2016

Light Therapy for Post-Treatment Cancer-Related Fatigue: An Investigation of Impact on Psychological Outcomes and Biological Mechanisms

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Light Therapy for Post-Treatment Cancer-Related Fatigue: An Investigation of Impact on Psychological Outcomes and Biological Mechanisms

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN PSYCHOLOGY

CALGARY, ALBERTA

SEPTEMBER, 2016

Abstract

OBJECTIVE: To investigate the impact of a one-month light therapy intervention on symptoms of fatigue, psychological outcomes, and diurnal cortisol rhythms in cancer survivors with clinical fatigue.

METHODS: Adult cancer survivors who met diagnostic criteria for cancer-related fatigue were eligible and randomized to receive either bright white light (BWL) or an active comparator (dim red light; DRL). Participants used the device for 30 minutes upon waking for 4 weeks. Baseline and post-intervention assessments of fatigue, mood disturbance, depression, sleep quality, and quality of life were obtained. Participants also provided four saliva samples per day over a period of 3 days both before and after the intervention. Linear mixed-model (LMM) analysis with random slopes and intercepts were conducted on the primary outcome of fatigue, and generalized estimating equations were employed to investigate the secondary psychological outcomes. Cortisol slopes, total cortisol output (area under the curve), and cortisol output at four sampling times were examined for time, group, and interaction effects using LMM analyses.

RESULTS: Eighty-one participants were randomized to either BWL (n=42) or DRL (n=39). The light therapy intervention was acceptable as evidenced by high adherence rates and low dropout (2.5%). Overall, participants in the BWL condition displayed greater improvements in symptoms of fatigue than those in the DRL condition (d=.30). Both groups showed improvements on symptoms of mood disturbance, depression, sleep quality, and quality of life over time. A subsample of participants (n=77) were included in the cortisol analyses. Cortisol slope and total cortisol output were unchanged after the intervention, but an increase in output was observed in both groups at the post-intervention noon sample, as well as decreased output at the post-intervention 5pm sample in the BWL condition.

CONCLUSION: Early morning exposure to bright white light resulted in improvements in symptoms of fatigue in cancer survivors with clinical fatigue. These findings, along with those of previous research of light therapy in cancer patients and survivors, support the use of light therapy for cancer-related symptoms. Furthermore, light therapy has the potential to impact the diurnal release of cortisol, though further research into the associations with symptoms of fatigue are required.

Keywords: cancer, cancer-related fatigue, randomized controlled trial, mood, quality of life, diurnal cortisol

Acknowledgements

First, I would like to extend sincere gratitude to my mentors, Dr. Tavis Campbell and Dr. Linda Carlson, for their constant and unwavering encouragement, guidance, and support throughout my graduate training. I am forever grateful for the time and energy you have both dedicated to ensuring my success. I would also like to extend a special thank you to Dr. Sheila Garland for her support with this project and for her guidance and advice.

Thank you to all of the participants who dedicated so much time and energy to being a part of the study. To my fellow colleagues, past and present, in the Behavioral Medicine Lab and the Department of Psychosocial Resources, thank you for all of the emotional support and words of encouragement. To my husband and family, thank you for believing in me and following me on this adventure. Finally, thank you to the examination committee members for dedicating their time to review this document and take part in the examination.

This project was funded by the Canadian Cancer Society. I would also like to acknowledge the following funding agencies for the scholarships and awards that afforded me the opportunity to pursue this graduate training: Alberta-Innovates Health Solutions, the Alberta Cancer Foundation, the Killam Trust, and the Lloyd and Florence Cooper Doctoral Scholarship in Integrative Medicine.

