Effects of Acupuncture Versus Cognitive Behavioral Therapy on Cognitive Function in Cancer Survivors With Insomnia: A Secondary Analysis of a Randomized Clinical Trial

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BACKGROUND: Cancer-related cognitive impairment is a prevalent, disruptive condition potentially exacerbated by sleep disturbances. The current study was performed to evaluate the effects of acupuncture versus cognitive behavioral therapy for insomnia (CBT-I) on objective and subjective cognitive function in cancer survivors with insomnia. **METHODS:** Using data from a randomized clinical trial (160 survivors) that compared acupuncture versus CBT-I for insomnia occurring in cancer survivors, the authors analyzed cognitive outcomes and their relationship to insomnia symptoms. Analysis was limited to 99 patients who reported baseline cognitive difficulties. Interventions were delivered over 8 weeks. Objective attention, learning, and memory were evaluated using the Buschke Selective Reminding Test. Subjective cognitive function was assessed using the Brown Attention-Deficit Disorder Scales. Insomnia symptoms were assessed using the Insomnia Severity Index. All outcomes were collected at baseline, week 8, and week 20. **RESULTS:** From baseline to week 8, acupuncture produced statistically significant within-group improvements in objective attention (Cohen *D*, 0.29), learning (Cohen *D*, 0.31), and memory (Cohen *D*, 0.33) that persisted to week 20 (all $P < .05$), whereas CBT-I produced a statistically significant within-group improvement in objective attention from baseline to week 20 (Cohen *D*, 0.50; $P < .05$); between-group differences were not statistically significant. Both interventions produced statistically significant within-group improvements in subjective cognitive function at weeks 8 and 20 compared with baseline (all $P < .001$); between-group differences were not statistically significant. In the acupuncture group, patients with clinically meaningful responses with regard to insomnia symptoms demonstrated a significantly greater improvement in subjective cognitive function compared with those without clinically meaningful insomnia responses ($P = .006$). **CONCLUSIONS:** Among cancer survivors with insomnia, both acupuncture and CBT-I produced significant improvements in objective and subjective cognitive function. However, the effect sizes varied and only survivors in the acupuncture group demonstrated a significant relationship between cognitive and sleep outcomes. These preliminary findings warrant further investigation to guide the personalized management of patients with cancer-related cognitive impairment. ***Cancer* 2020;126:3042-3052**. *© 2020 American Cancer Society*.

KEYWORDS: acupuncture, cancer, cognitive behavior therapy, cognitive impairment, comparative effectiveness, insomnia.

INTRODUCTION

Cancer-related cognitive impairment (CRCI) is a prevalent, disruptive condition occurring among cancer survivors.[1] Characterized by problems with memory, attention, executive function, and psychomotor speed, CRCI contributes to increased distress, diminished self-confidence, difficulties with performing daily activities, negative financial and social impacts, and poor quality of life.[2,3] To our knowledge, the majority of studies regarding CRCI have focused on patients with breast cancer[4-8]; however, growing research also has been conducted in other cancer populations, including individuals with prostate cancer,[9,10] colorectal cancer,[11] lymphoma,[12] and ovarian cancer.[13] The estimated prevalence of CRCI varies widely across studies, but has been reported to be as high as 81%.[14] Despite its variable presentation, CRCI is almost universally feared in the cancer population. In a recent study of 121 older adults with diverse cancer types who were initiating chemotherapy, >80% viewed preservation of their cognitive function as more important than their long-term survival.[15]

Emerging evidence has suggested that CRCI is not simply a consequence of chemotherapy exposure ("chemo-brain") but rather a multidimensional problem influenced by diverse factors, including treatment history

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(eg, chemotherapy, endocrine therapy, surgery, and radiotherapy), biological characteristics (eg, inflammation and genetic predisposition), sociodemographic characteristics (eg, age, race/ethnicity, and education level), lifestyle (eg, smoking and exercise), and psychosocial influences (eg, stress, anxiety, and depression).[1,5,16,17] A growing body of research has examined the role of sleep in cogniton.[18-21] It is well documented that sleep is required for normal functioning of key cognitive processes such as memory consolidation.[22-24] Recent studies also have demonstrated significant associations between sleep disturbances and cognitive difficulties in cancer populations.[25-28] In a cross-sectional analysis of 1072 breast cancer survivors, approximately 71.7% of patients with severe insomnia reported moderate or greater cognitive difficulties compared with only 20.0% of patients without insomnia.[28] Thus, improving sleep has been identified as a potential management strategy for patients with CRCI.[29-31]

