Integrative Medicine Research 12 (2023) 100922

Contents lists available at ScienceDirect

Integrative Medicine Research

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

Original Article

Addressing cancer-related fatigue through sleep: A secondary analysis of a randomized trial comparing acupuncture and cognitive behavioral therapy for insomnia

Xiaotong Li [a], Kevin T. Liou [a], Susan Chimonas [b,c], Karolina Bryl [a], Greta Wong [a], Eugenie Spiguel [a,d], Susan Q. Li [a], Sheila N. Garland [e], Ting Bao [a], Jun J. Mao [a,*]

[a] Integrative Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[b] Center for Health Policy and Outcomes, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[c] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[d] Department of Advanced Practice Providers, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[e] Department of Psychology and Oncology, Memorial University of Newfoundland, St. John's, NL, Canada

ARTICLE INFO

Article history:
Received 27 October 2022
Revised 29 January 2023
Accepted 30 January 2023
Available online 3 February 2023

Keywords:
Fatigue
Insomnia
Acupuncture
Cognitive behavioral therapy
Cancer

ABSTRACT

Background: Fatigue is a troublesome symptom in cancer survivors that often results from disrupted sleep. We sought to assess whether two insomnia-focused non-pharmacological interventions are also effective for improving fatigue.

Methods: We analyzed data from a randomized clinical trial comparing cognitive behavioral therapy for insomnia (CBT-I) versus acupuncture for insomnia among cancer survivors. Participants were 109 patients who reported insomnia and moderate or worse fatigue. Interventions were delivered over eight weeks. Fatigue was evaluated at baseline, week 8, and week 20 using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). We used both mediation analysis and t-tests to explore the extent to which fatigue reduction was attributable to insomnia response.

Results: Compared to baseline, both CBT-I and acupuncture produced significant reductions in total MFSI-SF scores at week 8 (−17.1 points; 95% confidence interval [CI]: −21.1 to −13.1, and −13.2 points; 95% CI: -17.2 to -9.2, respectively, all $p<0.001$) and week 20 (-14.6 points; 95% CI: -18.6 to -10.6, and −14.2 points; 95% CI: -18.1 to -10.3. respectively, all $p<0.001$), with no significant between-group differences. MFSI-SF total scores at week 8 were significantly associated with sleep improvements in both CBT-I and acupuncture groups ($p<0.001$ and $p=0.011$, respectively). Insomnia responders demonstrated significantly greater improvements in mean MFSI-SF total scores compared with non-responders in the CBT-I group ($p=0.016$) but not in the acupuncture group.

Conclusion: CBT-I and acupuncture produced similar, clinically meaningful, and durable fatigue reductions in cancer survivors with insomnia, primarily through improvements in sleep. Acupuncture may also reduce fatigue through additional pathways.

1. Introduction

Fatigue is one of the most prevalent, distressing, and persistent symptoms experienced by cancer survivors.[1,2] In a survey of 3032 survivors with diverse cancer types, approximately 30% had moderate to severe fatigue lasting months or even years after treatment completion.[3-5] Additionally, survivors reported that fatigue had worsened their quality of life, limited their ability to work, imposed burdens on family members and caregivers, and prevented them from leading "normal" lives.[6-8] In a survey of 379 survivors who had undergone chemotherapy, a quarter reported that fatigue was the side effect with the greatest impact after treatment completion,[8] lasting longer than all other common symptoms including nausea, depression, and pain.[8] However, there is still no widely accepted standard to manage cancer-related fatigue and a lack of evidence to guide personalized care.[2,8,9]

Insomnia treatment studies may provide relevant information for the management of fatigue. Research indicates that fatigue and insomnia have a close, reciprocal relationship.[10-12] In cancer pa-

* Corresponding author at: Integrative Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 321 East 61st Street, 4th Floor, New York, NY 10065, United States.
E-mail address: maoj@mskcc.org (J.J. Mao).

https://doi.org/10.1016/j.imr.2023.100922
2213-4220/

tients, insomnia is a significant predictor of severe fatigue and increases the risk for persistent fatigue, while fatigue increases both sleep disturbance and psychological distress in patients with insomnia.[13-19] Since fatigue and insomnia frequently coexist and are strongly associated, interventions that are effective for insomnia may also help with fatigue.[20,21] It is important to identify treatments that effectively target both fatigue and insomnia, thus reducing the need for multiple interventions for comorbid symptoms.

Insomnia interventions hold great potential for fatigue reduction. Among these, two non-pharmacological therapies are especially promising: acupuncture and cognitive behavioral therapy for insomnia (CBT-I). Both have demonstrated the ability to produce clinically meaningful reductions in insomnia among survivors of diverse cancer types[22 23.24,25] Preliminary evidence suggests that acupuncture and CBT-I may also effectively reduce fatigue compared with placebo, usual care, and wakefulness-promoting medications such as armodafinil.[26,27] However, these findings have significant limitations: the acupuncture studies were small and limited to breast cancer patients, while the CBT-I studies assessed only total fatigue scores, despite the fact that fatigue is a mutidimensional construct.[28] Thus, greater evidence is urgently needed to assess whether these interventions are, indeed, effective for fatigue in diverse cancer patients with comorbid insomnia.[29]

To address this critical issue, we sought to evaluate whether CBT-I and acupuncture can effectively reduce fatigue associated with comorbid insomnia. Through a randomized trial, we compared the effectiveness of acupuncture versus CBT-I for reducing fatigue in a sample of diverse cancer survivors with insomnia. Due to the observed relationships between insomnia and fatigue, we also assessed the extent to which any improvements in fatigue were attributable to a reduction in insomnia. Our findings may provide novel, preliminary evidence of tailored interventions for both insomnia and fatigue.

2. Methods

2.1. Study design

The present study is a secondary analysis of data from a dual-center, parallel group, randomized, comparative effectiveness trial evaluating acupuncture versus CBT-I for insomnia in cancer survivors.[22,30] The study was conducted from March 2015 to July 2017. Interventions were administered over eight weeks, and outcomes were assessed at baseline, week 8, and week 20. The institutional review boards at the University of Pennsylvania and Memorial Sloan Kettering Cancer Center approved this trial (ClinicalTrials.gov identifier NCT02356575).