Dedication

I dedicate this thesis to all of the participants who graciously donated their time to be a part of this study. The success of this trial was due to your unwavering dedication and commitment. Thank you for sharing your time and stories with me.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
ACTH	adrenocorticotropic hormone
ALBIA	Addressable Laser Bead Immunoassay
ANOVA	analysis of variance
AR1	autoregressive
ASCO	American Society of Clinical Oncology
ASCPRO	assessing the symptoms of cancer using patient-reported outcomes
AUCg	area under the curve with respect to ground
BWL	bright white light
CBT	cognitive behavior therapy
CBT-I	cognitive behavior therapy for insomnia
CES-D	Centre for Epidemiological Studies – Depression scale
CEQ	Credibility Expectancy Questionnaire
CLIA	chemiluminescence immunoassay
CRF	cancer-related fatigue
CRH	corticotropin-releasing hormone
CRP	c-reactive protein
DRL	dim red light
DSM-IV-TR	Diagnostic and Statistical Manual Version 4 Text Revision
EMM	estimated marginal mean
FACT-F	Functional Assessment of Cancer Therapy-Fatigue
FACT-G	Functional Assessment of Cancer Therapy-General
g	grams
HPA-axis	hypothalamic-pituitary-adrenal axis
ICD-10	International Classification of Diseases – 10th Edition
IL	interleukin
in	inches
ISI	Insomnia Severity Index
ISQ	Insomnia Screening Questionnaire
LED	light emitting diode
LMM	linear mixed models
lx	lux
MFSI-SF	Multidimensional Fatigue Symptom Inventory – Short Form
mins	minutes
NCCN	National Comprehensive Cancer Network

nm	nanometers
nmol/L	nanomoles per liter
POMS-SF	Profile of Mood States – Short Form
PSQI	Pittsburgh Sleep Quality Index
PVN	paraventricular nucleus
oz	ounces
TNF-α	tumor necrosis factor alpha
REML	restricted maximum likelihood estimate
SCN	suprachiasmatic nucleus
SD	standard deviation
SE	standard error
SPSS	Statistical Package for the Social Sciences
tx	treatment
UN	unstructured

Chapter 1: Introduction

Introduction

Cancer is the leading cause of death in Canada, accounting for one third of all deaths and affecting 2 in 5 Canadians (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015; Statistics Canada, 2012). In 2015, the Canadian Cancer Society reported that there would be an estimated 196,900 new cancer diagnoses in Canada, with 17,000 new diagnoses in Alberta alone (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015). However, with advances in detection and treatment, the five-year survival of Canadians diagnosed with cancer is predicted to be 63% (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015), meaning that many will live as long-term survivors. As the total number of cancer diagnoses is expected to rise by 79% by 2032, primarily as a result of an aging population, this increase, coupled with rising survival rates, will result in increased need for the management of symptoms that are a result of cancer and its treatments (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2015).

While most people are able to live full and rewarding lives following successful cancer treatment, it is common for many to report debilitating and distressing symptoms in the months and years following the conclusion of primary treatment. These symptoms include, but are not limited to, behavioural complications including sleep disturbances and cognitive dysfunction, physical symptoms such as pain, nausea, and fatigue, and emotional difficulties such as depression and anxiety (Shi et al., 2011). These symptoms can have a profound impact on quality of life and also give rise to substantial economic costs, resulting in an estimated $586 million in indirect costs from loss of productivity (Public Health Agency of Canada, 2014). Among the symptoms reported by cancer survivors, fatigue remains the most common and distressing, rivaling pain and nausea (Wang et al., 2014), but the mechanisms that serve to maintain it are not

well understood, and the lack of interventions that are mechanism-driven preclude effective treatment (Berger, Mitchell, Jacobsen, & Pirl, 2015).

Cancer-Related Fatigue

At present, there is no definition of cancer-related fatigue (CRF) universally accepted among the oncological community, though there have been numerous efforts to characterize it. In their practice guidelines for the clinical management of fatigue, the National Comprehensive Cancer Network (NCCN; 2015) has defined CRF as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning". Another working group, ASCPRO (Assessing the Symptoms of Cancer using Patient-Reported Outcomes), has defined CRF as "the perception of unusual tiredness that varies in pattern and severity and has a negative impact on ability to function in people who have or have had cancer" (Barsevick et al., 2010). In general, CRF is often characterized by feelings of physical tiredness or weakness, reduced energy, reduced motivation, and mental fatigue (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003), and has been described by words such as exhaustion, weariness, weakness, malaise, and impatience (Wang & Woodruff, 2015). It is distinct from normal or typical fatigue in that it is not relieved by rest or sleep, is disproportionate to exertion level, and is often more severe and more distressing (Glaus, Crow, & Hammond, 1996). Perhaps the most problematic characteristic of CRF is its profound impact on daily functioning and subsequent reductions in overall quality of life (Wang & Woodruff, 2015).