To our knowledge to date, research has been limited regarding the treatment of CRCI through modulation of sleep. As first-line therapy for insomnia,[32] cognitive behavioral therapy for insomnia (CBT-I) has demonstrated robust efficacy in treating insomnia in cancer populations,[33,34] but its effects on CRCI remain unclear. A recent systematic review (18 studies, each with a sample size of 7 to 229 patients) identified preliminary evidence that CBT-I produces small to moderate effects on subjective cognitive function.[35] However, only 6 studies were conducted in cancer populations; of the 4 studies that evaluated the effects of CBT-I on objective cognition, none included cancer survivors. Acupuncture, an integrative modality that originated from traditional Chinese medicine, has demonstrated promising effects on insomnia in both general[36,37] and cancer populations,[38,39] but to our knowledge only one small trial in China has demonstrated preliminary effects on subjective and objective cognitive function among 80 patients undergoing active treatment for breast cancer and notably did not include any assessments of sleep.[40] These scientific gaps need to be addressed to determine whether targeting sleep disturbances through nonpharmacologic interventions can improve CRCI in cancer survivors.

In our recently published comparative effectiveness trial, both acupuncture and CBT-I produced clinically meaningful improvements in insomnia symptoms among survivors of diverse cancer types.[39] In the study reported herein, we conducted secondary analyses of the parent trial above to generate hypotheses regarding the effects of acupuncture versus CBT-I on objective and subjective cognitive function in cancer survivors with insomnia. These preliminary findings will guide future research on personalized interventions for CRCI that target comorbid sleep disturbances.

MATERIALS AND METHODS

Study Design, Participants, and Procedures

The current study was embedded in a recently published dual-center, parallel group, 2-arm, randomized comparative effectiveness trial that evaluated acupuncture versus CBT-I for the treatment of insomnia in cancer survivors.[39] Interventions were delivered over 8 weeks. Outcomes were assessed at baseline, at week 8 (end of the intervention), and at week 20 (12 weeks after the intervention). Recruitment and interventions occurred from March 2015 to April 2017; follow-up assessments were completed in July 2017. The primary findings of the parent study, including the effects and safety of these interventions for insomnia, have been published elsewhere.[39] The study was approved by the institutional review boards at the University of Pennsylvania and Memorial Sloan Kettering Cancer Center (ClinicalTrials.gov identifier NCT02356575).

English-speaking adult patients diagnosed with cancer of all types and stages were eligible. Active treatment with surgery, chemotherapy, and/or radiotherapy must have been completed at least 1 month prior to study initiation. Patients also were required to score ≥8 on the Insomnia Severity Index (ISI)[41] and meet the criteria for insomnia disorder as defined by the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*.[42] Exclusion criteria included: 1) the presence of another sleep disorder not adequately treated (eg, delayed/advanced sleep phase syndrome, obstructive sleep apnea, or restless leg syndrome); 2) previous insomnia treatment with acupuncture or CBT-I; 3) the presence of a psychiatric disorder not adequately treated (eg, major depressive disorder, bipolar disorder, schizophrenia, generalized anxiety disorder, posttraumatic stress disorder, or dementia); and 4) employment in shift work that would impair the individual's ability to establish a regular sleep schedule. Trained research staff conducted a diagnostic interview with patients to confirm their study eligibility.

During the diagnostic interview, all patients also were asked whether they were experiencing cognitive difficulties and if they were interested in completing optional cognitive testing during the study. Those who replied "yes" to both questions were invited to complete the cognitive assessments at baseline, week 8, and week 20 (described under "Outcomes"); these patients were included in the current study.

After eligibility was confirmed, patients provided informed consent. Patients were sequentially randomized in a 1:1 ratio to 1 of the 2 treatment conditions using permuted block randomization with a secure computer system that ensured full allocation concealment. The study investigators, including outcome assessors, were blinded to treatment assignment. The study protocol has been described in detail separately.[43]

Interventions

Acupuncture, a therapeutic modality derived from traditional Chinese medicine, involves the insertion of thin, sterile, single-use, metallic needles into the body surface.[44] It is considered safe with few side effects.[45] Acupuncture services are available in approximately 75% of academic cancer centers in the United States.[46] Globally, its availability at cancer centers varies widely across other countries, with estimates ranging from 12% to 55% in non-Asian countries to as high as 90% in China.[47,48] For the parent trial, we used a semifixed, manualized acupuncture protocol that consisted of standardized points to address insomnia and supplementary points to treat comorbid symptoms (eg, anxiety or pain) if indicated. Participants received a total of 10 acupuncture treatments over 8 weeks (ie, twice per week for the first 2 weeks, then weekly for the 6 remaining weeks).

CBT-I is a manualized, multicomponent intervention that includes sleep restriction, stimulus control, cognitive restructuring, relaxation training, and sleep hygiene education.[32] Four licensed therapists and 5 psychology trainees delivered the CBT-I intervention. Patients received a total of 7 sessions over 8 weeks (ie, 5 weekly sessions of CBT-I followed by 2 biweekly sessions). The treatment protocols are available in the Supporting Information.