2.2. Participants and procedures

Patients diagnosed with cancers of all types and stages were eligible for the parent study if they were: (1) English speaking; (2) had completed active treatment (surgery, chemotherapy, and/or radiotherapy) at least one month prior to enrollment; (3) met the criteria for insomnia disorder as defined by the Diagnostic and Statistical Manual of Mental disorders, 5th Edition (DSM-5)[31]; and (4) scored at least 8 on the Insomnia Severity Index (ISI) .[32] We excluded patients with: (1) diagnosis of a sleep disorder other than insomnia, such as delayed/advanced sleep phase syndrome or restless legs syndrome; (2) prior or ongoing receipt of acupuncture or CBT-I; (3) employment in shift work that would impair the ability to establish a regular sleep schedule; and (4) presence of a psychiatric disorder with no adequate treatment. Participants using psychotropic medications (e.g., antidepressants, hypnotics, or sedatives) were eligible as long as the dose had been stable over the prior six weeks.

This secondary analysis was further limited to participants who reported moderate or worse fatigue at baseline, as assessed by the Patient Reported Outcomes Measurement Information System-Global Health Scale-fatigue item (PROMIS-GHS-fatigue).[33] PROMIS-GHS-fatigue is an item in PROMIS-GHS, a validated ten-item patient-reported-outcomes survey assessing key health-related quality of life domains (pain, fatigue, mental health, social health, and overall health).[34,35] Items may be evaluated separately to assess specific domains. PROMIS-GHS-fatigue has five response choices for fatigue severity: none, mild, moderate, severe, and very severe.

After initial screening, trained research staff interviewed participants to review their insomnia diagnoses and confirm eligibility. Eligible patients provided informed consent and completed baseline assessments. Participants were then randomly assigned to receive CBT-I or acupuncture in a 1:1 ratio using permuted block randomization, with a biostatistician generating the randomization sequence prior to recruitment. Allocation concealment was executed through sealed envelopes. Participants received randomization information after baseline assessments. All study investigators including the primary investigators, co-investigators, outcome assessors, and statisticians were blinded to treatment assignments. Participants, research coordinators, and treatment practitioners were not blinded.

2.3. Interventions

CBT-I is a manualized, multicomponent intervention that improves sleep through behavioral modifications that restructure habits and thoughts that contribute to insomnia.[36,37] The intervention consists of five components: sleep restriction, stimulus control, cognitive restructuring, relaxation training, and education. Four licensed CBT-I therapists and five psychology trainees delivered the intervention. Participants each received seven CBT-I sessions over eight weeks: six weekly sessions, with a final session at week 8. The first session was 60 minutes, and the remaining sessions were 30 minutes each.

Acupuncture is a component of traditional Chinese medicine (TCM) that promotes the healing process by stimulating strategic areas in the body using thin, sterile, single-use, metallic needles.[38] Acupuncture for insomnia follows a semifixed, manualized acupuncture protocol comprised of standardized points to address insomnia (Bilateral: Shenmen [HT.7], Sanyinjiao [SP. 6]; Midline: Baihui [GV. 20], Shenting [GV. 24]; Unilateral: Shenmen [Auricular], Sympathetic [Auricular]) and additional points to manage comorbid symptoms (e.g., pain, anxiety), with a total of 8–16 points. Acupoint selection was based on a TCM acupuncture textbook[39] with incorporation of points that were commonly used for treating pain, anxiety, and insomnia in cancer survivors.[40,41] The acupuncture protocol was verified through consultations with local and China-based acupuncturists. Four licensed acupuncturists delivered the intervention by manipulating the needles to achieve “De Qi,” a sensation of soreness, numbness, fullness, burning, heaviness, and/or aching around acupoints.[42] Participants received a total of ten treatments over eight weeks: two treatments per week for two weeks, followed by six weekly treatments. The first acupuncture visit was 60 minutes, and subsequent sessions lasted 30 minutes each.

2.4. Outcomes

2.4.1. Fatigue severity

The Multidimensional Fatigue Inventory-Short Form (MFSI-SF) is a 30-item self-report fatigue instrument that has been val-

