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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Abstract

Background: Cancer-related cognitive impairment (CRCI) is a prevalent, disruptive condition potentially exacerbated by sleep disturbances. This study evaluated 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 (N=160) that compared acupuncture versus CBT-I for insomnia in cancer survivors, we analyzed cognitive outcomes and their relationship to insomnia symptoms. Analysis was limited to 99 patients reporting baseline cognitive difficulties. Interventions were delivered over 8 weeks. Objective attention, learning, and memory was evaluated with Buschke Selective Reminding Test (BSRT). Subjective cognitive function was assessed with Brown Attention-Deficit Disorder Scale (BADDs). Insomnia symptoms were...
assessed with Insomnia Severity Index (ISI). 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’s $D=0.29$), learning ($D=0.31$), and memory ($D=0.33$) that persisted to Week 20 (all $P<0.05$), whereas CBT-I produced a statistically significant within-group improvement in objective attention from baseline to Week 20 ($D=0.50$, $P<0.05$); 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 to baseline (all $P<0.001$); between-group differences were not statistically significant. In the acupuncture group, patients with clinically meaningful responses in insomnia symptoms demonstrated a significantly greater improvement in subjective cognitive function, compared to those without clinically meaningful insomnia responses ($P=0.006$).

**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 the acupuncture group demonstrated a significant relationship between cognitive and sleep outcomes. These preliminary findings warrant further investigation to guide personalized management of CRCI.

**Trial Registration:** ClinicalTrials.gov Identifier NCT02356575

**2-sentence Summary for Table of Contents:**

Cancer-related cognitive impairment is a prevalent, debilitating condition that may be exacerbated by poor sleep. This study demonstrated that acupuncture and cognitive-behavioral therapy for insomnia produced promising differential effects on objective and subjective cognitive function in cancer survivors with insomnia.

**Keywords**

Cognitive Impairment; Insomnia; Cancer; Cognitive Behavior Therapy; Acupuncture; Comparative Effectiveness

**INTRODUCTION**

Cancer-related cognitive impairment (CRCI) is a prevalent, disruptive condition among cancer survivors. Characterized by problems in memory, attention, executive function, and psychomotor speed, CRCI contributes to increased distress, diminished self-confidence, difficulties with performing daily activities, negative financial and social impact, and poor quality of life. The majority of studies on CRCI has focused on patients with breast cancer, however, growing research has also been conducted in other cancer populations, including prostate, colorectal, lymphoma, and ovarian. The estimated prevalence of CRCI varies widely across studies, but has been reported to be as high as 81%. 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 starting chemotherapy, over 80% viewed preservation of their cognitive function as more important than their long-term survival.
Emerging evidence suggests that CRCI is not simply a consequence of chemotherapy exposure (“chemo-brain”), but rather a multi-dimensional problem influenced by diverse factors, including treatment history (e.g. chemotherapy, endocrine therapy, surgery, radiation treatment), biological characteristics (e.g. inflammation, genetic predisposition), sociodemographics (e.g. age, race/ethnicity, education level), lifestyle (e.g. smoking, exercise) and psychosocial influences (e.g. stress, anxiety, depression). A growing body of research has examined the role of sleep in cognition. It is well-documented that sleep is required for normal functioning of key cognitive processes, such as memory consolidation. Recent studies have also demonstrated significant associations between sleep disturbances and cognitive difficulties in cancer populations. In a cross-sectional analysis of 1,072 breast cancer survivors, 71.7% of patients with severe insomnia reported moderate or greater cognitive difficulties, compared to only 20.0% of patients without insomnia. Thus, improving sleep has been identified as a potential management strategy for CRCI.