Outcomes

Objective cognitive function

The Buschke Selective Reminding Test (BSRT) provides an objective validated measure of attention, learning, and memory.[49,50] It consists of a 16-noun word list that is read to patients at a rate of 1 word every 2 seconds. Patients are given 6 trials to attempt to recall as many words as possible. In trial 1, they are instructed to immediately recall as many words as possible after the entire list is read. In subsequent trials, the patients are selectively reminded of the words that they had not recalled on the preceding trial. This process is repeated until trial 6 is completed. Approximately 15 minutes after trial 6 is completed or 30 minutes after the initiation of trial 1, patients are instructed to recall the entire list of 16 words without any further reminders. Our analyses focused on 3 specific trials: 1) trial 1 (immediate recall), which measured attention; trial 6 (after multiple trials of selective reminding), which measured learning; and 3) the delayed recall trial, which measured memory. Three alternate equivalent forms were used at baseline, week 8, and week 20 to control for practice effects.[51] Higher scores indicated a greater number of recalled words (ie, better objective cognitive function).

Subjective cognitive function

The Brown Attention-Deficit Disorder Scales (BADDS) is a widely used instrument that has been validated to evaluate cognitive symptoms in adults (Cronbach α, .69-.81).[52] This 40-item instrument asks patients to rate on a 4-point scale (with 0 indicating never, 1 indicating once a week or less, 2 indicating twice a week, and 3 indicating almost daily) how frequently they were bothered by cognitive difficulties in the following domains: 1) organization (eg, difficulties in getting organized, initiating work-related tasks, or self-activating for daily routines); 2) attention (eg, difficulties in sustaining attention on tasks); 3) alertness (eg, daytime drowsiness, slowed processing of information, inadequate task completion, or difficulties in maintaining consistent alertness and effort for work-related tasks); 4) affective interference (eg, difficulties with mood, sensitivity to criticism, apparent lack of motivation, excessive frustration, or discouragement); and 5) memory (eg, forgetfulness in daily tasks and routines, losing track of needed items, and difficulties with recall of learned material). A total score is calculated by summing the domain scores. Total scores range from 0 to 120, with higher scores indicating worse subjective cognitive function and scores >50 considered to be clinically significant.[52]

Insomnia Severity

The ISI provides a reliable measure of insomnia and has been validated in cancer populations with a Cronbach α of .90.[53] This 7-item instrument evaluates the subjective symptoms and consequences of insomnia as well as the degree of associated distress. Items are scored on a 5-point scale, with higher scores representing more severe insomnia symptoms. A score >14 indicates