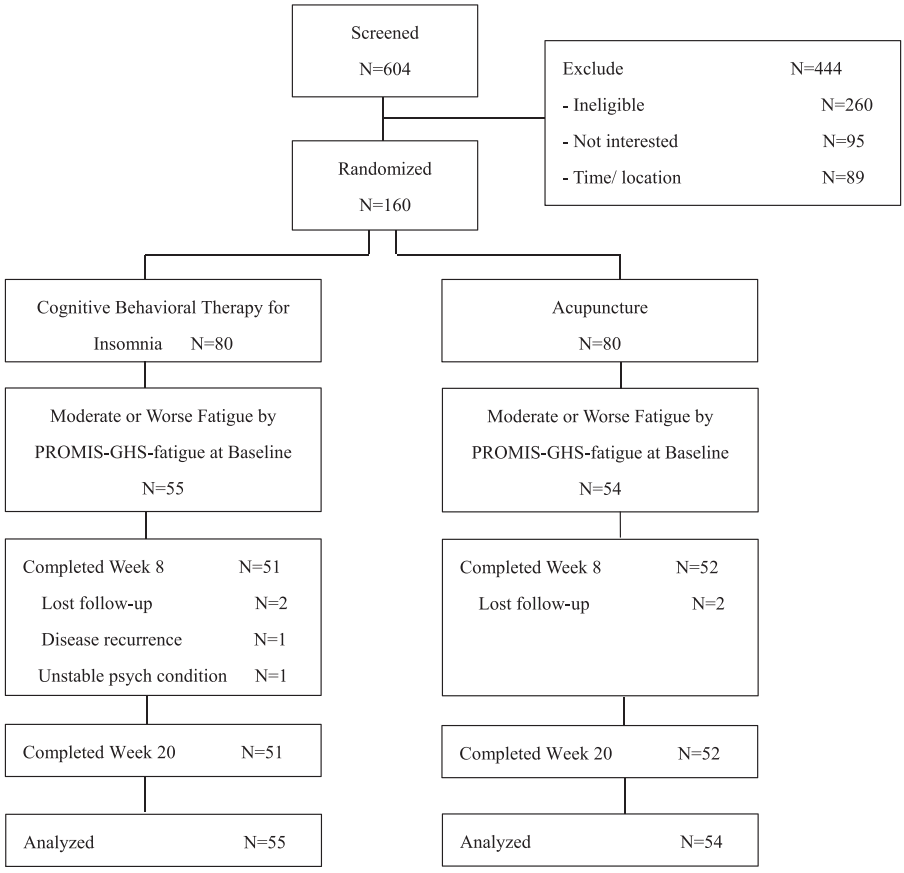

Fig. 1. Consort Diagram.
Abbreviation: PROMIS-GHS-fatigue, Patient Reported Outcomes Measurement Information System-Global Health Scale-fatigue item.

idated in cancer populations.[43] It assesses five empirically derived domains: general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor.[44] Items are rated on a five-point Likert scale ranging from 0 (Not at all) to 4 (Extremely). Total scores, calculated by subtracting the vigor score from the sum of the other four domains, range from −24 to 96, with higher scores indicating more severe fatigue. According to the established minimal clinically important difference range (4.50 to 10.79 points),[45] we conservatively defined a meaningful fatigue treatment response as a total MFSI-SF score reduction ≥10.[46] This approach is consistent with another study conducted in the cancer population.[46] Thus, participants with a reduction of ten or more points on the MFSI-SF scale from baseline were considered "fatigue responders."

2.4.2. Insomnia severity

ISI is a validated self-report instrument measuring subjective insomnia symptoms, consequences, and associated distress over the prior two weeks.[47] This seven-item questionnaire has been applied across a wide range of populations including cancer survivors.[48] Items are scored on a five-point Likert scale, ranging from 0 to 4, with higher scores representing more severe insomnia symptoms. Items are then summed to generate total scores of 0 to 28. Clinically meaningful cutoff values are: <8 (no insomnia), 8 to 14 (mild insomnia), 15 to 21 (moderate insomnia), and 22 to 28 (severe insomnia).[49] A reduction of eight or more points on the ISI scale indicates clinically significant improvement[32]; therefore, participants with a reduction of eight or more points on the ISI scale from baseline to week 8 (end of treatment) were considered "insomnia responders."

2.5. Statistical analysis

Data were analyzed following intent-to-treat (ITT) principles. The sample size of 109 participants was predetermined by the parent study.[22] Descriptive statistics were used to assess fatigue severity and demographic and clinical characteristics (e.g., age, gender, and cancer type) at baseline.

To examine the mean change in MFSI-SF scores (including total scores and individual domains) in both treatment groups from baseline to weeks 8 and 20, we built a linear mixed-effects model.[50] We used a subject-specific random intercept to account for the correlation between repeated measures of the outcome. Fixed effects included treatment, time, treatment by time interaction, and baseline outcome. We further compared fatigue responders to non-responders in both groups using Chi-square tests.

To explore the relationship between sleep improvement and fatigue reduction, we conducted mediation analyses in each treatment group. We built linear regression models with week 8 MFSI-SF total scores as the dependent variable and baseline MFSI-SF total scores as the independent variable. ISI change scores from baseline to week 8 were added to the models. Additionally, to further facilitate clinical interpretation of the results, we dichotomized participants into insomnia responders and non-responders using ISI. We used 2-sample t-tests to assess whether mean changes in MFSI-SF total scores differed between insomnia responders and non-responders within each treatment group. All analyses were two-sided with a p-value of less than 0.05 for statistical significance. Statistical analyses were conducted using STATA (version 15.0; STATA Corporation, College Station, TX) and SAS (version 9.4; SAS Institute, Inc, Cary, NC).

Table 1
Emographic and clinical characteristics.

Characteristics	Total (n = 109)		CBT-I (n = 55)		Acupuncture (n = 54)	
	No.	%	No.	%	No.	%
Age, mean (SD)	60.42 (11.8)		60.15 (11.9)		60.70 (11.8)	
Gender						
Male	42	38.5	18	32.7	24	44.4
Female	67	61.5	37	67.3	30	55.6
Race						
White	75	69.4	34	63.0	41	75.9
Non-white*	33	30.6	20	37.0	13	24.1
Education						
High school or less	12	11.0	3	5.5	9	16.7
College or above	97	89.0	52	94.6	45	83.3
Cancer type						
Breast	37	33.9	20	36.4	17	31.5
Prostate	18	16.5	9	16.4	9	16.7
Other†	54	49.5	26	47.3	28	51.9
Years since cancer diagnos, mean (SD)	6.14 (5.68)		6.15 (6.35)		6.13 (4.97)	
ISI total score, mean (SD)	19.0 (4.0)		19.2 (4.3)		18.7 (3.6)	
MFSI-SF total score, mean (SD)	28.8 (20.8)		30.9 (20.0)		26.7 (21.6)	
PROMIS-fatigue						
Moderate	63	57.8	30	54.5	33	61.1
Severe	36	33.0	18	32.7	18	33.3
Very severe	10	9.2	7	12.7	3	5.56

Abbreviations: CBT-I, Cognitive Behavioral Therapy for Insomnia; ISI, Insomnia Severity Index; MFSI-SF, Multidimensional Fatigue Inventory-Short Form; PROMIS-fatigue, Patient Reported Outcomes Measurement Information System-Global Health Scale-fatigue.
*Non-white includes Black, Asian, and more than one race.
†Other cancer types includes colorectal, head and neck, hematologic, gynecologic, other cancers, and more than one cancer type.