To date, research has been limited on the treatment of CRCI through modulation of sleep. As first-line therapy for insomnia, CBT-I has demonstrated robust efficacy in treating insomnia in cancer populations, but its effects on CRCI remain unclear. A recent systematic review (18 studies, sample size 7 to 229) identified preliminary evidence that CBT-I produces small to moderate effects on subjective cognitive function. However, only six studies were conducted in cancer populations; of the 4 studies that evaluated 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 and cancer populations, but 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. These scientific gaps need to be addressed to determine whether targeting sleep disturbances through non-pharmacologic 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. In the study reported here, we conducted secondary analyses of the parent trial above to generate hypotheses about 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 co-morbid sleep disturbances.

**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. Interventions were delivered over 8 weeks. Outcomes were assessed at baseline, Week 8 (end of intervention) and Week 20 (12 weeks post-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. The study was approved by the institutional review boards at the University of Pennsylvania and Memorial Sloan Kettering Cancer Center.

English-speaking adult patients of all cancer types and stages were eligible. Active treatment with surgery, chemotherapy, and/or radiotherapy must have been completed at least one month prior to study initiation. Patients were also required to score ≥8 on the Insomnia Severity Index and meet the criteria for insomnia disorder as defined by the Diagnostic and Statistical Manual of Mental disorders, 5th Edition (DSM-5). Exclusion criteria included: 1) presence of another sleep disorder not adequately treated (e.g. delayed/advanced sleep phase syndrome, obstructive sleep apnea, restless leg syndrome); 2) previous insomnia treatment with acupuncture or CBT-I; 3) presence of psychiatric disorder not adequately treated (e.g. major depressive disorder, bipolar disorder, schizophrenia, generalized anxiety disorder, post-traumatic stress disorder, dementia); and 4) employment in shift work that would impair 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 were also asked if 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 study reported here.

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

Interventions

Acupuncture, a therapeutic modality derived from Traditional Chinese Medicine (TCM), involves the insertion of thin, sterile, single-use, metallic needles into the body surface. It is considered safe with few side effects. Acupuncture services are available in approximately 75% of academic cancer centers in the United States. Globally, its availability at cancer centers varies widely across other countries, with estimates ranging from 12-55% in non-Asian countries to as high as 90% in China. For the parent trial, we used a semi-fixed manualized acupuncture protocol that consisted of standardized points to address insomnia and supplementary points to treat co-morbid symptoms (e.g. anxiety, pain) if indicated. Participants received acupuncture treatments a total of ten treatments over eight weeks, i.e. twice per week for the first two weeks, then weekly for the six remaining weeks.

CBT-I is a manualized multi-component intervention that includes sleep restriction, stimulus control, cognitive restructuring, relaxation training, and sleep hygiene education. Four licensed therapists and five psychology trainees delivered the CBT-I intervention. Patients received a total of seven sessions over eight weeks, i.e. five weekly sessions of CBT-I
followed by two bi-weekly sessions. The treatment protocols are available in Supplementary Materials.

Outcomes

**Objective Cognitive Function**—The Buschke Selective Reminding Test (BSRT) provides an objective validated measure of attention, learning and memory. 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 six 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 was 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 had been completed. Approximately fifteen minutes after Trial 6 is completed or thirty minutes after the initiation of Trial 1, patients are instructed to recall the entire list of 16 words without any further reminders. Our analyses focus on three specific trials: *Trial 1* (immediate recall), which measures attention; *Trial 6* (after multiple trials of selective reminding), which measures learning; and *Delayed Recall Trial*, which measures memory. Three alternate equivalent forms were used at baseline, Week 8, and Week 20 to control for practice effects. Higher scores indicate greater number of recalled words, i.e. better objective cognitive function.

**Subjective Cognitive Function**—The Brown Attention Deficit Disorder Scale (BADDS) is a widely used instrument that has been validated to evaluate cognitive symptoms in adults (Cronbach’s $\alpha$ 0.69-0.81). This 40-item instrument asks patients to rate on a 4-point scale (0 = never, 1 = once a week or less, 2 = twice a week, 3 = almost daily) how frequently they were bothered by cognitive difficulties in the following domains: 1) *Organization*, e.g. difficulties in getting organized, initiating work-related tasks, or self-activating for daily routines; 2) *Attention*, e.g. difficulties in sustaining attention on tasks; 3) *Alertness*, e.g. daytime drowsiness, slowed processing of information, inadequate task completion, or difficulties in maintaining consistent alertness and effort for work-related tasks; 4) *Affective Interference*, e.g. difficulties with mood, sensitivity to criticism, apparent lack of motivation, excessive frustration, or discouragement; and 5) *Memory*, e.g. 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 0-120 with higher scores indicating worse subjective cognitive function and scores greater than 50 considered clinically significant.

