TITLE: Brief Behavioral Intervention For Insomnia During Chemotherapy

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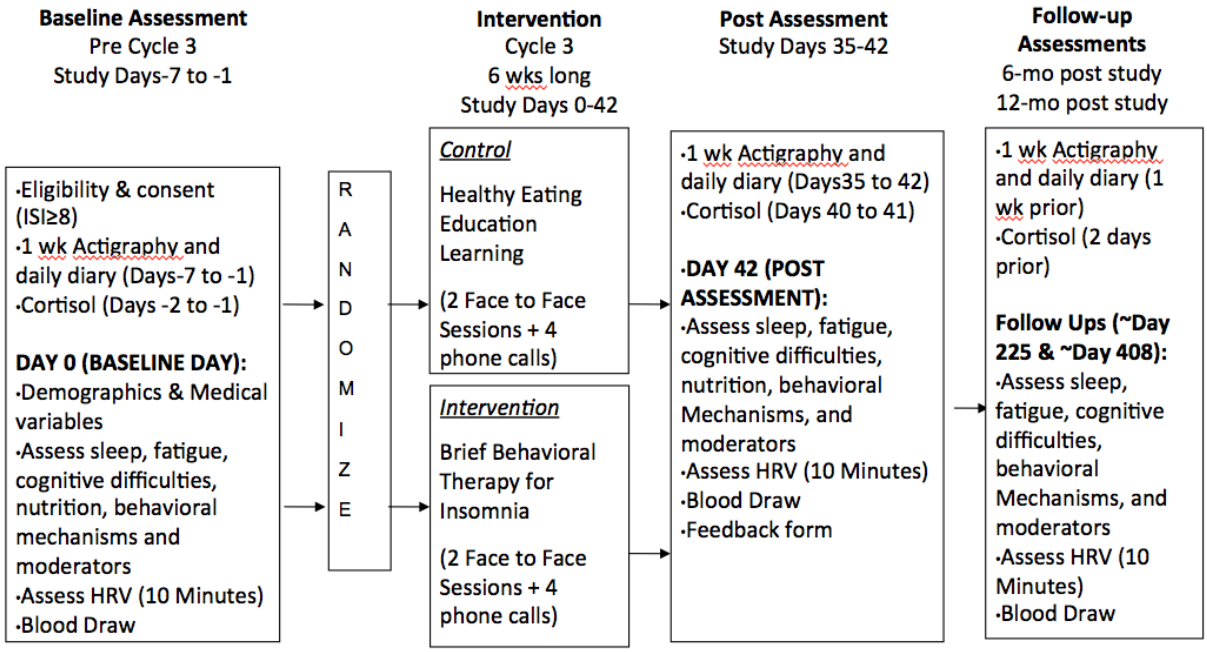
PROTOCOL SYNOPSIS

TITLE	Brief Behavioral Intervention For Insomnia During Chemotherapy
STUDY PHASE	Phase III
INDICATION	Insomnia
INVESTIGATIONAL PRODUCT OR PROCEDURE	Brief Behavioral Therapy for Insomnia (BBT-I) **H**ealthy **E**ating Educ**a**tion **L**earning (HEAL)
PRIMARY OBJECTIVE(S)	The purpose of this study is to test the efficacy of brief behavioral therapy versus control condition that accounts for time and attention (nutrition education) in the treatment of insomnia in humans.
SECONDARY OBJECTIVE(S)	To assess the impact of different biomarkers on sleep disruption and other patient reported outcomes
TREATMENT SUMMARY	This research is designed to determine the efficacy of the BBT-I in comparison with the attention-matched behavioral control in reducing insomnia, fatigue, and cognitive difficulties in breast cancer patients. In addition, this study will examine the potential involvement of moderators (age, depression, anxiety, and hot flashes), specific behavioral mechanisms (maladaptive sleep behaviors, dysfunctional beliefs and attitudes), and physiological mechanisms (dysregulated circadian rhythms, disrupted wake-sleep cycles, and autonomic tone) as potential mediators of intervention-related changes in insomnia and the secondary outcomes of fatigue and cognitive difficulties. To address these aims, 180 breast cancer patients with acute insomnia during chemotherapy treatment will be recruited and randomized to receive either BBT-I or a behavioral control focused on healthy eating education. Each intervention condition will consist of 2 face-to-face sessions + 4 phone calls, delivered over a period of six weeks. Assessments will include sleep diary, questionnaires, neuropsychological testing, actigraphy, heart rate variability measurement, and salivary cortisol collection at baseline, post-intervention, and 6- and 12 months follow ups. By offering this intervention during

	chemotherapy when patients are just beginning to develop insomnia, we hope to alleviate and avoid the development of chronic insomnia in the survivorship phase.
SAMPLE SIZE	180
STATISTICAL CONSIDERATIONS	The primary endpoint is insomnia. Secondary endpoints include cognitive functioning, fatigue, depression, HRV, cortisol and biomarkers of sleep and stress. The estimated power to detect the group difference in change in ISI is 0.88-0.99 (d=0.4 to 0.6, alpha=.05, two-tailed) with N=180 (90 BBT-I, 90 control).

SCHEMA


Baseline Assessment
Pre Cycle 3
Study Days-7 to -1
Intervention
Cycle 3
6 wks long
Study Days 0-42
Post Assessment
Study Days 35-42
Follow-up Assessments
6-mo post study
12-mo post study
•Eligibility & consent (ISI≥8)
•1 wk Actigraphy and daily diary (Days-7 to -1)
•Cortisol (Days -2 to -1)
DAY 0 (BASELINE DAY):
•Demographics & Medical variables
•Assess sleep, fatigue, cognitive difficulties, nutrition, behavioral mechanisms and moderators
•Assess HRV (10 Minutes)
•Blood Draw
RANDOMIZE
Control
Healthy Eating Education Learning
(2 Face to Face Sessions + 4 phone calls)
Intervention
Brief Behavioral Therapy for Insomnia
(2 Face to Face Sessions + 4 phone calls)
•1 wk Actigraphy and daily diary (Days35 to 42)
•Cortisol (Days 40 to 41)
•DAY 42 (POST ASSESSMENT):
•Assess sleep, fatigue, cognitive difficulties, nutrition, behavioral Mechanisms, and moderators
•Assess HRV (10 Minutes)
•Blood Draw
•Feedback form
•1 wk Actigraphy and daily diary (1 wk prior)
•Cortisol (2 days prior)
Follow Ups (~Day 225 & ~Day 408):
•Assess sleep, fatigue, cognitive difficulties, behavioral Mechanisms, and moderators
•Assess HRV (10 Minutes)
•Blood Draw

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Example)

BBT-I	Brief Behavioral Intervention for Insomnia
HEAL	Healthy Eating Education Learning
BC	Breast Cancer Patients
ISI	Insomnia Severity Index
HRV	Heart Rate Variability
RCT	Randomized Clinical Trial
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
ITA	Infusion Treatment Area
RSA	Respiratory Sinus Arrhythmia
CBT-I	Cognitive Behavioral Therapy for Insomnia
HPA	Hypothalamic Pituitary Axis
WRC	Waking Rise Cortisol
CTCAE	Common Terminology Criteria for Adverse Events
CRF	Case Report Form
RA	Research Assistant
QOL	Quality of Life
PNS	Parasympathetic Nervous System
SCN	Suprachiasmatic Nucleus
RCT	Randomized Clinical Trial
BCC	Breast Cancer Connections' Awareness Task Force
BFI	Brief Fatigue Inventory
ISI	Insomnia Severity Index
MCAB	Mobile Cognitive Assessment Battery
CAD	Clinical Assessment of Depression
CTMT	Comprehensive Trail Making Test
COWAT	Controlled Oral Word Association Test
HVLT-R	Hopkins Verbal Learning Test-Revised
GLTEQ	Godin Leisure Time-Exercise Questionnaire
SBSRS	Sleep Behavioral Self Rating Scale
PSQI	Pittsburgh Sleep Quality inventory
DBAS	Dysfunctional Beliefs about Sleep
DERS	Difficulties in Emotion Regulation Scale
NKQ	Nutrition Knowledge Questionnaire
rMEQ	Reduced Horne Ostberg Morningness Eveningness Questionnaire
EORTC	European Organization for Research and Treatment of Cancer
WASO	Wake After Sleep Onset

1. OBJECTIVES

1.1. Primary Objective

- To evaluate the efficacy of the BBT-I in treating insomnia among breast cancer patients receiving chemotherapy.