3. Results

3.1. Participant enrollment and characteristics

As previously reported,[22] we screened 604 cancer survivors between February 2015 and March 2017. A total of 160 were enrolled in the parent study and randomized to either CBT-I or acupuncture, with 80 patients in each group. Among these, 109 (68.1% of parent study participants) reported moderate or worse fatigue at baseline and were included in this secondary analysis. All 109 completed insomnia and fatigue assessments at baseline and went on to receive CBT-I (n=55) or acupuncture (n=54). A total of 103 participants (51 CBT-I and 52 acupuncture) completed week 8 and week 20 assessments. All 109 participants were included in this analysis (Fig. 1).

Table 1 shows participants' demographic and clinical characteristics. The mean age was 60.4 years (standard deviation [SD], 11.8 years). The majority of participants were women (67, 61.5%) and those who self-identified their race as white (76, 69.7%). Nearly all (97, 89.0%) had at least a college-level education. Diverse cancer types were represented, the most common being breast (33.9%) and prostate (16.5%). The mean time since diagnosis was 6.14 years (SD, 5.68 years). Nearly half of participants (47.7%) were diagnosed as stage 0-I, followed by stage II (23.9%), stage III (17.4%), and stage IV (8.3%). CBT-I and acupuncture participants were similar in all characteristics.

3.2. Insomnia and fatigue severity at baseline

CBT-I and acupuncture participants showed similar fatigue and insomnia severity at baseline. Mean ISI total insomnia scores were 19.2 (SD 4.3) in the CBT-I group and 18.7 (SD, 3.6) in the acupuncture group. As per PROMIS-GHS-fatigue, 30 of 55 CBT-I patients (55%) had moderate fatigue, 18 (33%) had severe fatigue, and 7 (13%) had very severe fatigue. Similarly, 33 of 54 acupuncture participants (61%) had moderate fatigue, 18 (33%) had severe fatigue, and 3 (6%) had very severe fatigue. Mean MFSI-SF total fatigue scores were 30.9 (SD, 20.0) in the CBT-I group and 26.7 (SD, 21.6) in the acupuncture group.

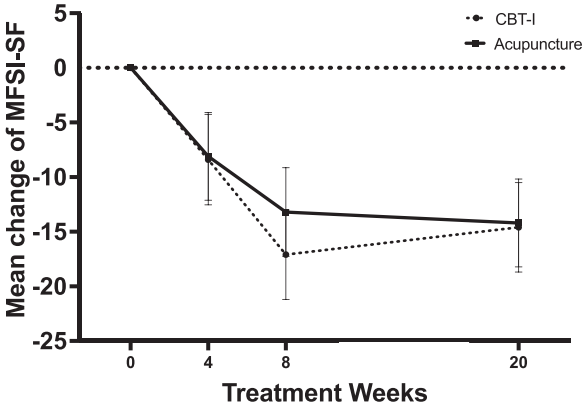

Fig. 2. Mean Change in MFSI-SF Over Time.
Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; MFSI-SF, Multidimensional Fatigue Inventory-Short Form.

3.3. The effects of acupuncture and CBT-I on fatigue

Acupuncture and CBT-I were associated with similar, clinically meaningful reductions in fatigue from baseline, with mean changes in MFSI-SF total scores at week 8 and week 20 indicating short- and long-term fatigue improvements (all p<0.001) (Fig. 2) (Table 2). At week 8, reduction in fatigue was 17.1 points in the CBT-I group (95% confidence interval [CI]: −21.1 to −13.1) and 13.2 points in the acupuncture group (95% CI: −17.2 to −9.2). At week 20 follow-up, the improvement of fatigue among patients receiving both treatments remained stable at (CBT-I: −14.6 points [95% CI: −18.6 to −10.6]; acupuncture: −14.2 points [95% CI: −18.1 to −10.3]). The between group difference was not statistically significant (p=0.49).

Table 2
Mean change from baseline in MFSI-SF domains by treatment group.

	CBT-I		Acupuncture		Between-group difference	
	Mean change (95% CI)	P	Mean change (95% CI)	P	Mean change (95% CI)	P
Total Fatigue Score						0.49
Week 8	−17.1 (−21.1 to −13.1)	<0.001	−13.2 (−17.2 to −9.2)	<0.001	3.9 (−1.7 to 9.5)	
Week 20	−14.6 (−18.6 to −10.6)	<0.001	−14.2 (−18.1 to −10.3)	<0.001	0.4 (−5.2 to 6.0)	
General						0.21
Week 8	−5.4 (−6.9 to −3.9)	<0.001	−3.8 (−5.2 to −2.4)	<0.001	1.6 (−0.4 to 3.6)	
Week 20	−4.6 (−6.0 to −3.2)	<0.001	−4.8 (−6.2 to −3.4)	<0.001	−0.2 (−2.2 to 1.8)	
Emotional						0.84
Week 8	−2.8 (−3.8 to −1.8)	<0.001	−2.6 (−3.6 to −1.6)	<0.001	0.2 (−1.2 to 1.6)	
Week 20	−1.9 (−2.9 to −0.9)	0.0002	−2.4 (−3.4 to −1.4)	<0.001	−0.4 (−1.8 to 1.0)	
Physical						0.72
Week 8	−1.9 (−3.0 to −0.8)	0.0007	−2.4 (−3.5 to −1.3)	<0.001	−0.5 (−2.1 to 1.1)	
Week 20	−1.7 (−2.8 to −0.6)	0.0024	−2.6 (−3.7 to −1.5)	<0.001	−0.9 (−2.4 to 0.6)	
Mental						0.019*
Week 8	−3.9 (−4.8 to −3.0)	<0.001	−2.1 (−3.0 to −1.2)	<0.001	1.8 (0.5 to 3.1)	
Week 20	−3.8 (−4.7 to −2.9)	<0.001	−2.0 (−2.9 to −1.1)	<0.001	1.8 (0.5 to 3.1)	
Vigor						0.83
Week 8	3.2 (2.0 to 4.4)	<0.001	2.5 (1.3 to 3.7)	<0.001	−0.8 (−2.5 to 0.9)	
Week 20	2.6 (1.4 to 3.8)	<0.001	2.4 (1.2 to 3.6)	<0.001	−0.2 (−1.9 to 1.5)	

For total fatigue score and general, emotional, physical, and mental domains, greater reduction indicates more improvement of fatigue relief. For vigor domain, greater increase indicates more improvement of fatigue relief.
Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; MFSI-SF, Multidimensional Fatigue Inventory-Short Form; 95% CI, 95% confidence interval.
* p (overall model) <0.05.

