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Tai Chi Chih Compared With Cognitive Behavioral Therapy for the Treatment of Insomnia in Survivors of Breast Cancer: A Randomized, Partially Blinded, Noninferiority Trial

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A B S T R A C T

Purpose

Cognitive behavioral therapy for insomnia (CBT-I) and Tai Chi Chih (TCC), a movement meditation, improve insomnia symptoms. Here, we evaluated whether TCC is noninferior to CBT-I for the treatment of insomnia in survivors of breast cancer.

Patients and Methods

This was a randomized, partially blinded, noninferiority trial that involved survivors of breast cancer with insomnia who were recruited from the Los Angeles community from April 2008 to July 2012. After a 2-month phase-in period with repeated baseline assessment, participants were randomly assigned to 3 months of CBT-I or TCC and evaluated at months 2, 3 (post-treatment), 6, and 15 (follow-up). Primary outcome was insomnia treatment response—that is, marked clinical improvement of symptoms by the Pittsburgh Sleep Quality Index—at 15 months. Secondary outcomes were clinician-assessed remission of insomnia; sleep quality; total sleep time, sleep onset latency, sleep efficiency, and awake after sleep onset, derived from sleep diaries; polysomnography; and symptoms of fatigue, sleepiness, and depression.

Results

Of 145 participants who were screened, 90 were randomly assigned (CBT-I: $n = 45$; TCC: $n = 45$). The proportion of participants who showed insomnia treatment response at 15 months was 43.7% and 46.7% in CBT-I and TCC, respectively. Tests of noninferiority showed that TCC was noninferior to CBT-I at 15 months ($P = .02$) and at months 3 ($P = .02$) and 6 ($P < .01$). For secondary outcomes, insomnia remission was 46.2% and 37.9% in CBT-I and TCC, respectively. CBT-I and TCC groups showed robust improvements in sleep quality, sleep diary measures, and related symptoms (all $P < .01$), but not polysomnography, with similar improvements in both groups.

Conclusion

CBT-I and TCC produce clinically meaningful improvements in insomnia. TCC, a mindful movement meditation, was found to be statistically noninferior to CBT-I, the gold standard for behavioral treatment of insomnia.

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INTRODUCTION

Insomnia is diagnosed by difficulty initiating sleep, frequent awakenings, and an inability to return to sleep, all of which lead to daytime impairments.¹ For survivors of cancer, insomnia poses a significant public health concern; nearly 30% of survivors of breast cancer meet diagnostic criteria for insomnia, a prevalence rate almost twice that of the general population.²⁻⁴ Distress associated with cancer diagnosis and treatment is thought to precipitate and perpetuate insomnia

symptoms^{5,6}; hence, treatments that target distress might improve insomnia.⁷

Cognitive behavioral therapy for insomnia (CBT-I), considered the treatment of choice by the American Academy of Sleep Medicine,⁸⁻¹¹ combines cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation to improve sleep outcomes, with demonstrated efficacy in survivors of cancer.^{12,13} With no serious contraindications, CBT-I is more effective than pharmacotherapy at improving sleep for both short-term and long-term periods¹⁴⁻¹⁶; however, some question the feasibility

ASSOCIATED CONTENT



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of implementing CBT-I in routine clinical practice and oncology care.¹⁴

Tai Chi Chih (TCC), a manualized form of Tai Chi, is a mind-body intervention (MBI) that combines slow physical activity with relaxation to serve as a movement meditation.¹⁷ TCC has been found to improve insomnia symptoms,¹⁸⁻²⁰ with one study demonstrating efficacy in the short-term that was comparable to CBT-I therapy in older adults with insomnia.²¹ It is not known whether TCC is an effective treatment of insomnia in survivors of breast cancer, even though up to 50% of survivors of breast cancer report annual use of MBIs, such as TCC, in an effort to promote health²²; this practice can be readily implemented in the community. TCC has broad benefits with effects on multiple other health outcomes,^{21,23-28} and TCC improves depression²⁹ and fatigue,³⁰ which are frequently comorbid in survivors of breast cancer, especially those with insomnia.^{31,32}

The primary objective of the current study was to establish whether TCC produces durable effects and effects that are similar to CBT-I in reducing insomnia symptoms in survivors of breast cancer. We hypothesized that TCC would be statistically non-inferior to CBT-I for reducing insomnia severity at 15 months, 1 year after intervention or treatment exposure. Secondary outcomes were insomnia remission, subjective and objective sleep outcomes, and severity of insomnia-related daytime impairments of fatigue, sleepiness, and depressive symptoms.

PATIENTS AND METHODS

Trial Design

Trial design was registered and ethical approval was obtained from the UCLA Institutional Review Board. The study is a single-masked (rater), single-site, parallel-group, noninferiority trial of TCC versus CBT-I on sleep and related behavioral outcomes, which follows CONSORT guidelines for noninferiority randomized trials.³³

After recruitment by advertisement, telephone screening, informed consent, completion of questionnaires and interviews, laboratory blood tests, and polysomnographic (PSG) exclusion of those with sleep apnea or nocturnal myoclonus,²¹ participants entered a 2-month phase-in period to establish stability of insomnia severity before intervention and to maximize participant retention and compliance for the subsequent random assignment portion. After a second baseline in which all questionnaires and interviews were readministered, participants were randomly assigned to CBT-I or TCC for 3 months. Assessments were at 2, 3, 6, and 15 months. Methods were not changed after trial commencement.