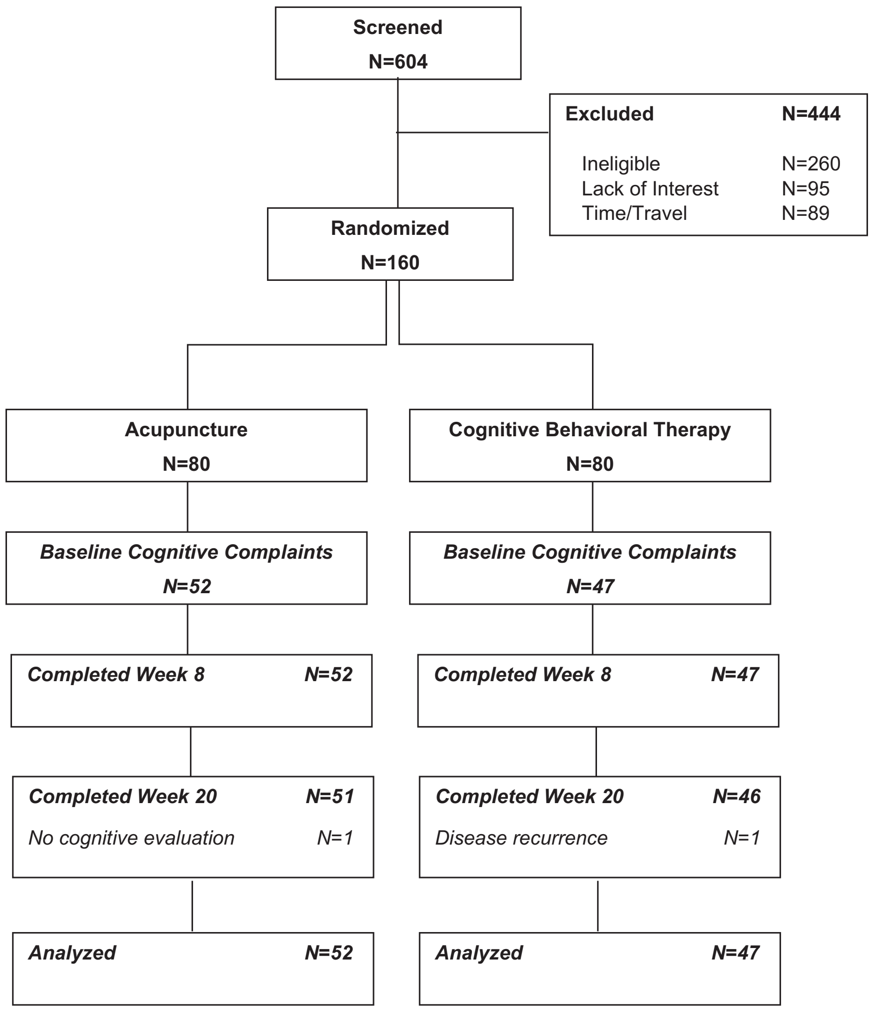

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. This figure describes participant flow through the study. The italicized sections refer to the current study that is embedded in the parent randomized clinical trial.

clinically significant insomnia.[53] The ISI also has demonstrated sensitivity to change and can be used to evaluate treatment response.[54] A reduction of ≥8 points on the ISI score after treatment is considered a clinically meaningful response to an intervention, and patients who meet this threshold are considered insomnia treatment responders.[54]

Statistical Analyses

The analyses in the current study were guided by intention-to-treat principles. We examined the change in mean BSRT and BADDS scores in both treatment groups from baseline to weeks 8 and 20 using a linear mixed-effects model.[55] The fixed effects were treatment, time, treatment by time interaction, and baseline outcome. Subject-specific random intercepts were used to account for the correlation between repeated outcome measures. To estimate the effect sizes of acupuncture and CBT-I, we calculated the Cohen *D* for statistically significant within-group changes in objective and subjective cognitive outcomes from baseline to weeks 8 and 20. To explore the relationship between sleep and cognition function within the context of insomnia treatment, we used 2-sample Student *t* tests to examine whether the mean changes in BSRT and BADDS scores differed between insomnia treatment responders versus nonresponders by treatment group. The sample size was predetermined by the parent study.[39] All statistical tests were 2-sided. Statistical significance was set at $P < .05$. All statistical analyses were conducted using Stata (version 12.0; StataCorp LLC, College Station, Texas) and SAS (version 9.4; SAS Institute Inc, Cary, North

Carolina) statistical software. Given that data were secondary outcomes from the parent trial, these analyses were hypothesis-generating rather than confirmatory.

RESULTS

Between February 2015 and March 2017, we screened 604 patients for eligibility. Among these, 444 patients were excluded due to ineligibility, lack of interest, lack of time, or inability to travel to study appointments. The remaining 160 patients were randomly assigned to receive acupuncture (80 patients) or CBT-I (80 patients) in the parent study. Of these 160 patients, 99 (62%) reported cognitive difficulties at baseline and were included in the study reported herein. Among these 99 patients, 52 were assigned to receive acupuncture and 47 were assigned to receive CBT-I. All 99 patients completed the cognitive assessments at baseline and week 8. Between weeks 8 and 20, 1 patient in each group withdrew from the study due to an inability to complete cognitive assessments (acupuncture group) and disease recurrence (CBT-I group). Figure 1 summarizes participant flow through the study.

Treatment groups were similar with regard to baseline sociodemographic and clinical characteristics (Table 1). The mean age of the patients was 60.4 years (SD, 11.8 years), 56.6% (56 patients) were women, and 26.3% (26 patients) were nonwhite. The most common cancer types were breast (31.3%) and prostate (19.2%). The majority of patients were diagnosed as stage I (50.5%), stage II (15.2%), or stage III (23.2%). The median time since the cancer diagnosis was 5.9 years (interquartile range, 0.9-22.3 years).

Treatment groups also demonstrated similar symptom profiles at baseline (Table 2). Clinically significant cognitive difficulties (ie, BADDS total score >50) were reported at baseline by 20 patients in the acupuncture group (38.5%) and 23 patients in the CBT-I group (48.9%). Clinically significant insomnia symptoms (ie, ISI total score >14) were reported at baseline by 41 patients in the acupuncture group (78.9%) and 40 patients in the CBT-I group (85.1%).

Effects on Objective Cognitive Function

Acupuncture produced statistically significant increases in the number of words recalled in trial 1, trial 6, and the delayed recall trial at weeks 8 and 20 compared with baseline (all $P < .05$), indicating short-term and long-term improvements in objective attention, learning, and memory, respectively. By contrast, CBT-I only demonstrated a statistically significant increase in the number of words recalled in trial 1 at week 20 compared with baseline ($P < .001$), suggesting a delayed improvement in objective attention. The between-group differences were not statistically significant.