CRF is not unique to a specific type of cancer or cancer treatment. Although increased symptoms of fatigue have been associated with chemotherapy treatment (Minton, Strasser, Radbruch, & Stone, 2012) and accumulating radiation dose (Wang, 2006), it is likely a result of a

combination of factors, including disease progression, acute or latent responses to cancer treatments, and even interactions with psychological factors such as depression and anxiety (Wang & Woodruff, 2015). As a result of its multifactorial origins, CRF is not limited to the active phase of cancer. Symptoms of fatigue have been reported before diagnosis, during treatment where symptoms typically worsen, and can persist long after treatment completion and into remission (Gosain & Miller, 2013; Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007). The impact of CRF is so profound that during cancer treatment, the increased symptom burden that occurs with increased symptoms of fatigue can lead to treatment discontinuation (Wang & Woodruff, 2015). Typically, patients anticipate that their levels of fatigue will return to normal following the conclusion of treatment, but approximately one-third of patients continue to experience fatigue for months or even years following treatment (Berger et al., 2015; Hofman et al., 2007; Wang et al., 2014).

The majority of cancer patients will experience fatigue at some point along the cancer continuum, with higher prevalence among those receiving active treatment (Hofman et al., 2007). A systematic review of 40 CRF studies revealed that the prevalence of CRF can range from 46% to 96% depending on the patient group assessed, the method of assessment, and cancer treatments received (Prue, Rankin, Allen, Gracey, & Cramp, 2006). A recent multicenter study of a heterogeneous sample of outpatients with a variety of diagnoses revealed the presence of moderate to severe fatigue in 45% of patients undergoing active treatment, and in 29% of survivors (Wang et al., 2014). For those more than 5 years post-treatment, the prevalence was lower at 18%, but still higher than fatigue in the general population (i.e., 10%; Cella, Lai, Chang, Peterman, & Slavin, 2002).

Despite its prevalence, CRF remains relatively under-reported and under-treated (Borneman et al., 2007; Stone et al., 2000). For example, one study found that only 23% of patients reported that they had received treatment specific to their fatigue (Henry et al., 2008), while another study reported that only 27% were offered treatment after discussing their fatigue with their oncologist (Vogelzang et al., 1997). The obstacles to receiving treatment are a result of factors associated with both patient and provider. That is, physicians may have insufficient knowledge about the screening, assessment, and/or treatment of fatigue, and may underestimate the impact on functioning and quality of life (National Institutes of Health State-of-Science Panel, 2003; Vogelzang et al., 1997). Conversely, patients may accept fatigue as an inevitable consequence of cancer treatment or fear that reporting severe fatigue may result in less aggressive treatment of their cancer (Luthy et al., 2011). This may be especially true given that severe symptoms of fatigue have been identified as an independent predictor of survival (Dirksen & Epstein, 2008).

Impact on Functioning

Quality of life. The impact of CRF on a patient's quality of life and ability to perform daily activities has been reported as more problematic than other cancer-related symptoms such as pain, depression, and nausea (Curt et al., 2000; Stone et al., 2000; Vogelzang et al., 1997). Among patients with a wide range of cancer diagnoses, CRF has been reported to have a profound impact across several facets of quality of life, including physical, social role, emotional, and cognitive function (Ahlberg et al., 2003; Alexander, Minton, Andrews, & Stone, 2009; Curt et al., 2000). Specifically, patients with fatigue report significant impairment in their ability to complete a variety of routine tasks, including walking long distances, cleaning the house, social activities, and food preparation (Curt et al., 2000). Among those with a history of

chemotherapy, a reported 91% of patients with CRF felt that it prevented them from leading a normal life, while 88% felt that their fatigue had changed their daily routine (Curt et al., 2000).

Fatigue is reported to have a considerable emotional impact including feelings of loss of emotional control and feelings of isolation and solitude. The impact on social functioning can be seen in the struggle to maintain interpersonal relationships and to find the energy to spend time with friends. There is increased difficulty associated with carrying out typical cognitive tasks such as remembering things, making decisions, and organization. CRF can affect employment as a result of lost work days, the need to take extra vacation or sick days, or "presenteeism"- under-functioning while at work. In severe cases it can also require transition into part-time work or disability status. Finally, these issues can influence the quality of life of caregivers, increasing burden to take on the tasks of the patient, subsequently increasing stress levels and leading to burnout and/or conflict (Curt et al., 2000).