Study Participants

Recruitment was conducted from April 2008 to July 2012. Participants were survivors of breast cancer (age range, 42 to 83 years) who fulfilled criteria for insomnia in the Diagnostic and Statistical Manual (Fourth Edition, Text Revision [DSM-IV-TR])³⁴ and for general insomnia in International Classification of Sleep Disorders (Second Edition),³⁵ reported sleep difficulties ≥ 3 times per week for > 3 months consistent with DSM-5 criteria,¹ had completed treatment with surgery, radiation, and/or chemotherapy at least 6 months before the study, who and showed no evidence of cancer recurrence or new primary tumor. Exclusion criteria were previously described.²⁵ The Charlson comorbidity scale was administered by interview to evaluate medical comorbidity.³⁶

Interventions

The CBT-I program was delivered to groups of 7 to 10 participants in weekly 120-minute sessions. CBT-I followed the format of previously

published trials in adults, older adults, and patients with cancer,^{9,12,15,37,38} and contained the following five validated components: cognitive therapy, stimulus control, sleep restriction, sleep hygiene, and relaxation, which together target sleep-related physiologic and cognitive arousal to re-establish restorative sleep function.¹⁴ CBT-I teaching components were administered in 2 months, which was consistent with the duration of the majority of CBT-I treatment trials.^{8,10,12,37,39} Intervention exposure was extended to 3 months with 1 month of skill consolidation and adherence

Table 1. Baseline Characteristics of Participants by Treatment Group

Variable	TCC (n = 45)	CBT-I (n = 45)
Age (42-83 years)	59.6 (7.9)	60.0 (9.3)
Race, white, No. (%)	34 (75.6)	43 (95.6)
Marital status, married/partner, No. (%)	19 (43.2)	28 (62.2)
Employment, working, No. (%)	28 (60.0)	27 (62.2)
Education (years)	15.8 (1.2)	15.7 (1.4)
Body mass index (kg/m ²)	25.6 (4.5)	26.2 (5.9)
Cancer history		
Age at Dx	49.6 (9.0)	51.4 (9.2)
Time since Dx (years)	9.4 (8.9)	8.3 (8.1)
Time since Tx (years)	7.8 (8.1)	6.3 (5.8)
Current hormone Tx, No. (%)	10 (28.6)	18 (42.9)
Cancer treatment history, No. (%)		
Surgery only	6 (17.1)	4 (9.5)
Radiation only	11 (31.4)	17 (41.5)
Chemotherapy only	7 (20.0)	4 (9.5)
Chemotherapy + radiation	11 (31.4)	17 (40.5)
Comorbidity		
Charlson comorbidity index	1.5 (1.0)	1.7 (2.0)
Depression history, No. (%)	17 (37.8)	23 (51.1)
Use of antidepressants, No. (%)	10 (22.2)	10 (22.2)
Sleep quality		
Sleep quality (PSQI, total score)	11.3 (2.1)	11.0 (3.7)
Sleep quality (AIS), total score)	11.0 (3.0)	10.1 (3.2)
Use of hypnotic medications, No. (%)	10 (22.2)	15 (33.3)
Total sleep time, minutes		
Sleep diary	352.4 (75.3)	352.2 (71.0)
Polysomnography	377.6 (60.5)	391.8 (47.7)
Sleep latency, minutes		
Sleep diary	34.9 (21.9)	41.5 (29.4)
Polysomnography	21.0 (20.9)	20.1 (15.7)
Sleep efficiency, %		
Sleep diary	72.1 (12.9)	70.6 (14.0)
Polysomnography	83.6 (11.6)	85.4 (10.1)
Wake after sleep onset, minutes		
Sleep diary	54.8 (33.4)	49.9 (34.7)
Polysomnography	73.2 (52.2)	67.2 (47.4)
Other behavioral symptoms		
Fatigue severity (MFSI)	21.7 (17.4)	12.9 (14.8)
Daytime sleepiness (ESS)	8.0 (4.5)	7.3 (4.6)
Depressive symptoms (IDS-C)	11.0 (6.5)	8.7 (4.4)

NOTE. Data are presented as mean (standard deviation) unless otherwise noted. Baseline most immediately before treatment, baseline 2.

Abbreviations: AISI, Athens Insomnia Severity Index; CBT-I, cognitive behavioral therapy for insomnia; Dx, diagnosis; ESS, Epworth Sleepiness Scale; IDS-C, Inventory of Depressive Symptoms; MFSI, Multidimensional Fatigue Symptom Inventory; PSQI, Pittsburgh Sleep Quality Index; TCC, Tai Chi Chih; Tx, treatment.

to specifically address issues related to adherence that might impact implementation of CBT-I during follow-up.

The TCC program was delivered to groups of 7 to 10 in weekly 120 sessions. TCC emphasized control over physical function and arousal-related responsiveness, which are thought to contribute to insomnia,⁴⁰ through the mindful performance of repetitious, nonstrenuous, slow-paced movement, that is, movement meditation, which made this MBI highly accessible. A week-by-week description of the program has been previously published.¹⁷ TCC teaching components were administered over 2 months, followed by 1 month of skill consolidation and adherence, for 3 months of treatment exposure.

Treatment Fidelity

Therapists were experienced and trained in one modality but not in the other. Another therapist who had extensive experience (> 10 years) in either CBT-I or TCC provided weekly supervision,

evaluated treatment integrity, and attended three or more sessions with rating of treatment elements, which contained > 95% of required components.

Treatment Credibility

After the second session, participants rated treatment acceptance, credibility, and expectation for change.⁴¹ At the end of treatment exposure, therapists and participants rated insomnia treatment credibility.

Primary Outcome

The primary outcome was insomnia treatment response at month 15, which was defined by a decrease (≥ 5 points) on the Pittsburgh Sleep Quality Index (PSQI) or marked clinical improvement of symptoms.⁴² A decrease of ≥ 5 points on the PSQI also corresponds to treatment response of > 7 points¹⁵ or > 8 points⁴³ derived from the Insomnia