For BSRT trial 1 (ie, objective attention), acupuncture demonstrated small effects at week 8 (Cohen *D*, 0.29) and week 20 (Cohen *D*, 0.29), whereas CBT-I demonstrated small to moderate effects at week 8 (Cohen *D*, 0.25) and week 20 (Cohen *D*, 0.50). For BSRT trial 6 (ie, objective learning), acupuncture demonstrated small effects at week 8 (Cohen *D*, 0.31) and week 20 (Cohen *D*, 0.31), whereas CBT-I demonstrated minimal effects

TABLE 1. Sociodemographic and Clinical Characteristics

Characteristics	Total No.	Total %	Acupuncture No.	Acupuncture %	CBT-I No.	CBT-I %
	99	100.0	52	52.5	47	47.5
Mean age (SD), y	60.4 (11.8)		60.6 (11.6)		60.3 (12.1)	
<65 y	59	59.6	35	67.3	24	51.1
≥65 y	40	40.4	17	32.7	23	48.9
Sex						
Male	43	43.4	25	48.1	18	38.3
Female	56	56.6	27	51.9	29	61.7
Race						
White	73	73.7	38	73.1	35	74.5
Nonwhite	26	26.3	14	26.9	12	25.5
Education						
Elementary school	1	1.0	1	1.9	0	0
High school graduate	7	7.1	5	9.6	2	4.3
Some college or trade school	14	14.1	7	13.5	7	14.9
College graduate	29	29.3	15	28.9	14	29.8
Graduate school degree	48	48.5	24	46.2	24	51.1
Employment						
Full time	38	38.4	22	42.3	16	34
Part time	18	18.2	10	19.2	8	17
Not currently employed	43	43.4	20	38.5	23	48.9
Cancer type[a]						
Breast	31	31.3	14	26.9	17	36.2
Prostate	19	19.2	12	23.1	7	14.9
Other	49	49.6	26	50.1	23	49.0
Cancer stage						
0-I	53	53.5	28	53.8	25	53.2
II	15	15.2	8	15.4	7	14.9
III	23	23.2	12	23.1	11	23.4
IV	6	6.1	3	5.8	3	6.4
Unknown	2	2.0	1	1.9	1	2.1
Cancer treatments[b]						
Surgery	80	80.8	43	82.6	37	78.7
Chemotherapy	48	48.5	24	46.2	24	51.1
Radiotherapy	53	53.5	28	53.8	25	53.2
Hormonal	20	20.2	11	21.2	9	19.2
Median y since cancer diagnosis (IQR)	5.9 (0.9-22.3)		5.7 (2.3-10.8)		6.1 (1.4-17.4)	

Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; IQR, interquartile range.

[a]Other cancer types included colorectal, head and neck, hematologic, gynecologic, skin, lung, other gastrointestinal, other genitourinary, and >1 cancer type.

[b]Subjects could have received >1 type of cancer treatment.

TABLE 2. Baseline Symptom Profile

	Total N = 99	Acupuncture N = 52	CBT-I N = 47
BSRT			
Objective cognitive function			
Trial 1 (attention) score, mean (SD)	6.3 (2.5)	6.5 (2.7)	6.2 (2.2)
Trial 6 (learning) score, mean (SD)	11.1 (3.3)	11.0 (3.1)	11.2 (3.5)
Delayed recall (memory) score, mean (SD)	9.7 (4.1)	9.4 (4.2)	10.0 (4.0)
BADDS			
Subjective cognitive function			
BADDS total score, mean (SD)	47.6 (22.7)	44.7 (22.4)	50.8 (22.7)
BADDS total score >50, no. (%)[a]	43 (43.4)	20 (38.5)	23 (48.9)
ISI			
ISI total score, mean (SD)	18.3 (4.1)	18.0 (4.3)	18.7 (4.0)
ISI total score >14, no. (%)[a]	81 (81.8)	41 (78.8)	40 (85.1)

Abbreviations: BADDS, Brown Attention-Deficit Disorder Scales; BSRT, Buschke Selective Reminding Test; CBT-I, cognitive behavioral therapy for insomnia; ISI, Insomnia Severity Index.
[a]Clinically significant.

at these time points. For the BSRT delayed recall test (ie, objective memory), acupuncture demonstrated small effects at week 8 (Cohen *D*, 0.33) and week 20 (Cohen *D*, 0.39), whereas CBT-I demonstrated minimal effects at these time points. Table 3 summarizes the mean changes in BSRT scores by treatment group and between-group differences.