1.2. Secondary Objectives

- To evaluate the efficacy of the BBT-I in treating cancer-related symptoms such as cancer-related fatigue and cognitive difficulties in breast cancer patients receiving chemotherapy.

- To examine potential moderators and mediators of BBT-I intervention effects on insomnia, cognitive difficulties, and fatigue. In particular, we are interested in age, depression and anxiety and side effects (hot flashes) as potential moderators of the intervention effects as well as evaluating modifiable behavioral and physiological mechanisms as hypothesized mediators

2. BACKGROUND

2.1 Study Disease

In the United States, breast cancer accounts for nearly 1 in 3 cancers diagnosed among women and causes the most cancer related deaths among women after lung cancer. It is estimated that 1 in 8 women will develop breast cancer during her lifetime in the United States, with over 230,000 new cases of invasive breast cancer and almost 40,000 breast cancer deaths expected in 2013 alone.[1] One major problem reported by breast cancer patients is sleep disruption, and this study looks to understand how receiving BBT-I impacts quality of life in women who have breast cancer.

2.2 Study Procedure

Cancer-related sleep problems are among the most frequently reported side effects resulting from cancer diagnosis and treatment. Nearly 80% of cancer patients report sleep problems during chemotherapy or radiation therapy, and 65% of cancer survivors continue to report sleep problems six months after the completion of treatments. Although not always specified, “sleep problems” or “sleep complaints” generally refer to one or more of the following symptoms of insomnia: difficulty falling or staying asleep, poor sleep quality, and short sleep duration. The pathophysiology of insomnia in cancer is not understood. However we previously found in breast cancer patients that poor sleep is associated with dysregulation of circadian rhythm changes in the HPA axis, and attenuation of parasympathetic tone as measured via respiratory sinus arrhythmia (RSA). A focus on insomnia is important for a variety of reasons. First, insomnia that occurs during acute illness and treatment exacerbates cancer progression and worsens treatment-related symptoms such as fatigue and cognitive difficulties. Second, insomnia that occurs following treatment is linked to reduced quality of life, development of psychiatric illness and

poor health status. Finally, our work suggests that objectively measured poor sleep efficiency is a significant independent prognostic factor for disease progression in breast cancer (Hazard Ratio (HR), 0.96, 95% CI, 0.93 to 0.98, $p<0.001$) 6 years later. We believe that research focused on the etiology and management of insomnia in cancer patients is crucial to help decrease morbidity and perhaps mortality associated with poor sleep.

The proposed project extends our previous research (NCI-funded K award) by testing a novel Brief Behavioral Therapy for Insomnia (BBT-I) in breast cancer patients receiving chemotherapy. Our pilot data suggests that BBT-I is an acceptable and feasible intervention that shows promise in reducing insomnia. In addition, we believe that treating insomnia will potentially lead to improvement in cancer-related symptoms such as fatigue and cognitive complaints, and it may also help produce positive effects on the overall health of cancer patients by normalizing circadian rhythms and autonomic tone (RSA). The proposed randomized clinical trial has 2 intervention arms (BBT-I vs. Healthy Eating Control). Both interventions consist of 2 face-to-face sessions + 4 phone calls over a six-week period. The study will recruit 180 female breast cancer patients receiving chemotherapy and will test the BBT-I efficacy in reducing insomnia and fatigue and alleviating cognitive difficulties. The BBT-I is modeled on standard cognitive behavioral therapy for insomnia (CBT-I) and includes both stimulus control and sleep scheduling but has been successfully modified to make it more suitable for cancer patients undergoing chemotherapy with recently developed insomnia symptoms. In addition, we will examine potential moderators of the intervention effects as well as modifiable behavioral and physiological mechanisms as mediators of changes in insomnia and other effects of the intervention.

For clinicaltrials.gov compliance

2.3 Rationale

Background: Sleep disturbance, particularly insomnia, is prevalent in cancer patients undergoing chemotherapy. Our preliminary data show that our novel intervention, Brief Behavioral Therapy for Insomnia (BBT-I), significantly reduces insomnia in breast cancer patients receiving chemotherapy. BBT-I is modeled on standard cognitive behavioral therapy for insomnia (CBT-I), including both stimulus control and sleep scheduling, and has been successfully modified to make it more suitable for breast cancer patients undergoing adjuvant or neoadjuvant chemotherapy with recently developed insomnia symptoms. Our preliminary research suggests that BBT-I is an acceptable and feasible intervention for insomnia in breast cancer patients that might also lead to improvement in fatigue and cognitive difficulties.

Methods: This research is designed to determine the efficacy of the BBT-I in comparison with the attention-matched behavioral control in reducing insomnia, fatigue, and cognitive difficulties in breast cancer patients. In addition, this study will examine the potential involvement of moderators (age, depression, anxiety, and hot flashes), specific behavioral mechanisms (maladaptive sleep behaviors, dysfunctional beliefs and attitudes), and physiological mechanisms (dysregulated circadian rhythms, disrupted wake-sleep cycles, and autonomic tone) as potential mediators of intervention-related changes in insomnia and the secondary outcomes of fatigue and cognitive difficulties. To address these aims, 180 breast cancer patients with acute insomnia during chemotherapy treatment will be recruited and randomized to receive either BBT-I or a behavioral control focused on Healthy Eating Education Learning. Each intervention condition will consist of 2 face-to-face sessions + 4 phone calls, delivered over a period of six weeks.

Assessments will include sleep diaries, questionnaires, neuropsychological testing, actigraphy, heart rate variability measurement, blood draw, and salivary cortisol collection at baseline, post-intervention, and 6- and 12 months follow ups. By offering this intervention during chemotherapy when patients are just beginning to develop insomnia, we hope to alleviate and avoid the development of chronic insomnia in the survivorship phase.

Insomnia in Cancer Patients is Prevalent and Undertreated. Insomnia is defined as difficulty falling or staying asleep, poor sleep quality, and/or short sleep duration. It is one of the most frequently reported side effects resulting from cancer treatment.[2] Our research and that of others suggest that insomnia among cancer patients is two to three times higher than in the general population.[3] Nearly 80% of cancer patients undergoing chemotherapy report insomnia symptoms, with 30 to 50% of newly diagnosed cancer patients meeting the criteria for an insomnia diagnosis.[3-5] Our prospective study showed that low sleep efficiency is a prognostic factor for significantly shorter survival in women with advanced breast cancer (BC) independent of known other prognostic medical factors.[6,7] Despite the high prevalence of insomnia in cancer patients, it is commonly undertreated[8] and our data shows that it doesn't respond to traditional talk therapy.[9] A sizeable number of women with early-stage BC (30%) report having mood problems or depression.[10] Data from multiple studies indicate that the frequency of depression in patients with a variety of diagnoses receiving various treatments can range from 15 to 38% and that depression interferes significantly with quality of life (QOL).[10,11] Frequently, patients report that depression begins with treatment, continues during the course of chemotherapy, and declines somewhat but persists at a higher-than-baseline rate after treatment is over. Research supports the concept that depression does not occur in isolation but instead occurs in association with insomnia. These data are consistent with the concept that depression and insomnia are highly correlated and suggest that treatment of insomnia might affect depression and influence QOL.[9,12,13]

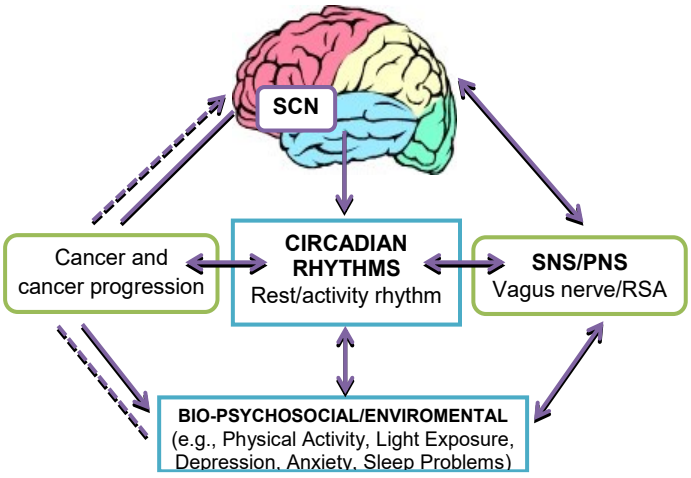
Insomnia and Cognitive Decline in Cancer are Understudied and May Share Common Causative Factors: Although insomnia is prevalent in cancer patients, it rarely occurs in isolation. Up to 78% of cancer survivors who have received adjuvant chemotherapy demonstrate significant difficulties with memory, attention, processing speed, and executive function.[14-16] Cancer is associated with increased risk for cognitive decline, extends disease-related disability, and interferes with treatment compliance.[17-20] Thus, sleep and cognitive problems may share common causative factors that result in an interaction between these two symptoms. Additionally, sleep deprivation is associated with cognitive impairment in healthy individuals, [21-24] and therefore may independently contribute to cognitive difficulties following cancer chemotherapy. Thus far, the role of sleep problems in chemotherapy-related cognitive deficits has not fully been examined.

