in the literature, the authors feel it is important to measure and report AEs to move toward improved standards of reporting for psychological interventions. Lastly, adherence to the intervention was not measured systematically, which may have impacted the presence of absence of an AE. Future research should examine AEs in CBT-I using a more balanced sample and adding a measure of treatment adherence.

The findings of this study show that CBT-I is a safe treatment that is well-tolerated by cancer survivors. The majority of participants experienced no AEs that could be attributed to treatment. There is a need for adequate and consistent reporting of AEs in CBT-I and other psychotherapy interventions. Concern about AEs should not be a barrier to recommending CBT-I but clinicians should attend to the possibility of AEs, particularly at the beginning of treatment.

Appendix A: Adverse Event Questionnaire

ACTION STUDY ASSESSING FOR ADVERSE REACTIONS TO CBT-I

"We will now ask you a few questions regarding your CBT-I treatment sessions

1. (Mid-treatment) How are your treatment sessions going? OR (post-treatment) How did your treatment sessions go?
2. In the past 4 weeks, have you experienced any distress, illnesses, or incidents since you started the treatment sessions? [if yes, specify]
3. In the past 4 weeks, have you developed any new symptoms? [if yes, specify]
4. In the past four weeks, have you had any unplanned medical visits, procedures, or accidents? [if yes, specify]
5. In the past 4 weeks, have you had an unplanned need to take any medication? [if yes, specify]
6. In the past 4 weeks, have you experienced any other physical or mental health concerns? [if yes, specify]

Severity Scale

If yes to any of the above questions: "Do you consider it mild, moderate, severe?":

- **Grade 1 Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 Moderate:** minimal, local or non-invasive intervention indicated
- **Grade 3 Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care.
- **Grade 4: Life-threatening** consequences; urgent intervention indicated.

Attribution Standards

"Do you feel this was related to your CBT-I treatments?":

1. **Unrelated**
2. **Unlikely**
3. **Possible**
4. **Probable**
5. **Definite**

Additional Details

If Possible, Probable, or Definite to the above question: "In what way do you feel this was related to your CBT-I treatments?" (Text entry question)

Abbreviations

AE	Adverse Event
CBT-I	Cognitive Behavioural Therapy for Insomnia
CONSORT	Consolidated Standards for Reporting Trials
CTCAE	Common Terminology Criteria for Adverse Events
RCT	Randomized Controlled Trial

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Authors' contributions

Conceptualization, S.G.; methodology, S.G., K. G., R.L., J.T.; formal analysis, K. G., R.L.; investigation, K.G., R.L., J.T and S.G.; resources, K.G, R.L., J.T., and S.G.; data curation, K.G and R.L.; writing—original draft preparation, K.G., R.L. and S.G.; writing—review and editing, J.T., S.H., Y.Y., K.A-B.; visualization, K.G, R.L, J.T.; supervision, S.G.; funding acquisition, S.G. and K.G. All authors have read and agreed to published version of the manuscript.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval for this study was by the Newfoundland and Labrador Health Research Ethics Board (#20200427).

Consent for publication

All authors have read and agreed to published version of the manuscript.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Psychology, Faculty of Science, Memorial University, 232 Elizabeth Ave, St. John's, NL A1B 3X9, Canada. [2]Discipline of Oncology, Faculty of Medicine, Memorial University, St. John's, NL, Canada. [3]Department of Biochemistry, Faculty of Science, Memorial University, St. John's, NL, Canada. [4]Division of Population Health and Applied Health Sciences, Faculty of Medicine, Memorial University, St. John's, NL, Canada. [5]Discipline of Family Medicine, Faculty of Medicine, Memorial University, St. John's, NL, Canada.

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