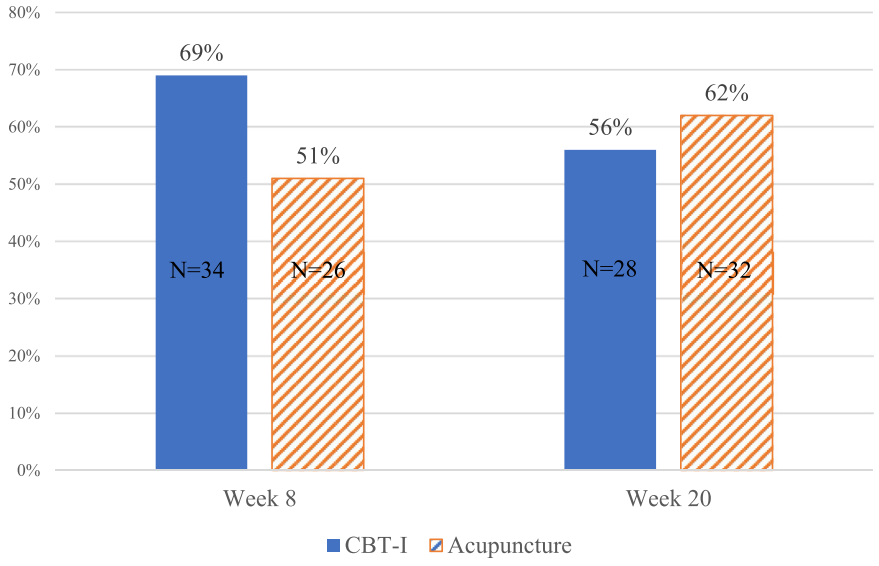

Fig. 3. Proportion of Responder Rate by MFSI-SF at Week 8 and Week 20.
Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; MFSI-SF, Multidimensional Fatigue Inventory-Short Form.

To further explore patients' response to CBT-I and acupuncture, we conducted additional analysis comparing fatigue responders and non-responders (Fig. 3). Although not statistically significant, patients receiving CBT-I had an 18% greater treatment response rate than those receiving acupuncture at week 8 (69% vs. 51%, p=0.06); however, by week 20, the treatment response rate by CBT-I was 6% less than that by acupuncture (56% vs. 62%, p=0.57).

In both interventions, a reduction in fatigue was observed across all MFSI-SF domains, with participants reporting greater vigor as well as improved general, emotional, physical, and mental fatigue at weeks 8 and 20 (all p<0.05). CBT-I demonstrated slightly greater mental fatigue improvement (1.8 points, 95% CI: 0.5 to 3.1) than acupuncture at both timepoints (p=0.019). No significant differences between CBT-I and acupuncture were observed for other fatigue domains.

3.4. Relationship between insomnia treatment response and reductions in fatigue

MFSI-SF total scores at week 8 were statistically significantly associated with ISI change scores from baseline to week 8 in both CBT-I and acupuncture groups. A 1-point reduction in ISI change scores was associated with an increase in MFSI-SF total scores (increased fatigue) at week 8 by 1.4 points in the CBT-I group (95% CI=0.7 – 2.0, p<0.001) and by 1.0 point in the acupuncture group (95% CI=0.2 – 1.8, p=0.011).

Among the 100 participants who completed the MFSI-SF and ISI assessments at baseline and week 8, mean MFSI-SF total scores indicate that insomnia responders (71 participants with ISI reductions of ≥8+ points) reported greater, clinically meaningful reductions in fatigue compared to non-responders (29 participants)

(−18.2 [SD=17.1] vs −7.1 [SD=9.4]; p=0.001). However, closer analysis showed that the relationship between insomnia response and fatigue response varied by treatment. In the CBT-I group, insomnia responders (38 participants) experienced greater, clinically meaningful reductions in mean MFSI-SF total scores compared with non-responders (11 participants) (−19.8 [SD=15.5] vs −7.5 [SD=9.7], p=0.016). In the acupuncture group, there was a non-statistically significant difference in mean MFSI-SF total scores between insomnia responders (33 participants) and non-responders (18 participants) (−16.4 [SD=18.9] vs −6.9 [SD=9.5]; p=0.052).

4. Discussion

This is the first study to compare CBT-I and acupuncture for fatigue in cancer survivors with insomnia. We found that both treatments delivered short- and long-term improvements in all domains of fatigue, primarily through improvements in sleep. This finding suggests that CBT-I and acupuncture are potentially effective treatment options for diverse cancer patients with fatigue and comorbid insomnia.

Our study contributes to a growing body of research reporting the beneficial effects of CBT-I on fatigue in cancer survivors.[51-53] However, to our knowledge, only two studies have evaluated the role of CBT-I on fatigue among cancer patients with insomnia.[27,54] Our study is consistent with both in showing that CBT-I produces significant and durable fatigue reduction with moderate to large effects. However, our study also explored the relationship between fatigue reduction and sleep improvement with CBT-I and found that insomnia responders achieved significantly greater fatigue reduction than non-responders. These results indicate that the observed fatigue relief may primarily derive from improved sleep after CBT-I. While current evidence consistently supports the role of CBT-I in fatigue reduction among cancer patients, there is still a need to evaluate the effect of CBT-I on fatigue unrelated to insomnia. As such, the results of this study should be interpreted with caution, especially for those without sleep difficulties.