Insomnia and Cancer-Related Fatigue (CRF) Frequently Co-Occur: A sizeable minority of women with early-stage breast cancer (30%) report having daytime sleepiness or fatigue.[25,26] Data from multiple studies indicate that in patients with a variety of diagnoses receiving various chemotherapy treatments the frequency of CRF can range from 70% to 100%. Frequently, patients report that fatigue begins with treatment, continues during the course of chemotherapy, and declines somewhat but persists at a higher-than-baseline rate after treatment is over, sometimes lasting for months or even years after the end of cancer treatment. In addition to the limits fatigue imposes on the patient's ability to engage in desired activities (during or after treatment), it also prompts patients to engage in behaviors to cope with their fatigue (i.e., lying down, taking naps, spending more time in bed [awake or asleep]). As discussed below, these

coping behaviors may set the stage for the development of insomnia. Davidson[5] et al. showed that patients who reported being overly fatigued were 2.5 times more likely to have insomnia than others. A body of literature now supports the concept that CRF does not occur in isolation but instead occurs in association with sleep disturbance. While most of these studies are correlational in nature, they all suggest that insomnia is: 1) positively correlated with fatigue, 2) more severe in fatigued than in non-fatigued patients, and 3) bidirectionally related to fatigue.[27-30] *These data are consistent with the concept that fatigue and insomnia are highly correlated and suggest that treatment of insomnia might affect fatigue.*

The HPA Axis and Circadian Rhythms May Contribute to Insomnia in Cancer Patients. The precise physiological pathways involved in the development of insomnia and their relationships with cancer and its treatments are unknown. There are many biophysiologic processes (e.g., circadian activity rhythms, heart rate variability, inflammation, diurnal cortisol, melatonin and other hormonal rhythms) through which behavioral interventions may influence sleep. It is not possible (practically or financially) to study all mechanisms in one phase II clinical trial. In this phase II trial we will focus on two specific possible biophysiologic mechanisms: circadian activity rhythms and heart rate variability. Circadian rhythms and stress-related responses—particularly involving the hypothalamic-pituitary-adrenal axis (HPA)—are two interrelated regulatory networks that communicate with each other through multiple signaling pathways. Research suggests that insomnia is prevalent in cancer patients and associated with dysregulated circadian rhythm and HPA axis function.[31-35] Studies have indicated that circadian disruption is prevalent in cancer patients and survivors, and that circadian disruption has been implicated as a risk factor for various cancers.[36-39] Flattened diurnal cortisol patterns are associated with more awakenings during the night, and are associated with shorter survival in metastatic BC.[40]

Figure 1. Relationship between sleep disruption, circadian rhythms and autonomic nervous system



In addition to circadian rhythm and HPA regulatory systems, emerging evidence suggests that the autonomic nervous system is implicated in the development of insomnia among cancer patients.[41] Falling asleep involves a neurophysiological switch from predominantly sympathetic to parasympathetic tone.[42] Our data showed that cancer patients who have insomnia also have attenuated parasympathetic tone as measured by respiratory sinus arrhythmia (RSA).[43] RSA measures the variation of heart rate with respiration and changes in heart rate and can be used as a proxy measurement of general parasympathetic tone.[44] The parasympathetic nervous system (PNS) is influenced by the circadian system, while the sympathetic nervous system is influenced by the sleep-wake system.[45] The suprachiasmatic nucleus (SCN) is a master circadian clock, which regulates autonomic and HPA function through endocrine modulation. Emerging evidence in both healthy people and cancer patients suggests that circadian rhythms and the autonomic nervous system are dysregulated in those with sleep problems via multiple photo (e.g., light exposure) and non-photo sensitizers (e.g., cancer treatments, physical activity). In cancer patients and survivors, circadian rhythm disruption,

autonomic dysfunction and sleep problems are prevalent (Figure 1).[3,8,9,43,46] However, no studies known to the authors have examined all three systems and attempted to intervene. Understanding the nature of the relationship between sleep problems, circadian rhythm and autonomic nervous system activity is of considerable clinical and research interest in cancer, because it may lead to the development of new therapeutic approaches. Treating insomnia in patients may improve quality of life and overall health by normalizing circadian rhythms and autonomic tone.

Cognitive Behavioral Therapy for Insomnia (CBT-I). CBT-I is considered the gold standard for insomnia management in the general population.[47,48] CBT- I is a 7-session therapist-led intervention consisting of stimulus control (instructions for behavior modification), sleep restriction, and cognitive restructuring to address maladaptive sleep cognitions. Recently, several randomized clinical trials have been conducted using CBT-I in cancer survivors. The largest of these studied 150 patients who had completed cancer therapy for various cancers.[49] The CBT-I group showed significant improvements in insomnia, depression, and QOL symptoms compared to no improvements on these parameters in the control group, with effects maintained at 6-months. Similar results were obtained in earlier RCTs that utilized CBT-I.[50,51] However, CBT-I is time-consuming (7 sessions), costly (conducted by a clinical psychologist who is certified in behavioral sleep medicine), and can make patients feel sleep-deprived.

Behavioral Trials in Cancer Patients Undergoing Chemotherapy are Extremely Limited. Although research suggests that patients undergoing chemotherapy have more insomnia and may be at risk for developing chronic insomnia compared to patients receiving other treatments or survivors, we identified only two RCTs attempts.[52-54] The first trial[54] utilized a non-specific sleep intervention and failed to show efficacy. The second trial [52,53] showed initial improvement, but failed to improve sleep at follow-up. The clinical significance of that trial is unclear given that the patients did not have clinically significant insomnia at baseline. Currently, there are no treatment recommendations specifically developed to treat insomnia in cancer patients undergoing chemotherapy. If results of our NCI-funded K award pilot study are confirmed, our intervention will impact how we treat symptoms during chemotherapy by showing that behavioral interventions can be successfully implemented in a clinic, change the standard of care for insomnia (reduce sleep medication use) and improve understanding of the pathophysiology (role of circadian and autonomic regulation) of insomnia in cancer patients.

2.4 Study Design

For clinicaltrials.gov and Stanford Clinical Trials Directory compliance

- Primary purpose for the protocol:
  - **Supportive Care**: protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects or mitigate against a decline in the subject's health or function. In general, supportive care interventions are not intended to cure a disease.

- Interventional model:
  - **Parallel:** one of two groups in parallel for duration of study.

- Intervention arms:
  - **There are 2 intervention arms:**
    Group 1: Brief Behavioral Therapy for Insomnia (BBT-I).

Group 2: Healthy Eating Education Learning (HEAL) control group.