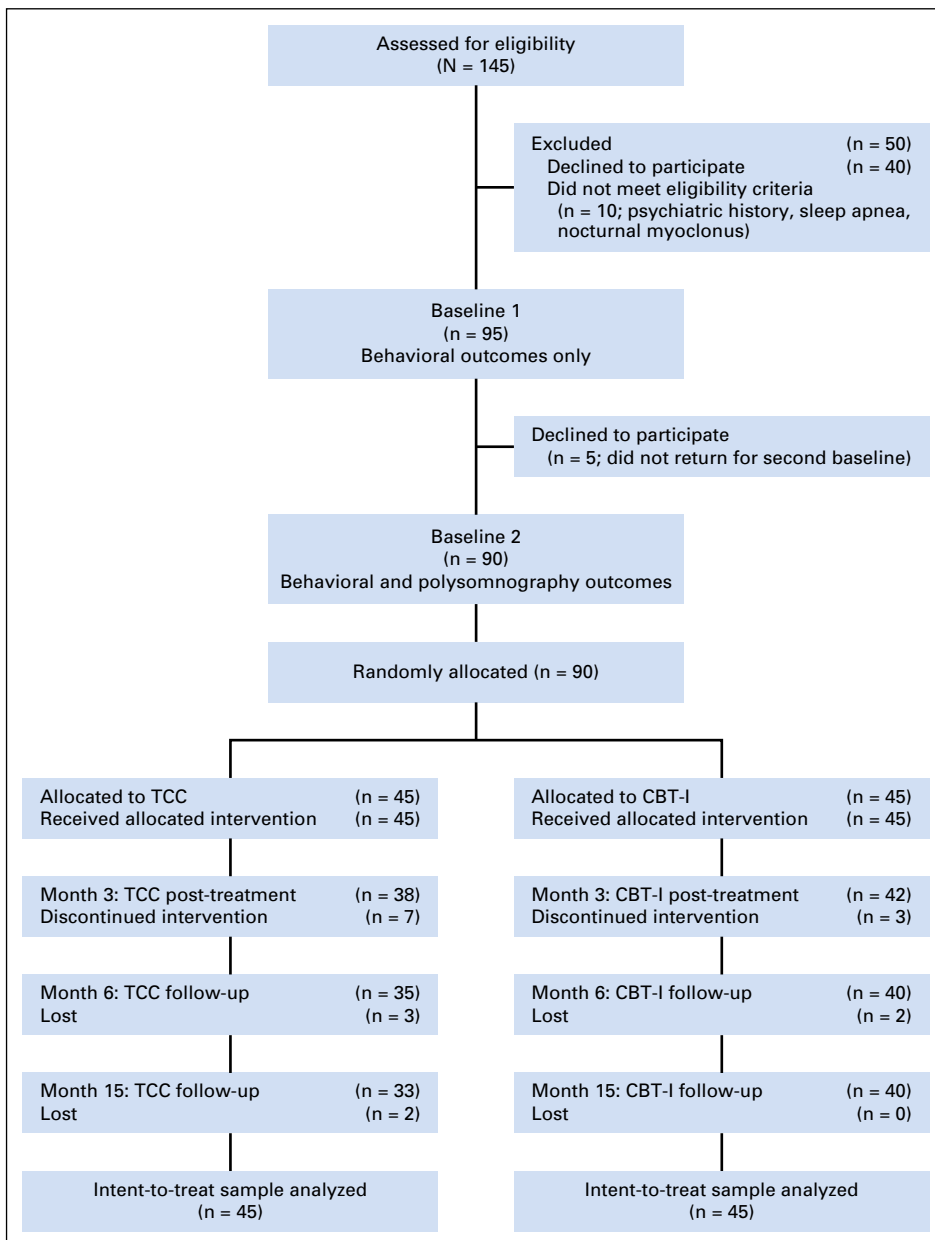


Fig 1. Screening, random assignment, and completion of postintervention. CBT-I, cognitive behavioral therapy for insomnia; TCC, Tai Chi Chih.

Severity Index, which also indicates marked improvement or nearly complete or complete remission of symptoms.⁴⁴ Furthermore, this response criterion is consistent with clinically meaningful improvements in insomnia severity in published clinical trials of survivors of cancer.^{7,12,45-48}

Secondary Outcomes

Insomnia remission was a secondary outcome. An assessor who was blind to treatment allocation administered a structured interview, and DSM-IV-TR criteria of insomnia remission were ascertained in a consensus meeting of at least two board-certified psychiatrists or psychologists.

Other secondary outcomes were sleep quality (PSQI and Athens Insomnia Severity Index [AISII]) and daily diaries of sleep parameters for 2 weeks (ie, Pittsburgh Sleep Diary).⁴⁹ After a night of adaptation, PSG was obtained at baseline and month 3, as previously described.^{50,51} Behavioral outcomes included insomnia-related daytime symptoms of fatigue (Multidimensional Fatigue Symptom Inventory),⁵² sleepiness (Epworth Sleepiness Scale),⁵³ and clinician-rated depressive symptoms (ie, Inventory of Depressive Symptoms).⁵⁴ Body mass index and physical activity (Yale Physical Activity Survey^{55,56}) were evaluated.

Sample Size

An a priori power analysis was conducted in G*Power (<http://www.gpower.hhu.de/en.html>). On the basis of prior meta-analytic findings and mean treatment effect ($d = 0.4$, a medium effect size),³⁹ in which there is, at minimum, complete or nearly complete remission of symptoms,⁴⁸ 25 participants per treatment group provided statistical power of 80% ($\alpha = .05$) to detect insomnia treatment response (ie, decrease of ≥ 5 points on the PSQI) at month 15 relative to baseline. The noninferiority margin was set at a minimum value of 50% of insomnia treatment response, which was consistent with two prior noninferiority trials on insomnia,⁷ or a 2.5-point decrease on the PSQI. With an estimated 20% attrition, 45 participants in each group provided adequate power (80% with $\alpha = .05$) to reject the null hypothesis that the insomnia treatment response induced by TCC is inferior to that achieved by CBT-I.

Random Assignment

Random assignment sequence was generated via a computerized random number generator in blocks of 7 to 10 participants in TCC and CBT-I (1:1) by R.O., who did not view participant data before allocation. To maintain concealment, no research staff had access to allocation sequence, which was recorded on sequentially numbered, opaque, and sealed envelopes.