To our knowledge, our study is the largest yet to assess the effect of acupuncture on fatigue in cancer survivors with insomnia. The only other study to address this topic had a sample size of 52 participants and compared auricular acupuncture to psychoeducation on fatigue severity, measured by Functional Assessment of Chronic Illness Therapy-Fatigue among breast cancer survivors with insomnia.[55] Consistent with our study, auricular acupuncture also significantly improved fatigue post-treatment, but the treatment effect was not as durable as in our study. It is worth noting that auricular acupuncture is a method in which needles are only inserted at specific points on the outer ear, whereas acupuncture in our trial used both body and auricular acupoints.[56] A study in a non-cancer population found that the combination of body and auricular acupuncture produced better fatigue reduction than a single modality.[57] There is also evidence that stimulating different acupoints may produce different therapeutic effects around fatigue in breast cancer survivors.[58] With accumulating evidence showing the effectiveness of acupuncture for cancer related fatigue,[58-60] more studies are needed to evaluate and compare the benefits of different acupuncture approaches.

Our study also contributes other novel research findings. It is particularly noteworthy that, in contrast to participants receiving CBT-I in our study, insomnia responders in the acupuncture group did not experience significantly greater fatigue reduction than non-responders. These results suggest that acupuncture may improve fatigue through mechanisms unrelated to sleep quality, such as increased daytime alertness and reduced sleepiness.[61] Therefore, acupuncture may be able to improve fatigue even when insomnia persists. However, the difference in MFSI-SF between insomnia responders and non-responders receiving acupuncture was close to significant with a p value of 0.052. It is possible that the limited sample size may have insufficient power to detect significant differences. Therefore, additional research is needed to explore these clinically important questions.

Similarly, our results suggest opportunities to better tailor fatigue interventions to diverse cancer patients and survivors. Since reduction in fatigue was mainly driven by sleep improvement, but patients appear to respond differently to these two interventions. More research is needed to explore the optimal way to deliver precision and tailored fatigue management according to an individual's experience of fatigue (cognitive, mental, physical, etc.), comorbid symptoms and the therapeutic characteristics of different interventions.

Optimal patient care also means screening for and managing fatigue and insomnia concurrently. Fatigue and insomnia are highly related and frequently co-exist in cancer patients.[10,11] According to a survey of breast cancer survivors receiving aromatase inhibitors who experienced clinically significant insomnia, the majority (93.4%) also reported moderate to severe fatigue.[16] In the 160 trial participants, 68.1% also had moderate or greater fatigue at baseline. As our study showed that both CBT-I and acupuncture produced promising effects for both symptoms, treatment choices may be based on patients' preference and the availability of providers. Notably, however, current medical resources for the two interventions are unequal: patients often have limited access to CBT-I,[62] while acupuncture has become the most common integrative medicine approach among National Cancer Institute–Designated Comprehensive Cancer Centers.[63,64] It is vital that healthcare payers and policymakers expand patient access to both CBT-I and acupuncture.

Our study has several limitations. First, since this is a secondary analysis, the sample size was not calculated to assess fatigue outcomes, which may limit the power to interpret the results. Second, our trial was designed as a pragmatic trial comparing two active interventions, so we do not have usual care or waitlist control arms. Some of the observed changes may be due to a natural progression of symptoms. However, cancer-related fatigue is persistent and prior trials of acupuncture or CBT-I have already demonstrated the effectiveness of these interventions relative to usual care or other controls.[27,60] Third, our study did not capture or control for other interventions (e.g., physical therapy or medications) that participants may have been using to manage fatigue. However, it should be noted that current clinical practice guidelines do not include specific recommendations regarding standard therapy for fatigue.[9] Fourth, the design and primary goal of the parent study was for insomnia management rather than fatigue. Thus, interventions were designed to address insomnia, while the population in the secondary analysis was limited to patients with both symptoms. Finally, this study was conducted in a large, urban academic cancer institute, where patients may have high adherence. Our findings may not be generalizable in other contexts or patient populations.

Nonetheless, this study has important strengths. We used multiple instruments previously validated in cancer populations to broadly evaluate the effects of both interventions on fatigue. Unlike most prior studies, we only included patients with clinically meaningful fatigue at baseline to avoid a floor effect. Moreover, we comprehensively assessed interventions across multiple domains of fatigue, and we investigated the extent to which reduction in fatigue was related to improved insomnia.

In conclusion, CBT-I and acupuncture hold promise for cancer survivors experiencing insomnia and fatigue, with both interventions yielding clinically meaningful and durable improvements in sleep and across all domains of fatigue, primarily through improvements in sleep. But acupuncture may also reduce fatigue through additional, yet unidentified pathways. Further research should ver-

ify these results and explore the optimal way to deliver more effective and personalized treatment using the two interventions for cancer survivors experiencing these common and burdensome symptoms.

Acknowledgements

The authors would like to thank Christina Seluzicki, in the Integrative Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, for her editorial assistance.

Conflict of interests

The authors declare the following financial relationships: JJM reports grants from Tibet CheeZheng Tibetan Medicine Co. Ltd. and from Zhongke Health International LLC outside the submitted work. Other authors declare no conflicts of interest.

Funding

This research was supported by Patient-Centered Outcomes Research Institute (PCORI) award (grant number CER-1403–14292). This research was also supported in part by a National Institutes of Health /National Cancer Institute (NCI) Cancer Center grant (number P30 CA008748).

Ethical statement

This research was reviewed and approved by the institutional review boards of the University of Pennsylvania (IRB Number: 821,497) and Memorial Sloan Kettering Cancer Center (IRB Number:16–947). Informed consent was obtained from all participants.