**Insomnia Severity**—The Insomnia Severity Index (ISI) provides a reliable measure of insomnia that has been validated in cancer populations with Cronbach’s $\alpha$ of 0.90. 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 five-point scale with higher scores representing more severe insomnia symptoms. A score greater than 14 indicates clinically significant insomnia. The ISI has also demonstrated sensitivity to change and can be used to evaluate treatment response. A reduction of 8 points or greater 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.
Statistical Analyses

Our analyses 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. 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’s 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 in the context of insomnia treatment, we used 2-sample t-tests to examine whether the mean changes in BSRT and BADDS scores differed between insomnia treatment responders versus non-responders by treatment group. The sample size was pre-determined by the parent study. All statistical tests were two-sided. Statistical significance was set at P<0.05. All statistical analyses were conducted using STATA (version 12.0; STATA Corporation, College Station, TX) and SAS (version 9.4; SAS Institute, Cary, NC). Given that data were secondary outcomes from the parent trial, these analyses are hypothesis-generating rather than confirmatory.

RESULTS

Between February 2015 to March 2017, we screened 604 patients for eligibility. Among these, 444 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 (N=80) or CBT-I (N=80) in the parent study. Of these 160 patients, 99 (62%) reported cognitive difficulties at baseline and were included in the study reported here. 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, one patient in each group withdrew from the study due to inability to complete cognitive assessments (acupuncture group) and disease recurrence (CBT-I group). Figure 1 summarizes participant flow through the study.

Treatments groups were similar in baseline sociodemographics and clinical characteristics (Table 1). The mean (SD) age was 60.4 (11.8) years, 56.6% (N=56) were women, and 26.3% (N=26) were non-white. 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 (interquartile range) time since cancer diagnosis was 5.9 years (0.9-22.3).

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

Acupuncture produced statistically significant increases in the number of words recalled in Trial 1, Trial 6, and Delayed Recall Trial at Weeks 8 and 20 compared to baseline (all \( P<0.05 \)), indicating short- and long-term improvement 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 to baseline \( (P<0.001) \), suggestive of a delayed improvement in objective attention. The between-group differences were not statistically significant.

For BSRT Trial 1 (i.e. objective attention), acupuncture demonstrated small effects at Week 8 \( (D=0.29) \) and Week 20 \( (D=0.29) \), whereas CBT-I demonstrated small-to-moderate effects at Week 8 \( (D=0.25) \) and Week 20 \( (D=0.50) \). For BSRT Trial 6 (i.e. objective learning), acupuncture demonstrated small effects at Week 8 \( (D=0.31) \) and Week 20 \( (D=0.31) \), whereas CBT-I demonstrated minimal effects at these timepoints. For BSRT Delayed Recall (i.e. objective memory), acupuncture demonstrated small effects at Week 8 \( (D=0.33) \) and Week 20 \( (D=0.39) \), whereas CBT-I demonstrated minimal effects at these timepoints. 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 to baseline (all \( P<0.001 \)), indicating short- and long-term improvement in subjective cognitive function. Acupuncture demonstrated moderate effects at Week 8 \( (D=0.54) \) and Week 20 \( (D=0.65) \), whereas CBT-I demonstrated moderate-large effects at Week 8 \( (D=0.73) \) and Week 20 \( (D=0.84) \). 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 \( (P<0.001) \), whereas CBT-I decreased the ISI score by 11.9 points \( (P<0.001) \); the between-group difference was 2.3 points (95% CI 0.3-4.3, \( P=0.023 \)).