Blinding

The study was advertised as a research study to evaluate whether one or another insomnia treatment would improve insomnia, and participants remained blind to hypotheses and the content of the other treatment group through study duration. Use of a modified blind-to-treatment protocol—that is, partial blinding—is thought to reduce selection bias that is frequently associated with trials of behavioral interventions. Investigators and outcome assessors were blinded to allocation.

Statistical Methods

Noninferiority of the primary outcome was assessed by using an *F* statistic from linear mixed models and the appropriate CI side; significant *P* values indicate noninferiority, in which the observed difference between the two treatment means is significantly less than the noninferiority margin *F*-statistic (2.5).⁵⁸ Intervention effects on secondary outcomes of proportion of insomnia remission and treatment response were tested by using Fisher's exact test.

Intervention effects on secondary, continuous outcomes were tested on an intention-to-treat basis using a mixed model approach. Data from all

randomly assigned participants were included. For each of the models, the random effect was participant and the fixed effects were group (TCC *v* CBT-I), time, and group \times time interaction. We tested whether two baselines differed for any secondary outcome and found no differences. Subsequent analyses covaried for baseline immediately before treatment, that is, baseline 2. The restricted maximum likelihood estimate method estimated model parameters and standard errors with a compound symmetry covariance structure to account for the correlation between measurements. We used type III fixed effects (*F* and *t*) and set the statistical significance at $P < .05$. The mixed model approach generated unbiased estimates under the assumption that data are missing completely at random and the missing completely at random assumption was tested. Additional comparisons were made by using either *t* test or Fisher's exact test as appropriate.

A priori linear contrasts tested group differences from baseline to 15-month follow-up, controlling for multiple comparisons. Data were available on $> 95\%$ of retained participants at all time points. Analyses were performed with SPSS for Windows version 21 (SPSS, Chicago, IL).

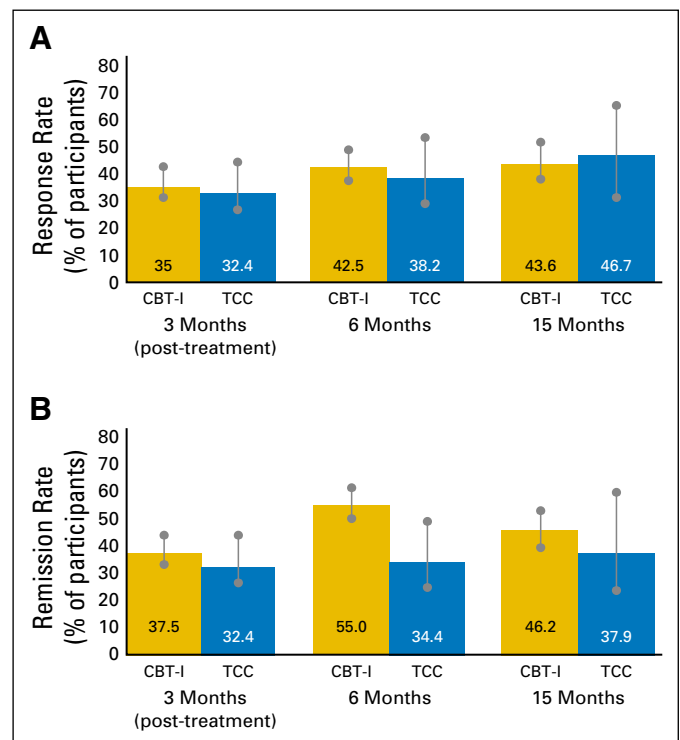


Fig 2. (A) Treatment response of patients with insomnia (change in Pittsburgh Sleep Quality Index score of ≥ 5 points) at 3 months (post-treatment), 6 months, and 15 months in the cognitive behavioral therapy for insomnia (CBT-I) and Tai Chi Chih (TCC) groups. Rate of response is indicated as a percentage of observed cases. Vertical bars indicate range of response with the assumption that missing cases are all responders or nonresponders. Rate of response was similar between the two groups at month 3 (35% and 32.4%, respectively; $P = 1.0$; $d = 0.06$) and month 6 (42.5% and 38.2%, respectively; $P = .82$; $d = 0.10$), and at the primary outcome end point, month 15 (43.6% and 46.7%, respectively; $P = .82$; $d = -0.07$). Effect sizes are reported using the *d* metric to reflect differences between groups. Positive values indicate CBT-I $>$ TCC, negative values TCC $>$ CBT-I. (B) Percentage of participants with remission of Diagnostic and Statistical Manual (Fourth Edition, Text Revision; DSM-IV-TR) insomnia at 3 months (postintervention), 6 months, and 15 months in the CBT-I and TCC groups. Insomnia diagnosis was made by clinician interview using DSM-IV-TR criteria. Rate of remission is indicated as a percentage of observed cases. Vertical bars indicate range of remission with the assumption that missing cases are all remitters or nonremitters. Rate of remission was similar between the two groups at 3 months (CBT-I, 37.5%; TCC, 32.4%; $P = .81$), 6 months (CBT-I, 55%; TCC, 34.4%; $P = .10$), and 15 months (CBT-I, 46.2%; TCC, 37.9%; $P = .62$).