Data availability

The data of this study will be available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Xiaotong Li: Conceptualization, Methodology, Writing – original draft. **Kevin T. Liou:** Writing – review & editing. **Susan Chimonas:** Writing – review & editing. **Karolina Bryl:** Writing – review & editing. **Greta Wong:** Writing – review & editing. **Eugenie Spiguel:** Writing – review & editing. **Susan Q. Li:** Formal analysis. **Sheila N. Garland:** Writing – review & editing. **Ting Bao:** Writing – review & editing. **Jun J. Mao:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

References

1. Mock V, Atkinson A, Barsevick A, Cella D, Cimprich B, Cleeland C, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology (Williston Park)*. 2000;14(11a):151–161.
2. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J Natl Cancer Inst Monogr*. 2004(32):40–50.
3. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-related fatigue, version 2.2015. *J Natl Compr Canc Netw*. 2015;13(8):1012–1039.
4. Wang XS, Zhao F, Fisch MJ, O'Mara AM, Cella D, Mendoza TR, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer*. 2014;120(3):425–432.
5. Mohandas H, Jaganathan SK, Mani MP, Ayyar M, Rohini Thevi GV. Cancer-related fatigue treatment: an overview. *J Cancer Res Ther*. 2017;13(6):916–929.
6. Brown DJ, McMillan DC, Milroy R. The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. *Cancer*. 2005;103(2):377–382.
7. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. *J Clin Oncol*. 2000;18(4):743–753.
8. Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist*. 2000;5(5):353–360.
9. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*. 2014;32(17):1840.
10. Yennurajalingam S, Palmer JL, Zhang T, Poulter V, Bruera E. Association between fatigue and other cancer-related symptoms in patients with advanced cancer. *Support Care Cancer*. 2008;16(10):1125–1130.
11. Kim SJ, Kim S, Jeon S, Leary EB, Barwick F, Mignot E. Factors associated with fatigue in patients with insomnia. *J Psychiatr Res*. 2019;117:24–30.
12. O'Donnell JF. Insomnia in cancer patients. *Clin Cornerstone*. 2004;6(1):S6–S14.
13. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol*. 2001;19(3):895–908.
14. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. *Eur J Cancer Care (Engl)*. 2001;10(4):245–255.
15. KO Anderson, Getto CJ, Mendoza TR, Palmer SN, Wang XS, Reyes-Gibby CC, et al. Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. *J Pain Symptom Manage*. 2003;25(4):307–318.
16. Mao H, Bao T, Shen X, Li Q, Seluzicki C, Im E-O, et al. Prevalence and risk factors for fatigue among breast cancer survivors on aromatase inhibitors. *Eur J Cancer*. 2018;101:47–54.
17. Aikens JE, Rouse ME. Help-seeking for insomnia among adult patients in primary care. *J Am Board Fam Pract*. 2005;18(4):257–261.
18. Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, Morin CM. Relations between sleep, fatigue, and health-related quality of life in individuals with insomnia. *J Psychosom Res*. 2010;69(5):475–483.
19. Alapin I, Fichten CS, Libman E, Creti L, Bailes S, Wright J. How is good and poor sleep in older adults and college students related to daytime sleepiness, fatigue, and ability to concentrate? *J Psychosom Res*. 2000;49(5):381–390.
20. Dirksen SR, Belyea MJ, Epstein DR. Fatigue-based subgroups of breast cancer survivors with insomnia. *Cancer Nurs*. 2009;32(5):404–411.
21. Roscoe JA, Kaufman ME, Matteson-Rusby SE, Palesh OG, Ryan JL, Kohli S, et al. Cancer-related fatigue and sleep disorders. *Oncologist*. 2007;12(1):35–42 Suppl.
22. Garland SN, Xie SX, DuHamel K, Bao T, Li Q, Barg FK, et al. Acupuncture Versus Cognitive Behavioral Therapy for Insomnia in Cancer Survivors: a Randomized Clinical Trial. *J Natl Cancer Inst*. 2019;111(12):1323–1331.
23. Jang A, Brown C, Lamoury G, Morgia M, Boyle F, Marr I, et al. The Effects of Acupuncture on Cancer-Related Fatigue: updated Systematic Review and Meta–Analysis. *Integr Cancer Ther*. 2020;19:1534735420949679.
24. Aricò D, Raggi A, Ferri R. Cognitive behavioral therapy for insomnia in breast cancer survivors: a review of the literature. *Front Psychol*. 2016;7:1162.
25. Ma Y, Hall DL, Ngo LH, Liu Q, Bain PA, Yeh GY. Efficacy of cognitive behavioral therapy for insomnia in breast cancer: a meta-analysis. *Sleep Med Rev*. 2021;55:101376.
26. Fleming L, Randell K, Harvey CJ, Espie CA. Does cognitive behaviour therapy for insomnia reduce clinical levels of fatigue, anxiety and depression in cancer patients? *Psychooncology*. 2014;23(6):679–684.
27. Heckler CE, Garland SN, Peoples AR, Perlis ML, Shayne M, Morrow GR, et al. Cognitive behavioral therapy for insomnia, but not armodafinil, improves fatigue in cancer survivors with insomnia: a randomized placebo-controlled trial. *Support Care Cancer*. 2016;24(5):2059–2066.
28. Bower JE. Cancer-related fatigue–mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11(10):597–609.
29. Zee PC, Ancoli-Israel S. Does effective management of sleep disorders reduce cancer-related fatigue? *Drugs*. 2009;69(2):29–41.
30. Liou KT, Root JC, Garland SN, Green J, Li Y, Li QS, et al. Effects of acupuncture versus cognitive behavioral therapy on cognitive function in cancer survivors with insomnia: a secondary analysis of a randomized clinical trial. *Cancer*. 2020;126(13):3042–3052.
31. Guha M. Diagnostic and statistical manual of mental disorders: DSM-5. *Reference Reviews*. 2014.
32. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34(5):601–608.
33. Darrith B, Khalil LS, Franovic S, Bazydlo M, Weir RM, Banka TR, et al. Preoperative Patient-Reported Outcomes Measurement Information System Global Health Scores Predict Patients Achieving the Minimal Clinically Important Difference in the Early Postoperative Time Period After Total Knee Arthroplasty. *J Am Acad Orthop Surg*. 2021;29(24):e1417–e1e26.
34. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res*. 2009;18(7):873–880.
35. Bevans M, Ross A, Cella D. Patient-Reported Outcomes Measurement Information System (PROMIS): efficient, standardized tools to measure self-reported health and quality of life. *Nurs Outlook*. 2014;62(5):339–345.
36. Bennett D. *Cognitive-Behavioral Therapy for Insomnia (CBT-I)* Sleep Medicine and Mental Health: Springer; 2020:47–66.