Among all 99 patients, there was no statistically significant difference between insomnia treatment responders \( (N=71) \) versus non-responders \( (N=28) \) with regards to mean changes in BSRT scores (i.e. objective cognition) from baseline to Week 8 (all \( P>0.05 \)); however, insomnia treatment responders demonstrated a statistically significant greater reduction in BADDS total scores (i.e. subjective cognition) compared to non-responders (score change [SD], \( -16.0 [16.1] \) vs \( -6.6 [10.4] \), \( P=0.006 \)).

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 non-responders (all \( P>0.05 \)) in the acupuncture or CBT-I groups.
However, within the acupuncture group, insomnia treatment responders (N=32) demonstrated a statistically significant greater reduction in BADDS total scores compared to non-responders (N=20) (−16.2 [16.0] vs. −4.5 [10.5], P=0.006), whereas in the CBT-I group, the insomnia treatment responders (N=39) did not demonstrate a statistically significant greater reduction in BADDS total scores compared to non-responders (N=8) (−15.8 [16.5] vs. −11.9 [18.8], P=0.51).

**DISCUSSION**

With American cancer survivors expected to exceed 20 million by 2026, there is a pressing need to address CRCI, a prevalent, disruptive condition in 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 two 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, the optimal treatment for CRCI has not been definitively established. Wakefulness-promoting agents, such as modafinil, have produced encouraging results in pilot placebo-controlled trials, but these findings have not been confirmed in larger trials, and one study has failed to demonstrate significant improvement in cognition. Other oral agents, such as methylphenidate, memantine, donepezil, gingko biloba, and estradiol, have shown poor or mixed results, and several have adverse side effect profiles. Polypharmacy remains a significant concern in the cancer population, particularly among elderly patients who are disproportionately affected by CRCI. As such, the National Comprehensive Cancer Network recommends pharmacologic interventions as last line of therapy for CRCI, highlighting the importance of developing and evaluating non-pharmacological approaches to CRCI. Cognitive rehabilitation/training, physical activity, yoga, qi gong, and mindfulness techniques 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. Our study contributes to this growing literature by highlighting two other non-pharmacological interventions that warrant further investigation in the development of effective treatments for CRCI.

An increasing number of studies have evaluated the cognitive effects of acupuncture, but few have been conducted in cancer populations. In a randomized controlled trial (N=80) of Chinese breast cancer patients undergoing chemotherapy, acupuncture significantly improved subjective cognitive function (measured by FACT-Cog) and objective cognitive performance (measured by auditory-verbal learning test and clock drawing test) compared to usual care; however, the durability of these effects after treatment was not assessed. Our study found that acupuncture produced significant small-to-moderate improvements in objective and subjective cognition that persisted up to 12-weeks post-intervention. In the Chinese trial described above, acupuncture also produced a significant increase in serum
brain-derived neurotrophic factor (BDNF) compared to usual-care controls; the change in BDNF correlated with improvements in cognitive function. Given its hippocampal expression, BDNF has been hypothesized to regulate key cognitive process, such as learning and memory, and is also thought to be involved in sleep homeostasis. 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 of our study. Incorporation of relevant biomarkers in future confirmatory trials will help to advance mechanistic understanding of acupuncture and its cognitive effects.

Our study also contributes to the emerging literature on the cognitive effects of CBT-I. To date, research in cancer populations have been mixed, with some studies demonstrating a significant improvement in subjective cognitive outcomes from pre- to post-intervention, and others noting only a trend towards significant improvement. No CBT-I studies of cancer patients have incorporated objective cognitive measures. In our study, we demonstrated that CBT-I produces significant moderate-to-large improvements on subjective cognition that persisted up to 12-weeks post-intervention. Given that maladaptive thought processes may maintain and exacerbate perceived cognitive difficulties in cancer survivors, 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 (e.g. anxiety) that have been shown to contribute to cognitive difficulties. 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 on objective attention at 12-weeks post-intervention. In a functional magnetic resonance imaging study of people with insomnia disorder, CBT-I reduced hyper-responsivity in the prefrontal cortex and insula, both of which are critical brain regions involved in attentional processes, thus providing a translational context for this finding.