Table 2. Sleep and Behavioral Outcomes by Treatment Group

Variable	Assessment						Group Effect		Time Effect		Group × Time Effect		
	Baseline	Baseline 2	2 Months	3 Months	6 Months	15 Months	F*	F(df)	P	F(df)	P	F(df)	P
Sleep quality													
PSQI								2.71 (1,90.3)	.11	52.8 (5,375.3)	< .001	2.71 (5,375.2)	.50
TCC	11.5 (0.5)	11.2 (0.4)	9.0 (0.4)†	8.2 (0.4)	7.6 (0.5)	7.4 (0.5)	1.27						
CBT-I	11.2 (0.4)	11.1 (0.4)	7.6 (0.4)†	7.3 (0.4)	7.0 (0.4)	6.8 (0.4)	1.44						
AISI								1.62 (1,88.4)	.21	50.6 (5,372.9)	< .001	0.33 (5,372.9)	.90
TCC	11.1 (0.5)	10.8 (0.4)	8.3 (0.5)	7.3 (0.5)	6.8 (0.5)	6.9 (0.5)	1.21						
CBT-I	11.1 (0.4)	10.4 (0.4)	7.8 (0.4)	6.6 (0.5)	6.1 (0.5)	6.0 (0.5)	1.34						
Sleep continuity													
Total sleep time, minutes								0.35 (1,83.3)	.56	22.7 (3,207.0)	< .001	0.07 (3,207.1)	.98
Diary													
TCC		350 (8.7)		389 (10.1)	400 (10.3)	399 (10.5)	0.64						
CBT-I		353 (8.7)		397 (9.0)	404 (9.5)	407 (9.2)	0.80						
PSG								0.02 (1,63.6)	.90	0.26 (1,70.7)	.62	0.35 (1,70.7)	.56
TCC		382 (6.0)		390 (6.7)									
CBT-I		387 (6.4)		386 (7.3)									
Sleep onset latency, minutes													
Diary								3.64 (1,73.2)	.06	22.0 (3,207.9)	< .001	3.12 (3,207.9)	.027
TCC		37.1 (2.7)		27.3 (3.2)‡	24.5 (3.2)	25.7 (3.3)†	0.28						
CBT-I		41.1 (2.7)		19.2 (2.8)‡	20.7 (3.0)	14.4 (2.9)†	0.87						
PSG								0.05 (1,71.0)	.84	2.53 (1,70.7)	.12	0.06 (1,70.4)	.81
TCC		20.5 (3.4)		20.3 (3.7)									
CBT-I		20.3 (3.7)		27.4 (4.3)									
Sleep efficiency, minutes													
Diary								8.31 (1,82.3)	.005	45.4 (3,211.1)	< .001	3.11 (3,211.3)	.027
TCC		71.4 (1.4)		79.8 (1.6)†	79.6 (1.6)†	80.6 (1.7)†	0.64						
CBT-I		70.8 (1.4)		85.4 (1.4)†	85.4 (1.5)†	86.0 (1.5)†	1.12						
PSG								0.99 (1,65.4)	.33	1.70 (1,70.6)	.20	1.46 (1,70.6)	.24
TCC		84.3 (0.9)		87.1 (1.0)									
CBT-I		84.7 (1.0)		84.8 (1.1)									
WASO, minutes													
Diary								3.60 (1,76.2)	.07	29.9 (3,205.0)	< .001	0.73 (3,205.3)	.54
TCC		56.0 (3.4)		34.8 (4.0)	39.9 (4.1)†	26.5 (4.3)	0.64						
CBT-I		52.2 (3.5)		26.6 (3.5)	28.4 (3.8)†	24.2 (3.7)	0.82						
PSG								1.37 (1,66.3)	.25	1.67 (1,70.6)	.20	1.60 (1,70.6)	.22
TCC		70.7 (4.0)		58.5 (4.5)‡									
CBT-I		69.4 (4.3)		69.3 (4.9)‡									
Fatigue													
MDFSI								1.32 (5,87.7)	.26	23.9 (5,372.7)	< .001	1.14 (5,372.8)	.34
TCC		20.3 (1.8)		9.4 (1.5)	7.4 (1.7)	10.4 (1.8)*	0.49						
CBT-I		17.6 (1.5)		11.6 (1.5)	6.6 (1.5)	6.4 (1.6)*	0.55						
PSG								0.43 (1,85.0)	.84	5.53 (5,369.7)	< .001	1.57 (5,369.6)	.17
TCC		8.1 (0.5)		6.3 (0.4)*									
CBT-I		7.6 (0.4)		7.4 (0.4)*									
Depression													
IDSC								0.95 (1,83.2)	.34	6.84 (5,369.0)	< .001	0.14 (5,369.1)	.99
TCC		10.3 (0.9)		8.8 (0.8)	7.7 (0.8)	7.0 (0.9)	0.49						
CBT-I		10.2 (0.8)		7.9 (0.8)	7.1 (0.8)	6.7 (0.8)	0.39						

NOTE: Data are presented as estimated means (standard error), baseline 2 covered.
 Abbreviations: AISI, Athens Insomnia Severity Index; CBT-I, cognitive behavioral therapy for insomnia; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; TCC, Tai Chi Chih; WASO, wake after sleep onset.
 †P < .05.
 ‡P < .10 pairwise within time point.

RESULTS

Baseline Characteristics of Participants

Table 1 lists the baseline characteristics of the two groups. Figure 1 shows participant flow and reasons for ineligibility. Those who completed and did not complete intervention and follow-up did not differ on any baseline characteristic. CBT-I and TCC showed similar rates of session attendance (80.6% v 75.8%; $t[65] = 1.12$; $P = .27$) and drop-out at month 3 (Fisher's $P = .32$), but an increased rate of drop-out for TCC at month 15 (Fisher's $P = .06$). CBT-I and TCC were perceived by participants as equally acceptable to improve insomnia after session 2 (100% v 94.7%; $P = .49$) and at month 3 (100% v 100%), with similar results rated by therapists. In TCC, 79.2% continued to practice > 30 min per day during follow-up, although days per week decreased from month 3 (5.3 ± 1.2) to month 15 (2.1 ± 1.6 ; $T_{23} = 3.5$; $P < .05$). No significant between-group change from baseline to month 15 was found for sedative-hypnotic medication use ($F_{1,77.0} = 0.99$; $P = .40$), body mass index ($F_{1,49.0} = 0.01$; $P = .94$), or physical activity (ie, metabolic equivalents per week⁵⁹; $F_{1,77.0} = 0.38$; $P = .55$).