The associations among increased fatigue and reduced quality of life are even more pronounced among cancer survivors. For example, one study of breast cancer survivors who were 3 months to 2 years post-treatment showed large differences between patients with clinically significant CRF and those without on almost all domains of quality of life (Alexander et al., 2009). More specifically, the survivors with CRF had worse physical, emotional, and social functioning, as well as worse body image and sexual functioning, in addition to greater mood disturbance than those without CRF (Alexander et al., 2009). These reports, when combined, highlight the profound impact that fatigue has on a patient's overall quality of life. Regardless, these symptoms are often not monitored as closely during follow-up are they are during active treatment (Shi et al., 2011).

Mood. The prevalence of depression among cancer patients who have been recently diagnosed or who are undergoing treatment ranges from 10% to 25% (Pirl, 2004), compared to 6.6% in the general population (Kessler et al., 2003). Research examining the prevalence of major depressive disorder in long-term cancer survivors suggests that, although cancer survivors in general do not have higher rates of major depressive disorder than those without CRF, they reported greater impairment from depression in their home, social, and work life (Pirl, Greer, Temel, Yeap, & Gilman, 2009). It is also common for symptoms of fatigue to co-occur with depression in cancer patients and survivors, resulting in overall increased symptom burden and reduced quality of life (Brown & Kroenke, 2009; Jacobsen, Donovan, & Weitzner, 2003). Greater depressive symptomatology may also have a negative impact on their treatment outcomes by reducing survival times (Satin, Linden, & Phillips, 2009).

For example, research investigating fatigue in long-term cancer survivors found that women who experienced depressive symptoms in the first year after diagnosis were at elevated risk for developing long-term fatigue (Bower et al., 2006), while another study reported that a history of depression was associated with increased levels of moderate to severe fatigue (Wang et al., 2014). Keeping this in mind, providers should consider educating patients on the associations between emotional distress and symptoms of fatigue, in order to encourage the tracking of symptoms over time and to allow survivors to make appropriate treatment decisions to target both mood and fatigue based on potential contributing factors.

The association between depression and CRF may be a result of a common etiology. There are three possible causal relationships that could exist: 1) fatigue causes depression; 2) depression causes fatigue; or 3) a third factor causes both depression and fatigue (Jacobsen et al., 2003). Though there is support for each of these theories, research has not been able to

disentangle the directionality of the relationship. For example, one study of 249 lung cancer patients in a trial for treatment of anemia suggested that improvements in symptoms of fatigue were also significantly associated with improvements in symptoms of depression and anxiety (Tchekmedyian, Kallich, McDermott, Fayers, & Erder, 2003). Conversely, research investigating the effect of antidepressant medication on symptoms of fatigue and psychological distress, showed that pharmacological treatment with antidepressants resulted in reductions in depressive symptomatology, but had no such effect on levels of fatigue (Roscoe et al., 2005). Though the directionality of this relationship is unclear, there is the potential for interventions that specifically target CRF to provide additional benefits for patients who struggle with depression, and vice versa.

Sleep quality. Poor sleep has been identified as a common symptom among cancer patients and survivors and is a known contributing factor to and predictor of CRF (Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2013; Pertl, Hevey, Collier, Lambe, & O'Dwyer, 2014). Sleep-wake disturbance refers to the perceived or actual alterations in nighttime sleep with concomitant daytime impairment (Berger, 2009). Overall, an estimated 30-75% of cancer patients report sleep disturbances (Berger et al., 2005), though the actual numbers may be higher as it is often underreported. That is, patients may not be aware of sleep problems other than experiencing fatigue and an increased need for sleep (Berger et al., 2015). Patients should therefore receive education about how common sleep disturbances are in cancer and that sleep disturbances are one of the contributing and treatable factors associated with fatigue (Berger et al., 2015).

Insomnia is the most common sleep disorder in cancer patients and survivors (Savard & Morin, 2001). One study reported that among a sample of 114 breast cancer survivors with CRF,

the prevalence of insomnia symptoms were 44%, compared to 16% in those without fatigue (Minton & Stone, 2012). Insomnia is characterized by difficulty falling asleep (i.e., greater than 30 minutes), difficulty staying sleep (i.e., wakeful episodes lasting more than 30 minutes), early morning awakenings (i.e., waking 30 minutes or more before the intended time), and non-restorative sleep, causing significant distress or impairment of daytime functioning (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). Interventions to improve sleep include cognitive behavioral therapy for insomnia (CBT-I), exercise, sleep medications and sedative-hypnotics, treating or controlling other symptoms such as pain, and using complementary therapies to enhance relaxation (Berger et al., 2015). Given the current understanding of the possible links between CRF and sleep, interventions that target sleep may lead to improvements in CRF as well (Berger & Mitchell, 2008). One example of this was demonstrated in a recent randomized controlled trial of CBT-I, an intervention to target insomnia symptoms, and its ability to significantly improve symptoms of fatigue in cancer survivors (Heckler et al., 2016).