As research accumulates on the link between sleep and cognition, there are efforts underway to investigate how to experimentally modulate sleep to enhance cognitive performance. Our study provides 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 to non-responders. By contrast, in the CBT-I group, there were no significant differences in subjective or objective cognitive outcomes between insomnia treatment responders versus non-responders. These preliminary findings suggest 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 our study lacked objective sleep measures and thus could not 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, future studies should incorporate both types of cognitive/sleep measures to comprehensively evaluate the mediating effects of sleep on cognitive outcomes in 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/ subjective patterns of sleep and cognitive dysfunction.

Our findings should be considered in 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 two active interventions and lacked placebo/attention control groups; therefore, the observed effects cannot be separated from placebo or other non-specific effects of the intervention. The acupuncture group received more therapist contact time compared to the CBT-I group, which may contribute to non-specific intervention effects. Given the lack of usual-care controls, regression to the mean and/or natural recovery of cognitive function over time must also be considered, although other studies have demonstrated that acupuncture and CBT-I significantly improved cognitive function compared to usual-care controls.\(^{35,40}\) Third, our 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, 74-79% of breast cancer patients with moderate of greater perceived cognitive difficulties reported co-morbid insomnia, suggesting that our study population represents a significant proportion of patients with CRCI.\(^{28}\) Lastly, 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, this is the largest randomized clinical trial to explore the effects of acupuncture versus CBT-I on objective and subjective cognitive outcomes in cancer survivors. Other strengths include dual-center conduct of the trial, excellent minority representation, strong adherence to interventions, long-term follow-up, and minimal missing data. Our 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 two interventions is warranted to inform personalized management of CRCI.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments:**

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REFERENCES


Figure 1. CONSORT Diagram
Note: Italicized sections refer to the current study embedded in the parent trial.
Table 1.

Sociodemographic and Clinical Characteristics.

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<td>Chemotherapy</td>
<td>48</td>
<td>48.5</td>
<td>24</td>
</tr>
<tr>
<td>Radiation</td>
<td>53</td>
<td>53.5</td>
<td>28</td>
</tr>
<tr>
<td>Hormonal</td>
<td>20</td>
<td>20.2</td>
<td>11</td>
</tr>
<tr>
<td><strong>Years since Cancer Diagnosis (Median, IQR)</strong></td>
<td>5.9 (0.9-22.3)</td>
<td>5.7 (2.3-10.8)</td>
<td>6.1 (1.4-17.4)</td>
</tr>
</tbody>
</table>

*Cancer* Author manuscript; available in PMC 2021 March 25.
Other cancer types include Colorectal, Head/Neck, Hematologic, Gynecologic, Skin, Lung, Other Gastrointestinal, Other Genitourinary, and >1 cancer type.

Subjects can have more than 1 type of cancer treatments
Table 2:

Baseline Symptom Profile.

<table>
<thead>
<tr>
<th></th>
<th>Total N=99</th>
<th>Acupuncture N=52</th>
<th>CBT-I N=47</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bushke Selective Reminding Test (BSRT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Cognitive Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1 (attention) score, mean (SD)</td>
<td>6.3 (2.5)</td>
<td>6.5 (2.7)</td>
<td>6.2 (2.2)</td>
</tr>
<tr>
<td>Trial 6 (learning) score, mean (SD)</td>
<td>11.1 (3.3)</td>
<td>11.0 (3.1)</td>
<td>11.2 (3.5)</td>
</tr>
<tr>
<td>Delayed recall (memory) score, mean (SD)</td>
<td>9.7 (4.1)</td>
<td>9.4 (4.2)</td>
<td>10.0 (4.0)</td>
</tr>
<tr>
<td><strong>Brown Attention-Deficit Disorder Scale (BADDs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjective Cognitive Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BADDs total score, mean (SD)</td>
<td>47.6 (22.7)</td>
<td>44.7 (22.4)</td>
<td>50.8 (22.7)</td>
</tr>
<tr>
<td>BADDs total score &gt;50, N (%) *</td>
<td>43 (43.4)</td>
<td>20 (38.5)</td>
<td>23 (48.9)</td>
</tr>
<tr>
<td><strong>Insomnia Severity Index (ISI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISI total score, mean (SD)</td>
<td>18.3 (4.1)</td>
<td>18.0 (4.3)</td>
<td>18.7 (4.0)</td>
</tr>
<tr>
<td>ISI total score &gt;14, N (%) *</td>
<td>81 (81.8)</td>
<td>41 (78.8)</td>
<td>40 (85.1)</td>
</tr>
</tbody>
</table>