- Masked:
  - **Open:** no masking is used

- Randomization:
  - **The study will be randomized.**

- Type of Primary Outcome:
  - **Efficacy.**

2.5 Correlative Studies Background

Cortisol: The precise physiological pathways involved in the development of sleep problems and their relationships with cancer and its treatments are largely unknown. Circadian rhythms and stress-related responses—particularly involving the hypothalamic-pituitary-adrenal axis (HPA)—are two interrelated regulatory networks that communicate with each other through multiple signaling pathways. Research suggests that sleep problems are prevalent in cancer patients and are associated with dysregulated circadian rhythm.[31,33-35,55] In the last two decades, studies have indicated that circadian disruption is prevalent in cancer patients and survivors,[36] and that circadian disruption associated with shift work has been implicated as a risk factor for various cancers.[37-39] Flattened diurnal cortisol patterns are associated with self-reports of more awakenings during the night, and are associated with shorter survival time with metastatic breast cancer (BC).[56]

Inflammatory Cytokines and Insomnia: Data show that sleep disruption and sleep loss are associated with dysregulated immune functioning as measured by increased production of interleukin-6 (IL-6)[19], tumor necrosis factor[20, 21] and C-reactive protein.[22] Several studies have found that insomnia disrupts immune functioning[23, 24] to a greater extent than depression, thus this increase cannot be explained by the comorbid depression. To date, the consequences of insomnia in cancer patients and survivors have not been fully examined; however, recent research suggests that sleep disturbances and/or circadian dysregulation might be adversely related to cardiac morbidity[25], immune functioning[26], cancer-stimulating cytokines, and psychiatric morbidity.[25,27-29] These preliminary results suggest that examination of pro inflammatory cytokines associated with insomnia can shed light on etiology and treatment of insomnia.

Telomeres are repeated regions of DNA at the ends of chromosomes that primarily serve to protect against loss of integral DNA sequence during DNA replication. However, the length of telomeres shorten with time and repeated cell replication, and studies have shown that telomere shortening often correlates with early mortality, lifetime depression exposure, psychological stress, oxidative stress, and increased risk for certain types of cancer. To date, the link between telomere shortening and sleep disruption or maintenance has not been fully explored. Because there is circumstantial evidence linking telomere shortening to Obstructive Sleep Apnea Syndrome, exploring the correlation between the length of telomere and sleep may uncover a novel way to both diagnose and treat sleep disruption in patients. Thus, measurement of telomere length can help explain presence of sleep disturbance. In addition, gene expression in relation to insomnia in cancer may be explored if additional funds or collaborations develop.

Preliminary Data

Pathophysiology of sleep problems in cancer. In our pathophysiologic study (Palesh et al.)[43] in women with metastatic BC, sleep was assessed by means of questionnaires and wrist actigraphy. Vagal regulation was assessed via respiratory sinus arrhythmia (RSA_{TF}). Longer nocturnal wake episodes were significantly associated with a flatter diurnal cortisol slope. Sleep problems were also associated with diminished RSA. Higher RSA was significantly related to higher sleep efficiency and a correspondingly lower number of wake episodes and lower waking after sleep onset (WASO), and lower average length of nocturnal wake episodes. While demographics, disease severity, and psychological variables all explained some portion of the development of sleep problems, 4 of the 6 sleep parameters examined (sleep efficiency, WASO, mean number of waking episodes, average length of waking episode) were best explained by RSA. These data provide evidence for an association between disrupted nocturnal sleep and reduced RSA the following day. They suggest that the stress-buffering effects of sleep may be associated with improved parasympathetic tone and normalized circadian rhythmicity as evidenced by cortisol patterns during the day and greater RSA.

Impact of BBT-I on Circadian Rhythms. [57,58] Salivary cortisol was measured pre and 1-month post BBT-I (5 x/day for 2 days) in 30 women. ANCOVA controlling for baseline waking rise cortisol (WRC) entered as a covariate and baseline WRC*Arm (BBT-I vs. education on sleep hygiene) yielded a significant interaction. Higher WRC is a sign of a healthy HPA reactivity, as having a higher WRC can lead to an increase in homeostatic drive for sleep. For BC patients participating in BBT-I, there was a significant difference between those with low and high baseline WRC scores at the 1-month follow-up ($F(1, 23)=6.46$, $p=0.018$, revised eta 0.47, a large effect). However, there were no significant differences for the patients who participated in the control group. These findings suggest that BBT-I influences circadian rhythms by improving WRC.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Be female and have a diagnosis of BC (Stage I-III).

3.1.2 Be scheduled for planned cancer treatment (e.g. chemotherapy or biologics such as herceptin).

3.1.3 Have at least 6 weeks of cancer treatment (e.g. chemotherapy or biologics such as herceptin) remaining.

3.1.4 Be at least 21 years of age.

3.1.5 Be able to understand written and spoken English.

3.1.6 Report sleep disturbance of 8 or greater on the ISI, and report insomnia that began or got worse with diagnosis of cancer or treatment with chemotherapy (to exclude pre-existing, chronic insomnia).

3.1.7 Have a Karnofsky score $\geq$ 70 to ensure that patients are able to participate in intervention and assessments.

3.2 Exclusion Criteria

MUST NOT have a documented or self-reported, current diagnosis of any of the following conditions that would make it unsafe or impossible to adhere to the study protocol &/or endorse the last criterion

3.2.1 /Unstable self-reported medical or psychiatric illness (Axis I – current or within the last 5 years) that would make it unsafe or impossible to adhere to the study protocol

3.2.3 Substance abuse or dependence or met criteria within past year

Sleep apnea or restless leg syndrome (RLS)

3.2.5 Are unable or unwilling to discontinue anxiolytics within 4 hours of education sessions

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Randomization Procedures

Participants will be randomized into one of two arms: BBT-I or HEAL. The study data manager will use a computerized random number generator to assign participants into arms. In order to keep study blinded from assessors, only the interventionist providing the intervention, the data manager, and the clinical intervention supervisor will know randomization.

3.5 Study Timeline

Primary Completion:

The study will reach primary completion 48 months from the time the study opens to accrual.

Study Completion:

The study will reach study completion 60 months from the time the study opens to accrual.

4. TREATMENT PLAN

Breast Cancer Patients: We will recruit our participants from the Stanford Women's Cancer Center utilizing clinician and support group referrals as we have done in our pilot study. The PI is the Director of Cancer Survivorship Research Program at Stanford Medical Center, and our team has an ongoing relationship with all of the breast medical oncologists at Stanford. Dr. Blayney is the Medical Director of Stanford University Cancer Center and Co-Investigator on the study. During the breast cancer disease management group meetings and tumor board, new cancer patients are discussed and evaluated by Dr. Blayney and the study's personnel for eligibility for the study. The first step, as with all protocols in our lab, is to identify potentially eligible patients via our center's electronic medical records system (EPIC). In the present study, at or around the time of the patient's first chemotherapy treatment, approval will be sought from the patient's oncologist to invite patients who meet the preliminary eligibility criteria to participate in the study. We also have ongoing support from the Breast Cancer Connections' (BCC) Advocacy Task Force. The BCC sees several hundred breast cancer patients and survivors annually and has agreed to continue referring new patients to this study.

Procedures: During the consent process, all study subjects will be screened for eligibility by research staff at Stanford University. By signing the consent form, participants will grant permission to obtain their cognitive test data from another source (such as another research study or clinical testing) for this study if they do not complete the neuropsychological testing portion in this study. Participants will undergo four assessments (~one hour each) at baseline, post-treatment (6 weeks), and 6-month (30 weeks), and 12-month (58 weeks) follow-ups. During each of the assessments, participants will wear a heart rate monitoring device (Bodyguard Firstbeat®) that records heart rate variability for 10 minutes at each assessment point. Heart rate variability data will not be collected from a participant if she has an implanted device for heart failure (e.g., pacemaker, defibrillator, left ventricular assist device, etc.).Study participants will be asked to maintain a daily sleep diary for 7 days at baseline, post intervention, 6-month follow-up and 12-month follow-up. Patients will also be requested to wear an actigraph on their wrist (Actiwatch 64®, MiniMitter) for 7 days at baseline, post intervention, and follow-ups, and collect saliva for 2 days at each assessment point. Participants will collect saliva starting 2 days prior to their chemotherapy appointments to avoid interaction with corticosteroids. The RA responsible for assessment will make follow-up calls at each assessment point to each participant to promote compliance, prompt completion, and assess potential side effects of the behavioral interventions. In addition, participants will be asked to provide a small amount of blood (approximately 1-2 tablespoons) at each assessment.