Screening and Measurement of CRF

At present, the use of validated, self-report assessments of fatigue are the standard method to quantify severity, frequency, and degree with which it interferes with functioning, although no single scale has been broadly adopted (Wang & Woodruff, 2015). Both unidimensional and multidimensional measures can be used, with the unidimensional scales typically used in clinical practice to briefly determine whether further assessment is required. CRF has also been accepted as a diagnosis in the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10; Cella, Peterman, Passik, Jacobsen, & Breitbart, 1998). A structured interview was developed to establish the presence of the clinical syndrome of CRF based on a set of diagnostic criteria (Cella et al., 1998). This criterion includes

the presence of a minimum of 2 weeks of fatigue during the previous month, with at least six or more of the listed symptoms present every day or nearly every day over the same two-week period. It also incorporates the requirement that fatigue symptoms result in clinically significant distress or impairment in social, occupational, or other areas of functioning.

A survey of cancer survivors revealed that 17% of those surveyed met the diagnostic criteria for CRF as outlined above, with 14% of those at or beyond 5-years post-treatment (Cella, Davis, Breitbart, Curt, & Fatigue Coalition, 2001). Though these numbers are considered a conservative estimate, the discrepancies among reports of the prevalence of CRF among cancer survivors highlight the need for the regular use of a universally accepted set of diagnostic criteria. Furthermore, among the published reports of prevalence using these diagnostic criteria, the lack of consistency also highlights the need for more guidance as to how these diagnostic criteria are applied (Donovan, McGinty, & Jacobsen, 2013).

Given the rising number of cancer survivors and the subsequent need for post-treatment support, there have been increased efforts to improve symptom management, quality of life, and overall functioning for people with CRF. To aid in this process, a number of national guidelines have been developed which summarize the research and provide evidence-based recommendations. In Canada, the *Pan-Canadian Practice Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue in Adults* was developed (Howell et al., 2013). The National Comprehensive Cancer Network (NCCN) in the USA has also released clinical practice guidelines specific to CRF that outline recommendations for the screening, assessment, and treatment of fatigue in patients undergoing treatment, in the post-treatment period, and those at the end-of-life (Berger et al., 2015). Finally, the *American Society of Clinical Oncology* (ASCO) has published an adapted set of guidelines specific to cancer survivors that incorporates the

recommendations from both the pan-Canadian and NCCN guidelines on CRF and survivorship (Bower et al., 2014). The development of these guidelines were informed by the ADAPTE methodology (ADAPTE Collaboration, http://www.adapte.org/) - a process of screening for and summarizing current, high quality clinical practice guidelines to provide a more efficient and accessible version of the best available evidence.

In general, the guidelines strongly encourage screening for symptom severity at the time of diagnosis, and recommend ongoing screening and follow-up throughout treatment and into recovery. This process includes assessing severity of symptoms with the patient and family using valid, quantitative or semi-quantitative scales, performing a comprehensive review of medical history and comorbid conditions, and performing a thorough physical exam and laboratory evaluation to rule out other potential health problems. Using this information, treatment recommendations should be made based on severity of fatigue - differentiating mild, moderate, and severe - and should be matched with patient preference and current ability. The use of these interventions should be modified over time to match changes in severity of fatigue throughout active treatment and into survivorship if necessary. The treatments that are currently available to manage fatigue upon the conclusion of treatment include those that are focused on education and counselling, physical activity, psychosocial interventions, mind-body interventions, and pharmacological interventions (Bower et al., 2014).

Treatment of CRF

Education and counseling. Given that fatigue may be experienced in the months and years following the conclusion of treatment (Curran, Beacham, & Andrykowski, 2004; Hofman et al., 2007), it is suggested that patients regularly monitor their fatigue levels and discuss ongoing screening for symptoms of fatigue with their physician (Bower et al., 2014). It is

important that all patients are offered specific information about the duration and severity of fatigue that may be experienced following active treatment (Bower et al., 2014). This can be achieved through attendance at psycho-education sessions, either in an individual or group setting, wherein an individual can learn about the differences between normal fatigue and CRF, the possibility for fatigue to persist post-treatment, and the potential causes and contributing factors (Bower et al., 2014). They should also be educated on the general strategies for self-management of symptoms, including maintaining physical activity, self-monitoring, coping skills training, and energy conservation (Bower et al., 2014).