Primary Outcome

CBT-I and TCC resulted in a similar rate of treatment response at the primary outcome end point, month 15 (43.6% and 46.7%, respectively; $P = .82$; $d = -0.07$), with a similar proportion of CBT-I and TCC participants showing treatment response at months 3 (35% and 32.4%, respectively; $P = 1.0$; $d = 0.06$) and 6 (42.5% and 38.2%, respectively; $P = .82$; $d = 0.10$; Fig 2). Reported effect sizes use the d metric to reflect differences between groups; positive values indicate CBT-I > TCC, negative values TCC > CBT-I. CBT-I and TCC were not substantively different if those lost were considered responders at months 3 ($P = 1.0$; $d = -0.05$), 6 ($P = .84$; $d = -0.10$), and 15 ($P = .29$; $d = -0.30$), or were considered nonresponders at months 3 ($P = .82$; $d = 0.12$), 6 ($P = .51$; $d = 0.22$), and 15 ($P = .66$; $d = 0.16$).

With the noninferiority margin equal to 50% of the treatment response, the observed difference between CBT-I and TCC supported noninferiority at the primary outcome end point, month 15 (mean 0.52; CI, 2.36; $P = .02$) and at months 3 (mean 0.84; upper 95% CI, 2.42; $P = .02$) and 6 (mean 0.42; CI, 1.97; $P < .01$). A sensitivity analysis was performed that assumed that all patients in the TCC arm who were lost showed no change and were nonresponders, and that all those in the CBT arm who were lost were responders. Estimated difference between CBT-I and TCC supported noninferiority at the primary outcome end point, month 15 (mean 1.21; CI, 2.77; $P = .05$) and at months 3 (mean 0.95; CI, 2.37; $P = .01$) and 6 (mean 0.86; CI, 2.25; $P < .01$).

Secondary Outcomes of Sleep

CBT and TCC resulted in a similar rate of insomnia remission at the primary end point, month 15 (46.2% and 37.9%, respectively; $P = .62$; $d = 0.18$) and at months 3 (37.5% and 32.4%, respectively; $P = .81$; $d = 0.12$) and 6 (55.0% and 34.4%, respectively; $P = .10$; $d = 0.46$; Fig 2). The number needed to treat at month 3 was 3.0 (95% CI, 1.9 to 4.2) for CBT-I and 3.0 (95% CI, 2.0 to 4.6) for TCC. CBT-I and TCC were not substantively

different if those lost were considered remitters at months 3 ($P = 1.0$; $d = 0.00$), 6 ($P = .68$; $d = 0.13$), and 15 ($P = .68$; $d = -0.15$), or were considered nonremitters at months 3 ($P = .65$; $d = 0.18$), 6 ($P = .028$; $d = 0.60$), and 15 ($P = .18$; $d = 0.40$).

PSQI showed overall treatment effects ($P < .001$), with large treatment effect sizes for CBT-I and TCC ($d = 1.34$ and 1.21, respectively; Table 2 and Fig 3) in which mean PSQI scores at month 15 were less than the threshold of clinical sleep disturbance (ie, PSQI < 8 in survivors of cancer).⁶⁰ AISI showed similar results. Between-group differences in change of PSQI or AISI from baseline to months 3, 6, and 15 were not significant (all $P > .3$; Table 3). TCC practice time was not correlated with PSQI or AISI at months 3, 6, or 15 (all $P < .3$).

For sleep diaries, there were overall treatment effects for total sleep time, sleep onset latency, sleep efficiency, and wake after sleep onset (all $P < .001$; Table 2). Between-group differences in change of total sleep time and wake after sleep onset from baseline to months 3, 6, and 15 were not significant (all $P > .4$), although CBT-I was more likely to reduce sleep onset latency at month 3 ($P < .05$) and improve sleep efficiency at month 6 ($P < .05$) compared with TCC (Table 3).

For PSG, no treatment effects were found (all $P > .10$; Table 2), and there were no between-group differences for any measure (all $P > .10$; Table 3).

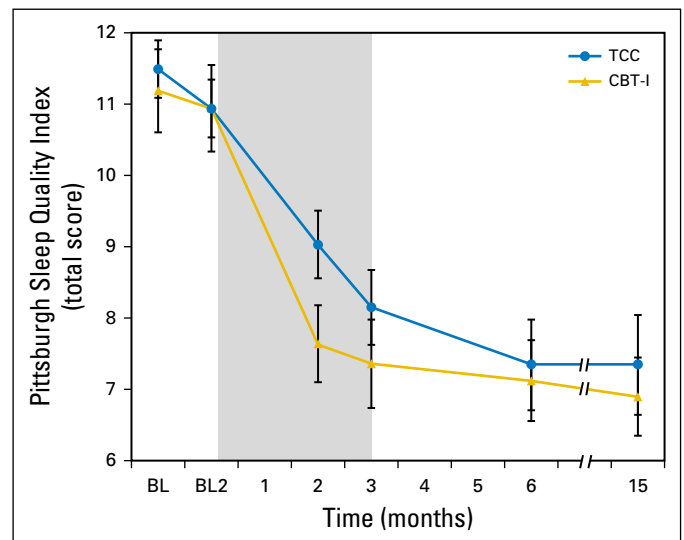


Fig 3. Change in global sleep quality from baseline to month 15 follow-up in the cognitive behavioral therapy for insomnia (CBT-I) and Tai Chi Chih (TCC) treatment groups. Total scores on the Pittsburgh Sleep Quality Index range from 0 to 21, with higher scores indicating worse sleep quality. Values are means and bars indicate standard error of measurement. Measurements were obtained at baseline 1 (BL1; 2 months before intervention) and baseline 2 (BL2; immediately before intervention), and months 2 (midintervention), 3 (postintervention), and 6 and 15 (follow-up). The numbers of participants evaluated at each time point for each group are as follows: BL1: TCC, $n = 45$; CBT-I, $n = 45$; BL2: TCC, $n = 45$; CBT-I, $n = 45$; month 2: TCC, $n = 38$; CBT-I, $n = 44$; month 3: TCC, $n = 38$; CBT-I, $n = 42$; month 6: TCC, $n = 35$; CBT-I, $n = 40$; and month 15: TCC, $n = 33$; CBT-I, $n = 40$. Shaded area indicates period of exposure to treatment after baseline assessment. Comparisons between BL1 and BL2 were not significant ($t_{377.7} = 0.2$; $P = .60$). Significant pairwise comparisons were found between BL2 and months 2, 3, 6, and 15 (all $P < .001$). No significant differences were found between CBT-I and TCC at BL1, BL2, months 3, 6, and 15 (all $P > .10$), but CBT-I and TCC differed at month 2 ($P < .02$).