4.1 General Concomitant Medication and Supportive Care Guidelines

The study permits patients to remain on medications prescribed as part of their treatment regimen. We are excluding patients on daily sleep medications for our clinical trial. Our study procedures and intervention are supportive care only. They are an add-on to their clinical care for breast cancer.

4.2 Criteria for Removal from Study

Patients can be removed from the study if they experience disease progression that requires extended hospitalization or experience symptoms that make participation in the study difficult or impossible (e g., development of psychosis, extreme pain, nausea). Participants are free to

withdraw at any time if the treating oncologist deems withdrawal necessary or if the patient decides to withdraw for any reason. All of our participants are receiving the behavioral interventions in addition to their usual care.

4.3 Alternatives

The patient may elect not to participate as an alternative to this study. They will continue to receive their normal care. During informed consent, we will describe our behavioral interventions, study procedures and questionnaires. We will inform our participants about potential risks despite their being minimal. We anticipate that a small proportion of our participants might potentially experience mild discomfort implementing BBT-I procedures (They might experience daytime fatigue and/or sleepiness, and/or memory and concentration difficulties). We will also inform them of the limits in confidentiality, because the intervention may take place in an open area in the ITA if absolutely necessary. We do not have an alternative treatment.

5. INVESTIGATIONAL PROCEDURE INFORMATION

5.1 Investigational Procedure

BBT-I Intervention Group: 90 BC patients will be randomized to receive the BBT-I. BBT-I includes both stimulus control and sleep scheduling, however it has been modified from CBT-I to make it more suitable for cancer patients undergoing chemotherapy with recently developed sleep problems. The main intervention component is one face-to-face 60-minute session with a trained staff member during which time an individually tailored "sleep prescription" is developed. There will also be four 15-minute phone calls and a second 60-minute face-to-face "booster" session. The second face-to-face session will ideally occur during the third or fourth week depending on the patient's chemotherapy regimen.

BBT-I is a novel intervention that applies innovative cancer-specific chronorehabilitation techniques to effectively treat acute insomnia among patients receiving chemotherapy in the infusion clinic. It is comprised of the following four components: 1) **chronorehabilitation education** (e.g., information on the contribution of circadian disruption to insomnia in the context of cancer and cancer treatment, a review of the cancer-specific behavioral model of insomnia, and discussion regarding how insomnia and fatigue may co-occur and interact.); 2) **light and stimulus control** (e.g., decrease light exposure at night and increase light exposure during the day, do not go to bed until sleepy, and get out of bed if not sleeping); 3) **encouragement of physical activity and discouragement of napping** (e.g., increase exercise and limit naps to 2 per day and no longer than 45 minutes); and 4) **sleep compression** (e.g. increasing motivation to regulate sleep and wake cycles, and go to bed later by at least 15 minutes if sleep efficiency is less than 85%). Patients are told that on their sick days (e.g., days post chemotherapy) they can nap and sleep as much as they need to. In our pilot, we found that patients successfully moderated their sleep prescription on the days when they were not feeling well.

Healthy Eating Education Learning (HEAL) control group**:** 90 BC patients will be randomized to receive HEAL. HEAL will control for attention and provide a behavioral "placebo." This control condition will consist of 2 face-to-face sessions and 4 phone calls. The content of the intervention is provided by the NCI: PDQ® Nutrition in Cancer Care. The topics will include nutritional implications of chemotherapy, nutrition screening and assessment, and nutritional suggestions for symptom management (e.g., nausea). To improve the credibility of HEAL

intervention for sleep; the therapists will discuss the connection between healthy eating and good sleep. We expect this to be an aspect of intervention that should bolster the credibility of the control condition as there are sound reasons to think that nutrition could have some effect on insomnia. Nevertheless, we anticipate the effects of HEAL on insomnia would be weak given the evidence behind behaviors that influence sleep which are not targeted by HEAL. In addition, the healthy eating education control has successfully been used as an attention control group for sleep intervention during chemotherapy.[52,59]

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Intervention Description

Women diagnosed with breast cancer receiving chemotherapy will be randomized to either Brief Behavioral Therapy for Insomnia (BBT-I) or Healthy Eating Education Learning (HEAL) control group. BBT-I is a novel intervention that combines chronorehabilitation and cognitive behavioral therapy for insomnia (CBT-I) techniques that are specifically adapted for women diagnosed with breast cancer who are undergoing treatment. Patients randomized to BBT-I will receive 2 face-to-face sessions and 4 phone calls. The control group is patterned after the control group used in a large RCT [52,53]. HEAL will control for the non-specific components of time, attention, and health education that are not specifically related to sleep management. The control treatment will involve 2 face-to-face sessions and 4 phone calls exactly like BBT-I.

5.2 Availability

Personnel who are trained in the BBT-I and HEAL interventions and are supervised by a clinical psychologist will conduct the sessions with each participant.

5.3 Agent Ordering

N/A; There is no drug utilized in this study.

5.4 Agent Accountability

N/A; There is no drug utilized in this study.

6. DOSE MODIFICATIONS

Half of the participants will be randomized to BBT-I and the other half will be randomized to HEAL. Both groups will receive 6 sessions. There will be no modification in the number of sessions received.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

BBT-I may result in temporary increases in daytime fatigue and/or sleepiness, and/or memory and concentration difficulties. Blood drawing may cause pain and bruising at the site where the blood is taken, and sometimes, it causes people to feel light-headed or even to faint. Rarely people might get an infection at the site of the needle stick. Heart rate monitor electrodes and the gel used to attach them may cause a skin reaction.

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 after the last dose of the study treatment.

SAEs CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

8.1.1 (Inflammation, Telomeres and Circadian Disruption and Sleep – Laboratory Correlative Study #1)

8.1.1.1 Blood collection will be done to estimate hematocrit, hemoglobin, and cytokines (and telomere length. Patients will collect saliva 5 times a day over a course of two days (when they first wake up, 30 minutes after waking, 12PM, 5PM and before bedtime). Saliva will be stored in the patients' refrigerator over the course of two days and then returned at assessment to be stored at the Department of Psychiatry.

8.1.1.2 Blood draws will be conducted at either Stanford Hospital Drop-In or CTRU labs. Ideally, the blood samples will be drawn first thing in the morning after patients have fasted since midnight. A minimum of 4 hours is required if the patient is unable to come for a blood draw the first thing in the morning. A one- hour resting period is required. However, if an afternoon fasting sample is the only time that a patient is available, then we will collect at that time point. Whether the collection time is in the morning or afternoon, the collection time will remain consistent within each subject once the baseline is collected. We will keep records of the patient's last meal, length of resting period and time of blood draw.

8.1.1.3 Samples will be processed at Stanford Labs where they will be spun and aliquoted, if shipment to another site is warranted, the samples will be shipped de-identified via FedEx and following bloodbourne pathogen protocol for shipping. All of the study staff arranging shipment will be certified and trained in handling of bloodbourne pathogens for shipment.

8.1.1.4 Blood analyses will be conducted at HIMC and saliva analyses will be conducted at Stanford Labs.

8.1.1.5 Blood collection tubes and saliva salivettes will be bar coded with study number rather than PHI. Each Tube will be labeled with the following information: MOSAIC, Subject#,

Date&Time Collected.

9. STUDY CALENDAR

	Baseline	Post Intervention	6 Month Follow-up	12 Month Follow-up
On Study Data (Demographic and clinical data)	X			
Clinical Record Information (Clinical data)	X			
Demographic Questionnaire/Medication	X			
Insomnia Severity Index (ISI)	X	X	X	X
Brief Fatigue Inventory (BFI)	X	X	X	X
Hopkins Verbal Learning Test (HVLT)	X	X	X	X
Clinical Assessment of Depression (CAD)	X	X	X	X
Mobile Cognitive Assessment Battery (MCAB)	X	X	X	X
Comprehensive Trail Making Test (CTMT)	X	X	X	X
Controlled Oral Word Association Test (COWAT)	X	X	X	X
Heart Rate Variability	X	X	X	X
Blood Draw	X	X	X	X
Actigraphy	1 week	1 week	1 week	1 week
Saliva Collection	X	X	X	X
Sleep Behavioral Self Rating Scale (SBSRS)	X	X	X	X
Pittsburgh Sleep Quality inventory (PSQI)	X	X	X	X
Dysfunctional Beliefs about Sleep (DBAS)	X	X	X	X
Difficulties in Emotion Regulation Symptoms (DERS)	X	X	X	X
European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life-Questionnaire-C30	X	X	X	X
Godin Leisure Time Exercise Questionnaire (GLTEQ)	X	X	X	X
Reduced Horne Ostberg Morningness Eveningness Questionnaire (rMEQ)	X	X	X	X
Nutrition Knowledge Questionnaire (NKQ)	X	X		
Sleep Diaries	1 week	1 week	1 week	1 week
Daily Diaries	1 week	1 week	1 week	1 week
BBT-I/HEAL Checklists		6 times during intervention		
Feedback	X	X		

10. MEASUREMENTS

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Primary Outcome Measure Insomnia.