An estimated 20% to 80% of cancer patients will develop malnutrition and cachexia as a result of treatment side effects, such as nausea and loss of appetite, at some point during their illness (Kubrak & Jensen, 2007), which may also contribute to symptoms of fatigue. Therefore, consultation with a dietician is recommended to help restore nutritional deficiencies that may be a result of treatment-induced illness and contribute to fatigue (Brown et al., 2003).

Non-pharmacological interventions.

Exercise and physical activity. For many patients, a common consequence of cancer treatment and associated fatigue is an overall reduction in physical activity. Interventions of exercise or enhanced physical activity to improve symptoms of fatigue are generally composed of structured and repetitive bodily movements that are performed to help improve or maintain current levels of physical fitness (Howley, 2001). These interventions are typically prescribed and monitored by an exercise physiologist and may include aerobic or resistance exercises, are located either in the home or at a local centre, and may be undertaken in a group or individual setting (Pearson, Morris, di Stefano, & McKinstry, 2016). In general, exercise results in improvements during both active treatment and in the post-treatment period (Puetz & Herring,

2012). A recent scoping review detected a total of 103 original studies of exercise or physical activity with CRF as an outcome (Pearson et al., 2016). With over 40 meta-analyses of this body of work also currently available that summarize the impact of exercise and physical activity on CRF, it is evident that exercise interventions are effective for a wide variety of patient populations and include a number of exercise modalities across a range of frequencies, durations, intensities, and degrees of supervision (Mitchell et al., 2014). However, the effect sizes associated with improvements from exercise overall are generally small (SMD = -.27; Cramp & Byron-Daniel, 2009).

One exercise modality that has been shown especially effective for CRF is supervised exercise (Meneses-Echávez, González-Jiménez, & Ramírez-Vélez, 2015). A systematic review of 11 studies involving 1530 participants showed that combined resistance and aerobic supervised physical activity has a favorable effect on CRF when compared with conventional care (SMD=-0.41; Meneses-Echávez et al., 2015). Though adherence to the interventions were not explicitly reported in this review, the improvements may be partially explained by increased adherence to exercise as a result of the supervision received (Velthuis, Agasi-Idenburg, Aufdemkampe, & Wittink, 2010) which may increase intensity and confidence in ability to perform the required movements (Meneses-Echávez et al., 2015). Supervised exercise also allows for some degree of individualization and tailoring of the intervention to the individual's needs, interests, and abilities, which follows the recommendations from exercise guidelines (Berger et al., 2015).

Another review of exercise interventions specifically targeting fatigue in cancer survivors across varying cancer types, stages, and treatments, reported on 44 studies with 48 different interventions included (Brown et al., 2011). Fatigue was decreased to a greater degree among

cancer survivors than usual care controls (d=0.31). The greatest reductions occurred among those engaging in moderate intensity exercise (p=0.01), and fatigue was reduced to a greater extent when interventions were theoretically driven (p<.001; Brown et al., 2011).

Based on the evidence in the literature, maintaining adequate levels of physical activity and avoiding physical inactivity represent one of the most effective methods for reducing fatigue in the post-treatment period, and should therefore always be recommended (Bower et al., 2014). The ASCO guidelines recommend that all patients engage in a moderate level of physical activity (i.e., 150 min of moderate intensity aerobic exercise per week with the addition of two or three resistance training sessions, unless contraindicated; Bower et al., 2014). Physical activity and exercise programs should be individualized for each patient (i.e., matched with preference), should begin at a low level of intensity and increase with the patient's abilities, and the duration of activity should be modified as the individual's condition changes (Bower et al., 2014).

Psychosocial interventions. Participation in psychosocial interventions is also recommended for the management of CRF (Bower et al., 2014). Psychosocial interventions, such as cognitive behavioral therapy (CBT), supportive expressive therapy, stress management, coping strategy training, and psychoeducational therapies, may help patients cope with fatigue and other psychological symptoms (e.g., symptoms of anxiety and depression) that are commonly associated with fatigue (Berger et al., 2015; Howell et al., 2015). These interventions may be particularly beneficial for individuals for whom exercise is not recommended.