Table 3. Changes by Treatment Group

Variable	Post-Treatment			6 Months			15 Months		
	Difference in Change*	P	d	Difference in Change*	P	d	Difference in Change*	P	d
Sleep quality, total score									
PSQI	0.84 (.80)	.30	.24	0.42 (.80)	.61	.12	0.52 (.94)	.59	.13
AISI	0.24 (.77)	.76	.07	0.29 (.86)	.74	.08	0.44 (1.06)	.69	.10
Sleep continuity									
Total sleep time, minutes									
Sleep diary	-4.64 (16.8)	.74	.07	1.00 (17.1)	.96	.01	7.39 (18.4)	.69	.10
Polysomnography	-8.51 (17.2)	.63	.14						
Sleep latency, minutes									
Sleep diary	14.5 (6.1)	.02	.57	6.91 (5.35)	.21	.32	13.3 (6.8)	.06	.49
Polysomnography	5.70 (6.8)	.41	.23						
Wake after sleep onset, minutes									
Sleep diary	1.50 (7.16)	.84	.05	7.13 (8.78)	.42	.20	-2.21 (7.47)	.77	.08
Polysomnography	-14.1 (11.0)	.21	.35						
Sleep efficiency, %									
Sleep diary	5.35 (3.04)	.09	.42	6.56 (3.14)	.041	.52	5.87 (3.47)	.10	.42
Polysomnography	-3.17 (2.6)	.23	.34						
Behavioral symptoms									
Fatigue severity (MDFSI)	-1.45 (2.3)	.53	.15	-2.22 (3.2)	.50	.16	0.98 (3.5)	.79	.07
Daytime sleepiness (ESS)	-0.20 (.70)	.78	.06	-.11 (.81)	.90	.03	0.86 (.90)	.34	.23
Depressive symptoms (IDS-C)	-0.18 (1.4)	.90	.03	0.06 (1.8)	.98	.01	-0.61 (1.5)	.69	.10

Abbreviations: AISI, Athens Insomnia Severity Index; ESS, Epworth Sleepiness Scale; IDS-C, Inventory of Depressive Symptoms; MDFSI, Multidimensional Fatigue Symptom Inventory; PSQI, Pittsburgh Sleep Quality Index.
 *Positive numbers indicate greater decrease for cognitive behavioral therapy for insomnia, negative numbers indicate greater decrease for Tai Chi Chih. Mean difference (standard error difference).

Secondary Outcomes of Fatigue, Daytime Sleepiness, and Depression

For behavioral outcomes of fatigue severity (Fig 4A), daytime sleepiness, and depression (Fig 4B), CBT-I and TCC produced robust improvements (overall treatment effects; all $P < .001$; Table 2). Between-group differences in change of fatigue, sleepiness, or depression from baseline to months 3, 6, and 15 were not significant (all $P > .5$; Table 3)

None of the background variables (Table 1) moderated treatment effects, except nonwhite participants, who showed more improvement for sleep quality with CBT-I than with TCC ($P < .04$). No adverse events, as monitored by project personnel and reported to the principal investigator and data safety monitoring board, occurred.

DISCUSSION

This randomized, partially blinded, noninferiority trial examined the effects of TCC versus CBT-I on insomnia treatment response and secondary outcomes of insomnia remission and sleep and behavior in survivors of breast cancer with comorbid insomnia. Both interventions yielded robust rates of insomnia treatment response, as indicated by marked clinical improvement, or complete or nearly complete remission of insomnia symptoms that were comparable to reported treatment response for CBT-I in survivors of cancer,^{7,12,43-46} adults, and older adults.^{15,21,39,47,61-64} Furthermore, TCC, a mindful movement meditation, was found to be noninferior to CBT-I. Indeed, TCC and CBT-I yielded equivalent rates of insomnia treatment response that were durably

maintained over 1 year of follow-up. The noninferiority of TCC relative to CBT-I contrasts with mindfulness-based stress reduction in which noninferiority was found only at 5 months of follow-up.⁷

Effect sizes of both TCC and CBT-I for improvement in sleep quality and sleep diary measures were large and exceeded mean efficacy of CBT-I for these outcomes in patients diagnosed with cancer, as reported in a recent meta-analysis.¹² Furthermore, CBT-I and TCC yielded improvements in sleep outcomes that were at the level of a minimally important difference for insomnia severity,⁴⁸ with effects comparable to all types of behavioral interventions, including CBT-I and pharmacotherapy.^{7,12,39,43-46,64-69} Both CBT-I and TCC showed similar rates of insomnia remission and similar improvements in sleep quality, sleep diary measures, and daytime impairments of fatigue, sleepiness, and depressive symptoms. The mechanisms that contribute to the benefit of TCC on insomnia are not known, although this practice has been found to reduce sympathetic arousal⁷⁰ and inflammation,^{25-27,71} both of which influence sleep.⁷²⁻⁷⁴

This study is characterized by several strengths, including defined eligibility criteria, use of a modified blinded-to-treatment protocol that was intended to reduce selection bias, random assignment, manualized interventions, matching of treatment exposure, and use of a no-treatment lead-in phase to establish stability of insomnia severity before intervention. TCC and CBT-I were equally credible with similar rates of session attendance, which is clinically significant because self-reported motivation to change sleep behaviors and adherence to treatment is one of the best predictors of treatment outcome. Compared with older adults,²¹ survivors of breast cancer report more severe insomnia