- **Title:** Insomnia Severity Index
- **Time Frame**: Pre, post intervention and at 6 and 12 months follow-ups.
- **Safety Issue**: No

Note: Each outcome measure listed within the protocol will necessitate legally required results reporting to clinicaltrials.gov within one year after the completion of the primary outcome measure.

10.1 Primary and Secondary Outcome measures

Primary Outcome Measure of Insomnia. The effects of the BBT-I intervention on insomnia will be measured by the Insomnia Severity Index (ISI), which is a well-validated self-report measure of sleep.[60-62] The primary outcome will be the change from baseline to 6-month follow-up. A change score of -6 is considered a minimally clinically significant difference for the ISI.[60-62] The measure consists of seven questions on a 5-point Likert Scale with a total score ranging from 0-28. Reliability and validity of this measure have been established.[60-62] The ISI is the primary outcome measure for the study.

Secondary Outcome: Fatigue will be assessed with the revised Brief Fatigue Inventory (BFI), a 9-item, patient-report instrument that we have used in previous studies with established reliability and validity.[63] The BFI allows for rapid assessment of fatigue level in BC patients and identifies those with severe fatigue.

Secondary Outcome: Cognitive Difficulties will be assessed using a cognitive battery of self-rating questionnaires including the Clinical Assessment of Depression (CAD), as well as the Self-Rating subtest of the Mobile Cognitive Assessment Battery (MCAB). CAD has been shown to discriminate between chemotherapy-treated BC patients and controls and also correlate significantly with neurobiologic and immunologic deficits in BC. [64-66] We will additionally administer a battery of neuropsychological assessments, including the Comprehensive Trail Making Test (CTMT), Hopkins Verbal Learning Test Revised (HVLT-R), Controlled Oral Word Association Test (COWAT), and the Mobile Cognitive Assessment Battery. The CTMT is an objective, standardized neuropsychological measure of executive function (switching/inhibition), attention, sequencing and processing speed.[67] The International Cognition and Cancer Task Force recommends the CTMT for harmonizing studies of cognitive function in cancer populations.[68] The CTMT requires 5 to 12 minutes to administer and is normed for individuals aged 8 to 74 years. It has a reliability coefficient of 0.90 or higher for all ages. [69-71] The COWAT is a verbal fluency task that assesses complex cognition. This test has been used in previous studies with breast cancer patients and has shown strong differences between cancer patients and controls.[72] The COWAT takes 4-5 minutes to administer. The HVLT-R is a list memory exercise that measures verbal learning and memory, as well as delayed recall. The test requires a total time of ten minutes with a 20-25 minute period between delayed recall and recognition. HVLT-R has been used in many clinical populations, including breast cancer.[73,74] The MCAB was specifically designed to be more sensitive at capturing cognitive impairments in the clinical

setting. The MCAB is comprised of three neuropsychological tests (in addition to a self-report measure) measuring cognitive flexibility, accuracy, processing speed, working memory and multitasking. The battery has been shown to be clinically significant in breast cancer populations and shows increased sensitivity compared to traditional tests.[75] This battery is delivered through the MCAB iPad application and takes approximately 15 minutes to complete.

Physiological Mediators Heart Rate Variability (HRV) will be calculated with the ambulatory monitoring heart-rate device Firstbeat® that measures RR intervals with a rating sample of 1ms. The device utilizes a valid and reliable method for sampling RR intervals and provides software to analyze the raw data.[76-78] We will calculate time and frequency domain measures of HRV: SDNN, (the standard deviation of all normal RR intervals measured between consecutive sinus beats) and RMSSD (the root mean square of successive differences between adjacent normal R-R intervals).[76,79] In addition, we will measure frequency domain measures, natural log of high frequency (HF, total spectrum power of all NN intervals between 0.15 to 0.4Hz) for vagal tone/RSA and natural log of low frequency (LF, total spectrum power of all NN intervals between 0.04 to 0.15Hz) and LF/HF ratio. Given our preliminary data in BC patients, we will use RSA as a primary HRV outcome. Heart rate variability data will not be collected from a participant if she has an implanted device for heart failure (e.g., pacemaker, defibrillator, left ventricular assist device, etc.).

Circadian Rhythm will be assessed using actigraphy and salivary cortisol at each of the 4 assessment points (sleep diaries are used for cross-checking the going to sleep and waking up times). A two-oscillator cosinor model (12 and 24 hours) will be calculated using nonlinear regression methods on the log (activity counts). This model was found to fit the data for cancer survivors[80] better than a single-oscillator model. Mesor (overall), Amplitude, and Acrophase for the 12- and 24-hour cycles will be calculated. In addition, we will collect salivary cortisol per modified McArthur protocol[81] for 2 days at wake, wake +30, 12PM, 5PM and before bedtime (baseline, 6-, 30-, and 58-weeks). Saliva samples will be refrigerated after collection and stored at -70 °C within a couple of days of collection. Samples will be assayed using a luminescence immunoassay (Immuno-Biological Laboratories Inc, Germany) at Stanford Labs.

Reduced Horne Ostberg Morning Evening Questionnaire (rMEQ) will determine the chronotype of the participant to help assess activity of various physical functions. This questionnaire is a shortened version of the Horne-Ostberg Morning Eveningness Questionnaire.[82] It is a seven-item questionnaire that asks various questions of daily choices regarding sleep and other activities.

Behavioral Mediators and Moderators Maladaptive sleep behaviors will be assessed with the Sleep Behavioral Self- Rating Scale (SBSRS),[83] the Pittsburgh Sleep Quality Inventory (PSQI)[84] sleep diaries and actigraphy. The SBSRS is a validated measure that helps understand patient's adherence to stimulus control. Sleep continuity will be assessed subjectively using Daily Sleep/Wake Diaries and via PSQI. These sleep continuity measures will be used in the meditational analyses and will provide important supplemental data on frequency, severity, and type of sleep problems encountered by patients, as well as contributing factors.

Participants will also have their sleep-wake exposure monitored through the use of a wrist-worn actigraphy-based data logger (Actiwatch-64, MiniMitter, Bend OR). We will set the Actiwatch to record activity counts every 1 minute; at this setting it can record up to 45 days worth of data before the internal memory is full. Actigraphy data will be analyzed using Actiware® software (v.5.04.003, MiniMitter, Bend OR). The program uses a validated sleep algorithm to provide an

assessment of sleep by delineating the "in bed" and "out of bed" portions of the day. The actigraphy, in conjunction with the sleep/wake diaries, can be used to approximate the timing of both daytime and nighttime sleep and provide information on maladaptive sleep behaviors (i.e., increased time in bed, bedtime and rise time variability).[85] While daily sleep diaries are a method commonly used to examine patterns of sleep and wakefulness, we will internally validate the at-home monitoring by comparing actigraphy data collected during baseline and follow-ups to the daily diaries. This measurement strategy allows for an assessment of sleep problems (WASO), that is free from either subjective or observer bias and requires minimal subject compliance, allows for the detection of periods of wakefulness as brief as 30 seconds in duration, and allows for the continuous assessment of sleep and wakefulness for periods of up to 30 days.

The dysfunctional beliefs about sleep will be measured utilizing the Dysfunctional Beliefs and Attitudes about Sleep Scale,[86] a self-report measure that was designed to examine changes in erroneous sleep beliefs and attitudes. Potential moderators will be assessed using age, baseline anxiety and depression (Clinical Assessment of Depression), hot flashes (daily diary), caregiver status (questionnaire), as well as emotional regulation (Difficulties in Emotion Regulation Symptoms). The Nutrition Knowledge Questionnaire (NKQ) will also be used to control for attention.