As discussed earlier, there are associations between CRF and sleep disturbances (Goedendorp et al., 2013; Pertl et al., 2014), and in particular insomnia (Savard & Morin, 2001). Therefore, it is possible that interventions that target sleep may lead to improvements in CRF as well (Berger & Mitchell, 2008). At present, CBT-I is considered the gold-standard non-

pharmacological treatment for insomnia (National Institutes of Health, 2005). The CBT-I model is an integration of cognitive therapy and behavioral modification techniques that have been tailored for the treatment of insomnia. In general, the purpose of CBT is to stimulate behavior change through the alteration of cognitive distortions (Woodward, 2011). The most common components of CBT-I include stimulus control (i.e., re-associating the bed and bedroom with rapid sleep onset, developing a stable sleep-wake cycle), sleep restriction (i.e., restricting time in bed to number of hours needed for sleep), relaxation therapies (e.g., progressive muscle relaxation, guided imagery, etc.), sleep hygiene education (i.e., education about healthy lifestyle choices that improve sleep and minimize sleep disturbance), and cognitive restructuring (i.e., challenging the accuracy of beliefs, thoughts, and perceptions about sleep; Savard & Morin, 2001; Schutte-Rodin et al., 2008). These techniques and strategies are typically delivered in group or individual settings over a period of five to eight weeks, and patients are required to implement the techniques learned during weekly sessions into their daily lives.

A recent meta-analysis of CBT-I for insomnia in cancer survivors showed medium effects for improvements in sleep efficiency (d=0.53), sleep latency (d=0.43), and wake after sleep onset (d=0.41; Johnson et al., 2016). Large effects were also observed for insomnia severity (d=0.77). In addition, CBT-I was shown to improve CRF in cancer survivors with chronic insomnia (Heckler et al., 2016). Therefore, sleep disturbance and insomnia should be screened for among those with CRF, and interventions that target sleep, such as CBT-I, should be considered as a potential treatment that could also help to improve symptoms of fatigue.

Mind-body therapies, with a particular focus on mindfulness-based interventions, yoga, and acupuncture have been identified as interventions associated with improvements in fatigue (Bower et al., 2014). Unlike other interventions available for CRF, mind-body interventions

typically provide additional benefits of more broad symptom reduction and overall improved quality of life. For example, a randomized controlled trial of mindfulness-based stress reduction for persistent fatigue in cancer survivors reported large reductions in fatigue interference and severity after a 7-week intervention (Johns et al., 2015). Additional improvements were also observed in outcomes of depression, sleep disturbance, disability, and anxiety, with treatment effects maintained at 6-months post-intervention (Johns et al., 2015). Yoga interventions have also been identified as effective for improving CRF in cancer survivors (Bower et al., 2012; Kiecolt-Glaser et al., 2014; Sprod et al., 2015). Though the use of mind-body interventions among cancer patients and survivors are generally supported, continued research in patients other than those with breast cancer are required.

Recently, recommendations for the use of integrative therapies have been included in the clinical practice guidelines of CRF listed above, but have also been summarized and graded based on levels of evidence for a variety of cancer-related symptoms in guidelines specific to patients with breast cancer (Greenlee et al., 2014). Although there is generally limited empirical support for a widespread recommendation for use of a broad range of complementary therapies, there are a number of interventions available that have the potential to benefit cancer survivors with residual fatigue. A systematic review of 20 studies found six which have evaluated the effectiveness of various complementary and alternative medicine interventions for reducing fatigue specifically in patients who have completed cancer treatment (Finnegan-John, Molassiotis, Richardson, & Ream, 2013). One study investigating the impact of a Reiki intervention CRF in a sample of 16 cancer survivors found that fatigue was reduced within the Reiki condition, but that there were no differences between the intervention and control conditions (Tsang, Carlson, & Olson, 2007). Another blinded, randomized trial of biofield

healing found improvements in symptoms of fatigue after the intervention relative to a control condition, but found no differences between the biofield healing and mock healing conditions (Jain et al., 2012). One small study of a combined education and acupuncture intervention found improvements in fatigue relative to usual care (Johnston et al., 2011), while another found an acupuncture intervention to be superior to both acupressure and sham acupuncture (Molassiotis et al., 2012). The authors of this analysis suggest that integration of these therapies into standard care could be considered while larger, more robust trials are conducted (Finnegan-John et al., 2013).