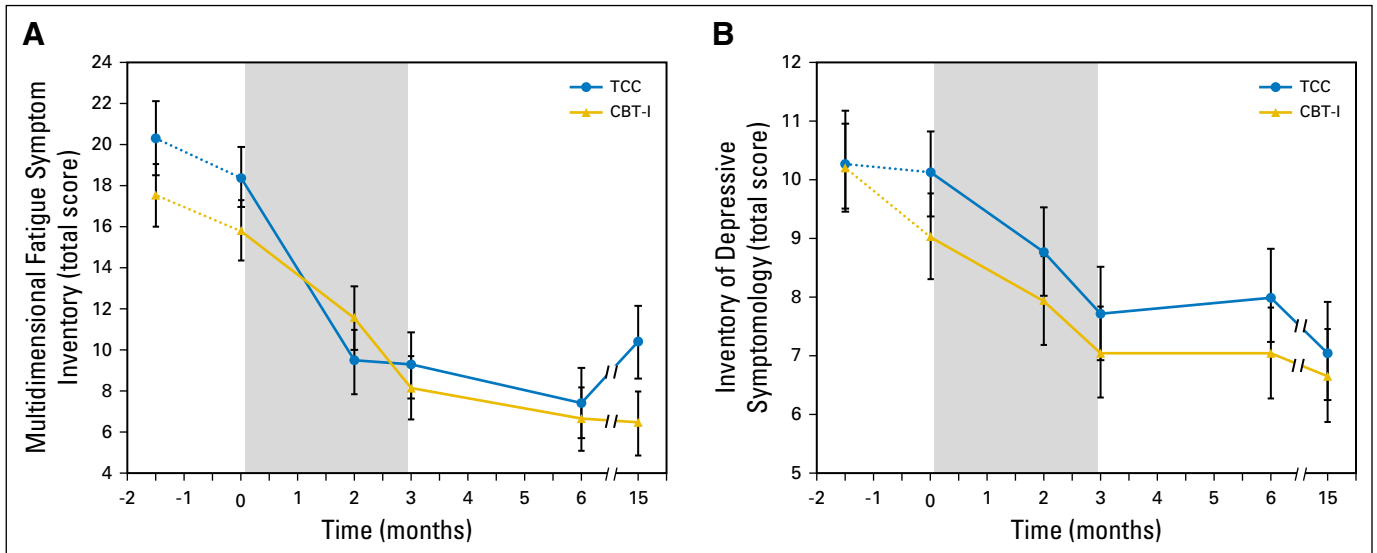


Fig 4. (A) Change in severity of fatigue symptoms from baseline to month 15 follow-up in the cognitive behavioral therapy for insomnia (CBT-I) and Tai Chi Chih (TCC) treatment groups. Higher scores on the Multidimensional Fatigue Symptom Inventory indicate more fatigue severity. Values are means, and bars indicate standard error of measurement. Measurements were obtained at baseline 1 (BL1), baseline 2 (BL2), and months 2, 3, 6, and 15. The numbers of participants evaluated at each time point for each group are as follows: BL1: TCC, n = 45; CBT-I, n = 45; BL2: TCC, n = 45; CBT-I, n = 45; month 2: TCC, n = 38; CBT-I, n = 44; month 3: TCC, n = 38; CBT-I, n = 42; month 6: TCC, n = 35; CBT-I, n = 40; and month 15: TCC, n = 33; CBT-I, n = 40. Shaded area indicates period of exposure intervention after baseline assessment. Comparisons between BL1 and BL2 were not significant ($t_{374.9} = 1.8$; $P = .20$). Significant pairwise comparisons were found between BL2 and months 2, 3, 6, and 15 (all $P < .001$). No significant differences were found between CBT-I and TCC at BL1, BL2, months 2, 3, 6, and 15 (all $P > .10$). (B) Change in clinician-rated severity of depressive symptoms from baseline to month 15 follow-up in the CBT-I and TCC intervention groups. Higher scores on the Inventory of Depressive Symptomology indicate worse depressive symptoms. Values are means, and bars indicate standard error of measurement. Measurements were obtained at BL1, BL2, and months 2, 3, 6, and 15. The numbers of participants evaluated at each time point for each group are as follows: BL1: TCC, n = 45; CBT-I, n = 45; BL2: TCC, n = 45; CBT-I, n = 45; month 2: TCC, n = 38; CBT-I, n = 44; month 3: TCC, n = 38; CBT-I, n = 42; month 6: TCC, n = 35; CBT-I, n = 40; and month 15: TCC, n = 33; CBT-I, n = 40. Shaded area indicates period of administration of intervention after baseline assessment. Comparisons between BL1 and B2 were not significant ($t_{371.5} = 0.7$; $P = .34$). Significant pairwise comparisons were found between BL2 and months 2, 3, 6, and 15 (all $P < .01$). No significant differences were found between CBT-I and TCC at BL1, BL2, months 2, 3, 6 and 15 (all $P > .10$).

complaints and impairments in daytime functioning, which might contribute to motivation and sustained practice of TCC.

This study had several limitations. Women were primarily white and well educated. There was a lack of treatment effect on PSG, which is consistent with prior treatment studies.^{16,21,44,61,68} A lack of correlation between subjective and objective sleep measures is common and is often interpreted as a consequence of the weak ecologic validity of PSG—that is, only one night in the laboratory—rather than a lack of validity of subjective measures.⁷⁴ Finally, there was evidence of a differential rate of drop-out in TCC at month 15 as a result, in part, of reported difficulties adhering to TCC practice outside of sessions, although tests of noninferiority remained robust when taking this into account.

This investigation demonstrates that a mindful movement meditation, TCC, was noninferior to CBT-I for long-term treatment of insomnia in survivors of breast cancer. Given that standardized TCC is both scalable and community accessible compared with the limited availability of CBT in most medical centers, immediate access to TCC would address the need to reduce the morbidity associated with insomnia in survivors of breast and

other cancers with treatment benefits commensurate with the status quo of clinical treatment approaches to insomnia.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Tai Chi Chih Compared With Cognitive Behavioral Therapy for the Treatment of Insomnia in Survivors of Breast Cancer: A Randomized, Partially Blinded, Noninferiority Trial**

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No relationship to disclose