Effects on Subjective Cognitive Function

Acupuncture and CBT-I produced statistically significant within-group reductions in mean BADDS total scores at weeks 8 and 20 compared with baseline (all $P < .001$), indicating short-term and long-term improvements in subjective cognitive function. Acupuncture demonstrated moderate effects at week 8 (Cohen *D*, 0.54) and week 20 (Cohen *D*, 0.65), whereas CBT-I demonstrated moderate to large effects at week 8 (Cohen *D*, 0.73) and week 20 (Cohen *D*, 0.84). These between-group differences were not statistically significant. Table 4 summarizes the mean change in BADDS total scores by treatment group and between-group differences.

Relationship Between Insomnia and Cognitive Function

Among the 99 patients who reported baseline cognitive difficulties, both acupuncture and CBT-I produced statistically significant and clinically meaningful improvements in the ISI score from baseline to week 8. Acupuncture decreased the ISI score by 9.0 points ($P < .001$), whereas CBT-I decreased the ISI score by 11.9 points ($P < .001$); the between-group difference was 2.3 points (95% CI, 0.3-4.3 points; $P = 0.023$).

Among all 99 patients, there was no statistically significant difference noted between insomnia treatment responders (71 patients) versus nonresponders (28 patients) with regard to mean changes in BSRT scores (ie, objective cognition) from baseline to week 8 (all $P > .05$); however, insomnia treatment responders demonstrated a statistically significant greater reduction in BADDS total scores (ie, subjective cognition) compared with nonresponders (score change, −16.0 [SD, 16.1] vs −6.6 [SD, 10.4]; $P = .006$).

When stratified by treatment group, the mean changes in BSRT scores from baseline to week 8 did not demonstrate statistically significant differences between insomnia treatment responders versus nonresponders (all $P > .05$) in the acupuncture or CBT-I groups. However, within the acupuncture group, insomnia treatment responders (32 patients) demonstrated a statistically significant greater reduction in BADDS total scores compared with nonresponders (20 patients) (−16.2 [SD, 16.0] vs −4.5 [SD, 10.5]; $P = .006$), whereas in the CBT-I group, the insomnia treatment responders (39 patients) did not demonstrate a statistically significant greater reduction in BADDS total scores compared with nonresponders (8 patients) (−15.8 [SD, 16.5] vs −11.9 [SD, 18.8]; $P = .51$).

DISCUSSION

With the number of cancer survivors in the United States expected to exceed 20 million by 2026,[56] there is a pressing need to address CRCI, a prevalent, disruptive condition occurring within this growing population. In this dual-center comparative effectiveness trial of diverse cancer survivors with insomnia, both acupuncture and CBT-I demonstrated promising effects on objective and subjective cognitive function. However, the effect sizes varied by treatment group, and a significant relationship between cognitive and sleep outcomes was observed only in the acupuncture group, suggesting that these 2 interventions may differentially target cognitive domains through distinct mechanisms. This preliminary evidence should be leveraged in future studies to refine and personalize interventions for CRCI.

Despite growing research, to our knowledge the optimal treatment of CRCI has not been definitively established. Wakefulness-promoting agents, such as modafinil, have produced encouraging results in pilot placebo-controlled trials,[57,58] but these findings have not been confirmed in larger trials, and one study failed to demonstrate significant improvements in cognition.[59] Other oral agents, such as methylphenidate,[60] memantine,[61]

TABLE 3. Mean Change From Baseline in BSRT Test Scores by Treatment Group

	Acupuncture		CBT-I		Between-Group Difference	
	Mean Change (95% CI)	*P*	Mean Change (95% CI)	*P*	Mean Change (95% CI)	*P*
Trial 1 (attention)						.32
Wk 8	0.7 (0.1 to 1.3)	.017	0.6 (−0.005 to 1.2)	.054	0.1 (−0.7 to 1.0)	
Wk 20	0.7 (0.1 to 1.3)	.024	1.2 (0.6 to 1.8)	.0002	−0.5 (−1.4 to 0.3)	
Trial 6 (learning)						.64
Wk 8	0.8 (0.04 to 1.6)	.040	0.4 (−0.4 to 1.2)	.35	0.4 (−0.7 to 1.6)	
Wk 20	1.2 (0.5 to 2.0)	.0021	0.8 (−0.04 to 1.6)	.065	0.5 (−0.6 to 1.6)	
Delayed recall (memory)						.18
Wk 8	1.0 (0.4 to 1.7)	.0020	0.6 (−0.06 to 1.3)	.077	0.4 (−0.5 to 1.4)	
Wk 20	1.4 (0.7 to 2.0)	<.001	0.5 (−0.2 to 1.1)	.18	0.9 (−0.05 to 1.8)	

Abbreviation: BSRT, Buschke Selective Reminding Test; CBT-I, cognitive behavioral therapy for insomnia.
Higher scores indicate better objective cognitive function.