The Difficulties in Emotion Regulation Scale (DERS) [87]will be used to determine emotion regulation. The DERS is a brief, 36-item, self-report questionnaire devised to assess several aspects of emotion dysregulation. The measure yields a total score as well as scores on six scales produced through factor analysis: Nonacceptance of emotional responses (NONACCEPTANCE), difficulties engaging in goal directed behavior (GOALS), impulse control difficulties (IMPULSE), lack of emotional awareness (AWARENESS), limited access to emotion regulation strategies (STRATEGIES), and lack of emotional clarity (CLARITY). This measure has been found to have high internal consistency, good test–retest reliability, and adequate construct and predictive validity.

Other variables. We will extract the following medical variables from the patients' medical records: disease stage, chemotherapy type (e.g., doxorubicin), prior treatment (e.g., surgery), and receptor status. We will record the treatment that the patient is on during each assessment point to account for differences that might be associated with their particular treatment regimen. We will also determine exercise and physical activity through the Godin Leisure Time Exercise Questionnaire (GLTEQ). The GLTEQ is a 4-item test that asks the frequency of strenuous, moderate and mild exercise. It has been validated to examine changes of behavior in activity. [88] The NKQ will be given to enhance the validity of the control intervention. It is a 15-item questionnaire that measures competency of nutrition.

Expectancy/Feedback will be obtained by 2 checklists assessing the usefulness and acceptability of the experimental interventions and intervention outcome expectancy. Participants will complete the expectancy checklist at the end of their first face-to face session and feedback questionnaire at post-intervention to assess whether they found our interventions helpful for their symptoms. For these baseline variables that are not considered as potential moderators, given our strong design based on random assignment to treatment and control groups, it is reasonable to assume that they will be balanced between the intervention and control groups (i.e., no need to worry about controlling for them). Nonetheless, we will test sensitivity of our results to presence/absence of these potential baseline covariates, especially those that differ between groups due to natural experimental error.

10.1.1 Relevant Subset

N/A

10.1.2 Measurement Definition

The measurement is self-report of changes in symptomatology.

10.1.3 Measurement Methods

The measures are self-report (questionnaires), objective (actigraphy, saliva, heart rate monitor, blood sample).

10.1.4 Measurement Time Points
Baseline, 6 weeks, 6 months and 12 months.

10.1.5 Response Review
N/A

10.2 Secondary Outcome

Described in section 10.1.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director, or her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case

Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the Qualtrics and SPSS database system and will be maintained by the data manager. CRFs will be kept in a locked office, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This is a 2 arm randomized control clinical trial phase III.

12.1.1 Randomization

After consent has been obtained, patients will be randomized 1:1 by a computerized random number generator to one of two arms: BBT-I or HEAL. In order to ensure blinding of assessors, only the data manager, intervener delivering intervention and clinical intervention supervisor will know the randomization assignment. All other study staff will be blinded.

12.2 Interim analyses

There are no interim analyses planned.

12.3 Descriptive Statistics and Exploratory Data Analysis

As hypothesized mediators, we will carefully examine behavioral (measured by DBAS, SBSRS and sleep diaries) and physiological mechanisms (measured by HRV, salivary cortisol and actigraphy). Examination of moderators will be exploratory. As potential moderators, we will examine age, baseline anxiety and depression, baseline hot flashes and baseline emotion regulation. Among these potential moderators, some will not be qualified as moderators but predict outcome regardless of the intervention assignment status (we will classify these as non-specific predictors of the outcome). For the moderator/mediator investigation, we will apply the McArthur framework. Our analysis strategy in detecting moderators and mediators is mixed effects modeling, where the McArthur approach will be embedded. We will also look at cognitive data to analyze whether interventions change cognitive domain.

12.4 Primary Analysis

Aim 1 (Primary): To evaluate the efficacy of the BBT-I in treating insomnia among breast cancer patients receiving chemotherapy.

Hypothesis 1 (Primary): BBT-I compared to an attention control group, will be associated with greater reduction of insomnia symptoms (as measured by the Insomnia Severity Inventory) from baseline to the 12 month follow up.

12.4.1 Analysis Population

Include treatment of missing data and handling of non-adherence to protocol described in 12.4.2 and 12.5.1.

12.4.2. Analysis Plan

For our primary Hypothesis 1, we will examine whether the BBT-I group will show more improvement, compared to the attention control group for insomnia symptoms measured by ISI from baseline to the 12-month follow-up. The group comparison will be made in line with the

intention to treat principle. We will analyze the data using mixed effects (growth curve) modeling[89,90] fully utilizing outcome data repeatedly measured four times for most participants (baseline, 6, 30, and 58 week). For estimation of mixed effect models, maximum likelihood (ML) estimation will be used. For ML estimation of these models, the Mplus program version 7.11 or above will be used.[91] Data points that are missing due to subject attrition will be handled assuming that data are missing at random[92] conditional on observed information, which is less restrictive than missing completely at random[92] assumed in fixed effects analyses such as ANCOVA and regression analysis. In this procedure, all available cases including the ones with missing information will be included in the analyses. By including every subject who completed at least one assessment, we are not only more likely to conserve power, but also less likely to produce biased effect estimates. Given the sample and baseline covariates we will be collecting, we believe mixed effects modeling using ML is a reasonable approach. Nonetheless, we will conduct additional analyses at least for key hypotheses as a form of sensitivity analysis. For this purpose, we will apply the multiple imputation approach[93] utilizing various auxiliary variables in the data. We will conduct additional analyses allowing for some deviation from MAR, for example assuming MAR conditional on intervention adherence status.[94-97]

In our mixed effects analyses, the change in the outcome will be modeled as the key dependent variable predicted by the treatment status. The results of these longitudinal analyses can be easily converted to treatment effect at each assessment point to directly respond to our specific hypotheses. In particular, we are interested in the main effect of treatment (BBT-I vs. Control) at 12-month follow-up (58 week) assessment. The same analysis strategy will be employed for Hypothesis 2, where we will examine the treatment effects on secondary outcomes such as fatigue (measured by BFI) and cognitive difficulties (measured by Cognitive Battery). In Hypothesis 3, we will examine the mediators of treatment effects on insomnia, fatigue, and cognitive difficulties.

12.5 Secondary Analysis

Aim 2 (Secondary): To evaluate efficacy of the BBT-I in treating cancer-related symptoms such as cancer-related fatigue and cognitive difficulties in breast cancer patients receiving chemotherapy.

Hypothesis 2 (Secondary): BBT-I compared to an attention control group will be associated with greater improvements in fatigue and cognitive difficulties (as measured by the Brief Fatigue Inventory, and our Cognitive Battery that includes neuropsychological testing) from baseline through the 12 month follow up.

Aim 3 (Secondary): To examine potential moderators and mediators of BBT-I intervention effects on insomnia, cognitive difficulties, and fatigue. In particular, we are interested in age, depression and anxiety, emotion regulation and side effects (hot flashes) as potential moderators of the intervention effects as well as evaluating modifiable behavioral and physiological mechanisms as hypothesized mediators.

Hypothesis 3 (Secondary): In women with breast cancer receiving chemotherapy, intervention effects on insomnia, fatigue, and cognitive difficulties will be mediated by select behavioral mechanisms [i.e., maladaptive sleep behaviors (The Sleep Behavior Self-Rating Scale, sleep diaries, actigraphy), dysfunctional beliefs and attitudes (Dysfunctional Beliefs and Attitudes about Sleep) and physiological mechanisms [i.e., dysregulated circadian rhythms (measured by salivary cortisol), disrupted sleep wake cycles (actigraphy), and autonomic tone (RSA)].

As hypothesized mediators, we will carefully examine behavioral (measured by DBAS, SBSRS and sleep diaries) and physiological mechanisms (measured by HRV, salivary cortisol and actigraphy). Examination of moderators will be exploratory. As potential moderators, we will examine age, baseline anxiety and depression, baseline emotion regulation and baseline hot flashes. Among these potential moderators, some will not be qualified as moderators but predict outcome regardless of the intervention assignment status (we will classify these as non-specific predictors of the outcome). For the moderator/mediator investigation, we will apply the McArthur framework.[98,99] Our analysis strategy in detecting moderators and mediators is mixed effects modeling, where the McArthur approach will be embedded.