37. Woodward SC. Cognitive-behavioral therapy for insomnia in patients with cancer. *Clin J Oncol Nurs*. 2011;15(4).
38. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med*. 2002;136(5):374–383.
39. Cheng X, Deng L. *Chinese acupuncture and moxibustion*. Foreign Language Press Beijing; 1999.
40. Mao JJ, Bruner DW, Stricker C, Farrar JT, Xie SX, Bowman MA, et al. Feasibility trial of electroacupuncture for aromatase inhibitor—Related arthralgia in breast cancer survivors. *Integr Cancer Ther*. 2009;8(2):123–129.
41. Mao JJ, Xie SX, Farrar JT, Stricker CT, Bowman MA, Bruner D, et al. A randomised trial of electro-acupuncture for arthralgia related to aromatase inhibitor use. *Eur J Cancer*. 2014;50(2):267–276.
42. MacPherson H, Asghar A. Acupuncture needle sensations associated with De Qi: a classification based on experts' ratings. *J Altern Complement Med*. 2006;12(7):633–637.
43. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *J Pain Symptom Manage*. 2004;27(1):14–23.
44. Donovan KA, Stein KD, Lee M, Leach CR, Ilozumba O, Jacobsen PB. Systematic review of the multidimensional fatigue symptom inventory-short form. *Support Care Cancer*. 2015;23(1):191–212.
45. Chan A, Lew C, Wang XJ, Ng T, Chae JW, Yeo HL, et al. Psychometric properties and measurement equivalence of the Multidimensional Fatigue Syndrome Inventory- Short Form (MFSI-SF) amongst breast cancer and lymphoma patients in Singapore. *Health Qual Life Outcomes*. 2018;16(1):20.
46. Chan A, Yo TE, Wang XJ, Ng T, Chae JW, Yeo HL, et al. Minimal clinically important difference of the multidimensional fatigue symptom inventory-short form (MFSI-SF) for fatigue worsening in Asian breast cancer patients. *J Pain Symptom Manage*. 2018;55(3):992–997 .e2.
47. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2(4):297–307.
48. Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. *Psychooncology*. 2005;14(6):429–441.
49. Thorndike FP, Ritterband LM, Saylor DK, Magee JC, Gonder-Frederick LA, Morin CM. Validation of the insomnia severity index as a web-based measure. *Behav Sleep Med*. 2011;9(4):216–223.
50. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982:963–974.
51. Squires LR, Rash JA, Fawcett J, Garland SN. Systematic review and meta-analysis of cognitive-behavioural therapy for insomnia on subjective and actigraphy-measured sleep and comorbid symptoms in cancer survivors. *Sleep Med Rev*. 2022;63:101615.
52. Bean HR, Diggens J, Ftanou M, Alexander M, Stafford L, Bei B, et al. Light enhanced cognitive behavioral therapy for insomnia and fatigue during chemotherapy for breast cancer: a randomized controlled trial. *Sleep*. 2022;45(3).
53. Garland SN, Johnson JA, Savard J, Gehrman P, Perlis M, Carlson L, et al. Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatr Dis Treat*. 2014;10:1113–1124.
54. Espie CA, Fleming L, Cassidy J, Samuel L, Taylor LM, White CA, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. *J Clin Oncol*. 2008;26(28):4651–4658.
55. Höxtermann MD, Buner K, Haller H, Kohl W, Dobos G, Reinisch M, et al. Efficacy and safety of auricular acupuncture for the treatment of insomnia in breast cancer survivors: a randomized controlled trial. *Cancers (Basel)*. 2021;13(16).
56. Hou P-W, Hsu H-C, Lin Y-W, Tang N-Y, Cheng C-Y, Hsieh C-L. The history, mechanism, and clinical application of auricular therapy in traditional Chinese medicine. *Evid-Based Complement Altern Med*. 2015 2015.
57. Chung KF, Yeung WF, Yu BY, Leung FC, Zhang SP, Zhang ZJ, et al. Acupuncture with or without combined auricular acupuncture for insomnia: a randomised, waitlist-controlled trial. *Acupunct Med*. 2018;36(1):2–13.
58. Zick SM, Sen A, Wyatt GK, Murphy SL, Arnedt JT, Harris RE. Investigation of 2 types of self-administered acupressure for persistent cancer-related fatigue in breast cancer survivors: a randomized clinical trial. *JAMA Oncol*. 2016;2(11):1470–1476.
59. Zhang Y, Lin L, Li H, Hu Y, Tian L. Effects of acupuncture on cancer-related fatigue: a meta-analysis. *Support Care Cancer*. 2018;26(2):415–425.
60. Molassiotis A, Bardy J, Finnegan-John J, Mackereth P, Ryder DW, Filshie J, et al. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. *J Clin Oncol*. 2012;30(36):4470–4476.
61. Harris RE, Ichesco E, Cummiford C, Hampson JP, Chenevert TL, Basu N, et al. Brain connectivity patterns dissociate action of specific acupressure treatments in fatigued breast cancer survivors. *Front Neurol*. 2017;8:298.
62. Koffel E, Bramoweth AD, Ulmer CS. Increasing access to and utilization of cognitive behavioral therapy for insomnia (CBT-I): a narrative review. *J Gen Intern Med*. 2018;33(6):955–962.
63. Brauer JA, El Sehamy A, Metz JM, Mao JJ. Complementary and alternative medicine and supportive care at leading cancer centers: a systematic analysis of websites. *J Alternat Complement Med*. 2010;16(2):183–186.
64. Zia FZ, Olaku O, Bao T, Berger A, Deng G, Yin Fan A, et al. The National Cancer Institute's conference on acupuncture for symptom management in oncology: state of the science, evidence, and research gaps. *JNCI Monographs*. 2017;2017(52):lgx005.