TABLE 4. Mean Change From Baseline on BADDS Total Scores by Treatment Group

	Acupuncture		CBT-I		Between-Group Difference	
	Mean Change (95% CI)	*P*	Mean Change (95% CI)	*P*	Mean Change (95% CI)	*P*
Wk 8	−11.7 (−15.7 to −7.7)	<.0001	−15.2 (−19.3 to −11.0)	<.0001	3.5 (−2.3 to 9.2)	.28
Wk 20	−14.4 (−18.4 to −10.4)	<.0001	−18.9 (−23.1 to −14.7)	<.0001	4.5 (−1.3 to 10.3)	

Abbreviations: BADDS, Brown Attention-Deficit Disorder Scales; CBT-I, cognitive behavioral therapy for insomnia.
Lower scores indicate better subjective cognitive function.

donepezil,[62] gingko biloba,[63] and estradiol,[64] have shown poor or mixed results, and several have adverse side effect profiles.[1,65] Polypharmacy remains a significant concern in the cancer population,[66,67] particularly among elderly patients, who are disproportionately affected by CRCI.[1] As such, the National Comprehensive Cancer Network recommends pharmacologic interventions as a last line of therapy for patients with CRCI,[68] highlighting the importance of developing and evaluating nonpharmacological approaches for this condition. Cognitive rehabilitation and/or training,[69-73] physical activity,[74-78] yoga,[79-81] qi gong,[82] and mindfulness techniques[83,84] have demonstrated preliminary benefits for subjective and/or objective cognitive function in cancer populations, but these findings need to be confirmed in larger, rigorously designed trials. The results of the current study have contributed to this growing literature by highlighting 2 other nonpharmacological interventions that warrant further investigation in the development of effective treatments of CRCI.

An increasing number of studies have evaluated the cognitive effects of acupuncture,[85-88] but to the best of our knowledge few have been conducted in cancer populations. In a randomized controlled trial of 80 Chinese patients with breast cancer who were undergoing chemotherapy,[40] acupuncture significantly improved subjective cognitive function (as measured by the Functional Assessment of Cancer Therapy–Cognitive Function [FACT-Cog]) and objective cognitive performance (as measured by the Rey Auditory-Verbal Learning Test and clock drawing test) compared with usual care; however, the durability of these effects after treatment was not assessed. The current study found that acupuncture produced significant, small to moderate improvements in objective and subjective cognition that persisted up to 12 weeks after the intervention. In the Chinese trial described above, acupuncture also produced a significant increase in serum brain-derived neurotrophic factor (BDNF) compared with usual-care controls; the change in BDNF correlated with improvements in cognitive function.[40] Given its hippocampal expression,[89,90] BDNF has been hypothesized to regulate key cognitive processes such as learning and memory, and also is thought to be involved in sleep homeostasis.[91,92] Taken together, these findings suggest that BDNF may play a key role in understanding the relationship between sleep and cognitive outcomes observed in the acupuncture group in the current study. The incorporation of relevant biomarkers[93-95] into future confirmatory trials will help to advance mechanistic understanding of acupuncture and its cognitive effects.

The results of the current study also have contributed to the emerging literature regarding the cognitive effects of CBT-I.[35] To our knowledge to date, research in cancer populations has been mixed, with some studies demonstrating a significant improvement in subjective cognitive outcomes from before to after the intervention,[96-98] and others noting only a trend toward significant improvement.[99,100] To the best of our knowledge, no CBT-I studies of patients with cancer have incorporated objective cognitive measures.[35] In the current study, we demonstrated that CBT-I produced significant, moderate to large improvements in subjective cognition that persisted up to 12 weeks after the intervention. Given that maladaptive thought processes may maintain and exacerbate perceived cognitive difficulties in cancer survivors,[101] it is perhaps not surprising that the cognitive restructuring component of CBT-I may produce benefits for subjective cognitive function. Other CBT-I components, such as eliciting the relaxation response, may target underlying mood disturbances (eg, anxiety) that have been shown to contribute to cognitive difficulties.[102,103] As such, future research should explore mood and other psychological factors as potential mechanisms for the cognitive effects of CBT-I. Finally, we found that CBT-I produced small to moderate improvements in objective attention at 12 weeks after the intervention. In a functional magnetic resonance imaging study of individuals with insomnia disorder, CBT-I reduced hyperresponsivity in the prefrontal cortex and insula,[104] both of which are critical brain regions involved in attentional processes,[105,106] thus providing a translational context for this finding.