12.5.1 Analysis Population

All patients contributing both baseline measurement and 12-month follow up will define the efficacy population.

Missing data

In our primary analytical strategy, we proposed to employ the statistical analysis method widely known as the mixed effects modeling approach using the maximum likelihood (ML) estimation. The use of mixed effects modeling is critical in implementing the intention-to-treat principle and therefore maintaining the validity of our inferences in the presence of missing data. Data points that are missing due to attrition and nonresponse will be handled assuming that data are missing at random (MAR[100]), conditional on observed information. We would like to emphasize that our method is less restrictive and therefore less likely to result in bias and misleading conclusions than alternative procedures utilizing missing completely at random (MCAR[100]), assumed in fixed effects analyses such as ANOVA and regression analysis. In analyses utilizing MCAR, cases with missing information are simply excluded from the computations. By including every participant who completes at least one assessment in the analysis utilizing MAR, we are not only more likely to conserve power, but also less likely to produce biased effect estimates. Given the sizable sample and baseline covariates assessed, we believe mixed effects modeling using ML is a reasonable approach. Nonetheless, we are aware that the assumption of missing at random conditional on observed information can be somewhat violated in practice (because we cannot possibly collect every variable related to the missing data). To address this concern, we will conduct additional analyses at least for the key hypotheses (1 & 2) as a form of sensitivity analysis. For this purpose, we will apply the multiple imputation approach[101] utilizing various auxiliary variables in the data. Additionally, we will conduct sensitivity analysis allowing for some deviation from MAR, for example assuming MAR conditional on intervention adherence status.[97,102-104]

We recognize that the best way to handle missing data is to minimize the missing data during the study. To minimize missing data, our questionnaires will be collected electronically utilizing Qualtrics and having participants complete these assessments on either iPads or study computers, a strategy that we have now successfully piloted in our randomized clinical trial of bone marrow recipients, resulting in minimal missing data. If warranted, we will add another site to recruit additional patients. However, in our pilot study, attrition was about 8%, and missing data in the completers were very low (0 to 7%) for the key variables.

12.5.2 Analysis Plan

The group comparison will be made in line with the intention to treat principle. We will analyze the data using mixed effects (growth curve) modeling[89,90] fully utilizing outcome data repeatedly

measured four times for most participants (baseline, 6, 30, and 58 week). For estimation of mixed effect models, maximum likelihood (ML) estimation will be used. For ML estimation of these models, the Mplus program version 7.11 or above will be used.[91]

12.6 Sample Size

12.6.1 Accrual estimates

Stanford Cancer Center sees approximately 500 new breast cancer patients per year and about 341 patients (Range 318-376) are currently undergoing chemotherapy per STRIDE database. In our pilot, we were able to recruit a new participant every week. Thus, we anticipate that we would be able to meet our recruitment goal within 4 years even after accounting for attrition.

To minimize attrition, we will schedule participants for assessments during their clinic days. We budgeted funds for participants' travel, parking, and refreshments to improve retention. We will maintain close contact with participants with letters and projects updates, call or email (based on their preference) to remind participants to follow the study procedures. We also will send birthday cards and provide recruitment updates on our website to keep participants interested throughout the duration of the study. The proposed study involves a lower participant burden than our pilot that required more follow-ups, longer actigraphy and saliva collection and more measures. We found that we were able to minimize attrition in our current pilot with the above mentioned strategies. We will work closely with the Breast Cancer Connections advocacy group as we have done in the past, to provide training to our staff to ensure supportive and rewarding experiences for our participants. We will monitor our accrual closely and based on our current experience, we anticipate being able to recruit our participant sample. However, if we are unable to meet our recruitment target during the first year, we will expand our recruitment area to other local oncology clinics.

12.6.2 Sample size justification

For the primary Hypothesis 1 (BBT-I will show greater reduction of insomnia symptoms measured by ISI from baseline to the 12-month follow-up compared to the control), we estimated power in the proposed mixed effects modeling framework fully accounting for the longitudinal study design and projected attrition rate. The primary outcomes, ISI, will be measured at baseline, 6 weeks (end of treatment), 30 weeks, and 58 weeks (primary end point). For our power estimation, we used ML based mixed effects modeling assuming a linear trend. We assumed that at least 60% of variance is explained by the growth model for the primary outcome (i.e., reliability of 0.6), given that previous studies reported reliability ranging from 0.65-0.83.[105,106] For attrition, we assumed gradually increasing attrition over time, resulting in 25% attrition by the 6-month follow-up assessment. We assumed a medium effect size, Cohen's d of 0.4 to 0.6, based on a previous study.[107] We also consider this range of effect size as the lower bound of a clinically meaningful treatment effect. Under this scenario, the estimated power to detect the group difference in change in ISI is 0.88-0.99 (d=0.4 to 0.6, alpha=.05, two-tailed) with N=180 (90 BBT-I, 90 control). We estimated power for the secondary Hypothesis 2 (BBT-I compared to the control will show greater improvements in fatigue and cognitive difficulties) using the same mixed effects modeling strategy. We assumed a moderate effect size of d = 0.35 to 0.4, based on a previous study. [108,109] We do not adjust for testing of multiple outcomes given that fatigue and cognitive difficulties are secondary outcomes. Under this scenario with reported reliability of 0.67 and higher, [108,109] the estimated power to detect the group difference in change in BFI is 0.84-0.91 (d=0.35 to 0.4, alpha=.05, 2-tailed). For the mediator Hypothesis 3, we estimated power focusing on the main effect of the mediator on the outcome.[98,99] We assumed a

moderate correlation between the hypothesized mediators and the outcome (r=0.2 to 0.3). We do not adjust for testing of multiple mediators given our concerns in failing to detect possible mediators due to insufficient power (note that our trial is powered based on our primary hypothesis). Under this scenario, the estimated power to detect the mediation effect is 0.76-0.99 (r=0.2 to 0.3, alpha=.05, two-tailed). For all hypotheses, we will carefully monitor both statistical (i.e., p-value) and clinical (i.e., effect size) significance, with more emphasis on clinical significance in the secondary hypotheses.

12.6.3 Effect size justification
See above.

12.7 Criteria for future studies
This study is fully powered to determine efficacy of BBT-I versus attention and time-controlled group. Changes on the ISI measure of 6 points constitute clinically meaningful results. If this trial replicates our pilot findings, future studies will focus on dissemination of this intervention via multicenter clinical trials.

13. REFERENCES

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APPENDICES

APPENDIX A: Participant Eligibility Checklist

Protocol Title:	**Brief Behavioral Intervention For Insomnia During Chemotherapy**
Protocol Number:	
Principal Investigator:	**Palesh, Oxana**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☒ IRB Approved ☒ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Be female and have a diagnosis of breast cancer (Stage I-III)	☐	☐	
2. Be scheduled for planned cancer treatment (e.g. chemotherapy or biologics such as herceptin)	☐	☐	
3. Have at least 6 weeks of cancer treatment (e.g. chemotherapy or biologics such as herceptin) remaining	☐	☐	
4. Be at least 21 years of age	☐	☐	
5. Be able to understand written and spoken English	☐	☐	
6. Report sleep disturbance of 8 or greater on the ISI, and report insomnia that began or got worse with diagnosis of cancer or treatment with chemotherapy (to exclude pre-existing, chronic insomnia)	☐	☐	
7. Have a Karnofsky score ≥ 70 to ensure that patients are able to participate in intervention and assessments	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Have an unstable self-reported medical or psychiatric illness (Axis I – current or within the last 5 years) that would make it unsafe or impossible to adhere to the study protocol	☐	☐	
2. Be currently pregnant or nursing	☐	☐	
3. Meet current or within 1 year criteria for current alcohol abuse or dependence	☐	☐	

4. Have a self-reported history of sleep apnea or restless leg syndrome (RLS)	☐	☐	
5. Are unable or unwilling to discontinue anxiolytics within 4 hours of education sessions	☐	☐	
6. Have irregular heartbeats or arrhythmia (self-reported or in the medical record)	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Study Coordinator Signature:	Date:
Printed Name:	