* Clinically significant
## Table 3.
Mean Change from Baseline in Buschke Selective Reminding Task Scores by Treatment Group.

<table>
<thead>
<tr>
<th>Trial 1 (Attention)</th>
<th>Acupuncture</th>
<th>CBT-I</th>
<th>Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change (95% CI)</td>
<td>P Value</td>
<td>Mean Change (95% CI)</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.7</td>
<td>0.017</td>
<td>0.6</td>
</tr>
<tr>
<td>(0.1 to 1.3)</td>
<td>(−0.005 to 1.2)</td>
<td></td>
<td>(0.6 to 1.8)</td>
</tr>
<tr>
<td>Week 20</td>
<td>0.7</td>
<td>0.024</td>
<td>1.2</td>
</tr>
<tr>
<td>(0.1 to 1.3)</td>
<td>(0.6 to 1.8)</td>
<td></td>
<td>(1.4 to 0.3)</td>
</tr>
<tr>
<td>Trial 6 (Learning)</td>
<td>0.8</td>
<td>0.040</td>
<td>0.4</td>
</tr>
<tr>
<td>(0.04 to 1.6)</td>
<td>(−0.4 to 1.2)</td>
<td></td>
<td>(−0.7 to 1.6)</td>
</tr>
<tr>
<td>Week 20</td>
<td>1.2</td>
<td>0.0021</td>
<td>0.8</td>
</tr>
<tr>
<td>(0.5 to 2.0)</td>
<td>(−0.04 to 1.6)</td>
<td></td>
<td>(−0.6 to 1.6)</td>
</tr>
<tr>
<td>Delayed Recall (Memory)</td>
<td>1.0</td>
<td>0.0020</td>
<td>0.6</td>
</tr>
<tr>
<td>(0.4 to 1.7)</td>
<td>(−0.06 to 1.3)</td>
<td></td>
<td>(−0.5 to 1.4)</td>
</tr>
<tr>
<td>Week 20</td>
<td>1.4</td>
<td>&lt;0.001</td>
<td>0.5</td>
</tr>
<tr>
<td>(0.7 to 2.0)</td>
<td>(−0.2 to 1.1)</td>
<td></td>
<td>(−0.5 to 1.8)</td>
</tr>
</tbody>
</table>

Note: Higher scores indicate better objective cognitive function.
Table 4.

Mean Change from Baseline on Brown Attention Deficit Disorder Scale Total Scores by Treatment Group.

<table>
<thead>
<tr>
<th></th>
<th>Acupuncture</th>
<th>CBT-I</th>
<th>Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change (95% CI)</td>
<td>P value</td>
<td>Mean Change (95% CI)</td>
</tr>
<tr>
<td>Week 8</td>
<td>−11.7 (−15.7 to −7.7)</td>
<td>&lt;0.0001</td>
<td>−15.2 (−19.3 to −11.0)</td>
</tr>
<tr>
<td>Week 20</td>
<td>−14.4 (−18.4 to −10.4)</td>
<td>&lt;0.0001</td>
<td>−18.9 (−23.1 to −14.7)</td>
</tr>
</tbody>
</table>

Note: Lower scores indicate better subjective cognitive function.