As research accumulates regarding the link between sleep and cognition, there are efforts underway to investigate how to experimentally modulate sleep to enhance cognitive performance.[107] The current study has provided preliminary evidence that cancer survivors may experience cognitive benefits when their insomnia symptoms are addressed. In the acupuncture group, insomnia treatment responders reported significantly greater improvements in subjective cognitive function compared with nonresponders. Conversely, in the CBT-I group, there were no significant differences in subjective or objective cognitive outcomes observed between insomnia treatment responders versus nonresponders. These preliminary findings have suggested that acupuncture may improve specific aspects of cognition through mechanisms involving sleep, whereas CBT-I may affect cognitive function through other mechanisms; however, it is important to note that the current study lacked objective sleep measures and therefore we were unable to evaluate the relationship between objective sleep parameters and cognitive function. Given the well-documented discrepancies between objective and subjective outcomes in cognitive and sleep research,[108,109] future studies should incorporate both types of cognitive and/or sleep measures to comprehensively evaluate the mediating effects of sleep on cognitive outcomes within the context of treatment with acupuncture or CBT-I. This will facilitate the research and development of personalized interventions that target CRCI based on individual objective and/or subjective patterns of sleep and cognitive dysfunction.

The findings of the current study should be considered within the context of several limitations. First, the cognitive outcome measures and analyses were exploratory and hypothesis-generating; future research can use these findings to design adequately powered confirmatory trials. Second, this was a comparative effectiveness trial that evaluated 2 active interventions and lacked placebo and/or attention control groups and therefore the observed effects could not be separated from placebo or other nonspecific effects of the intervention. The acupuncture group received more therapist contact time compared with the CBT-I group, which may have contributed to nonspecific intervention effects. Given the lack of usual-care controls, regression to the mean and/or natural recovery of cognitive function over time also must be considered, although other studies have demonstrated that acupuncture and CBT-I significantly improved cognitive function compared with usual-care controls.[35,40] Third, the study participants were cancer survivors with insomnia who were well educated and thus may not be fully representative of the broader population with CRCI; however, based on prior research, approximately 74% to 79% of patients with breast cancer with moderate or greater perceived cognitive difficulties reported comorbid insomnia, suggesting that the population in the current study represented a significant percentage of patients with CRCI.[28] Last, we used cognitive measures that are validated but not commonly applied in oncology populations. Future research should follow the recommendations of the International Cognition and Cancer Task Force to improve research design and facilitate between-study comparisons and meta-analyses.[110]

Despite these limitations, to the best of our knowledge, the current study is the largest randomized clinical trial to date to explore the effects of acupuncture versus CBT-I on objective and subjective cognitive outcomes in cancer survivors. Other strengths include the dual-center conduct of the trial, excellent minority representation, strong adherence to interventions, long-term follow-up, and minimal missing data. The current study also used validated instruments to evaluate both objective and subjective cognition, enabling us to broadly capture the cognitive effects of the interventions. Based on our preliminary findings, acupuncture and CBT-I demonstrated promising differential effects on subjective and objective cognitive function in cancer survivors with insomnia. Further investigation of these 2 interventions is warranted to inform personalized management of CRCI.

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CONFLICT OF INTEREST DISCLOSURES

Philip W. Kantoff has received personal fees from Bavarian Nordic Immunotherpeutics; has received personal fees from and has a current investment interest in DRGT; has received personal fees from Genentech/Roche, Janssen, Merck, OncoCellMDx, Progenity, and Sanofi; has received personal fees from and had a prior investment interest in Tarveda Therapeutics (formerly Blend); has received personal fees from Thermo Fisher Scientific and GE Healthcare; has received personal fees from, has a current investment interest in, and is a company board member for Context Therapeutics; has received personal fees from New England Research Institutes Inc; has received personal fees from and has a current investment interest in SEER Biosciences; and has a current investment interest in Placon for work performed outside of the current study. Jun J. Mao has received grants from the Patient-Centered Outcomes Research Institute, National Institutes of Health/National Cancer Institute, and the Translational and Integrative Medicine Research Fund at Memorial Sloan Kettering Cancer Center for work performed as part of the current study and received grants from Tibet Cheezheng Tibetan Medicine Co Ltd and Zhongke Health International LLC for work performed outside of the current study. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Kevin T. Liou: Investigation, writing–original draft, and writing–review and editing. **James C. Root:** Methodology and writing–review and editing. **Sheila N. Garland:** Conceptualization, funding acquisition, and writing–review and editing. **Jamie Green:** Project administration, data curation, and writing–review and editing. **Yuelin Li:** Formal analysis and writing–review and editing. **Q. Susan Li:** Formal analysis and writing–review and editing. **Philip W. Kantoff:** Resources and writing–review and editing. **Tim A. Ahles:** Methodology and writing–review and editing. **Jun J. Mao:** Conceptualization, funding acquisition, investigation, supervision, and writing–review and editing.

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