Pharmacological interventions. At present, very few pharmaceuticals have been investigated for the treatment of CRF. A recent meta-analysis examined the use of psychostimulants as a treatment for CRF in mixed samples of patients that were either receiving active cancer treatment or were post-treatment (Minton, Richardson, Sharpe, Hotopf, & Stone, 2011). The medications examined in these trials were methylphenidate, a psychostimulant commonly used in the treatment of attention-deficit hyperactivity disorder and narcolepsy, and dexamphetamine. In their analysis, the authors reported a small but significant effect of psychostimulants over placebo (SMD=-.28), which is about the same size as the treatment effect reported in another meta-analysis of exercise for CRF (Cramp & Byron-Daniel, 2009). They recommend that with this small effect, the use of these medications should be restricted to patients with advanced disease or for short-term treatment only (i.e., less than 8 weeks). These medications offer benefits of rapid onset of effects and low risk for adverse events, but long-term use is not recommended as this can lead to dependence and tolerance issues (Minton et al., 2011).

Research has also examined the efficacy of modafinil, a central nervous system stimulant and analeptic drug used in the treatment of narcolepsy and other fatigue disorders. One study included patients with metastatic prostate or breast cancer receiving active chemotherapy treatment (Hovey et al., 2014). After 15 days of treatment, modafinil was no better than placebo in relieving symptoms of fatigue. A second trial including lung cancer patients found similar results, with no difference between treatment with modafinil and placebo (Spathis et al., 2014). As a result of these findings, modafinil is not currently recommended as a treatment for CRF, though further research into its potential therapeutic effects is ongoing. With these results, psychostimulants may be recommended for managing CRF during active treatment or for those with advanced disease, but are not currently recommended for use in the post-treatment period (Bower et al., 2014); other treatment options should be considered first.

Given the links between fatigue and depression and the potential role of serotonin in maintaining symptoms of fatigue, antidepressants have been examined as a potential treatment for CRF as well. Two trials of paroxetine (Paxil), a selective serotonin reuptake inhibitor, found similar results (Morrow, 2003; Roscoe et al., 2005). Both trials were conducted with patients undergoing chemotherapy, and both found no improvements on levels of fatigue after treatment with Paxil compared to control, but did observe improvements in levels of depression. These results suggest that alterations in serotonin may not be the primary mechanism of CRF, or at least not in patients undergoing chemotherapy.

Finally, there has been limited investigation into the use of natural health products, such as ginseng and guarana, as a treatment for fatigue so they are generally not recommended at this time. A recent study of American ginseng (*Panax quinquefolius*) on symptoms of CRF in a sample of both patients receiving treatment and survivors found more improvement after 8

weeks of 2000mg per day ginseng treatment relative to a placebo (Barton et al., 2013). Another study of guarana (*Paullinia cupana*) extract from the seeds of the guarana plant in the Amazon basin, reported significant improvements in CRF among breast cancer patients on active treatment who had received 50mg of guarana extract when compared to a placebo (de Oliveira Campos et al., 2011). Finally, significant improvements in fatigue were also reported in a trial of the Bojungikki-Tang herbal combination, a traditional Chinese medicine (Jeong et al., 2010). Further research into the impact of natural health products on fatigue among cancer survivors is required to determine whether it should be included in treatment recommendations. In this case, special attention should also be taken to examine potential drug interactions.

Summary. Despite the high prevalence of CRF and a paucity of research of the behavioral correlates associated with CRF (Minton et al., 2013), there is currently no single effective intervention available. At present, education, physical activity, and psychosocial interventions such as cognitive-behavior therapy and mind-body interventions represent the first line of treatment for CRF (Bower et al., 2014). Yet, there are challenges and barriers to the uptake of these recommendations among patients and providers (Berger et al., 2015). Perhaps one of the primary barriers to the uptake of screening and treatment recommendations is the absence of a single biological mechanism or marker of CRF, and the subsequent lack of mechanism-driven interventions for it (Berger et al., 2015). Particularly in cancer survivors, research that aims to extend current understanding of the underlying mechanisms of CRF is essential to complete the framework to fully understanding and treat this currently intractable problem (Minton et al., 2013).

Mechanisms of CRF

Although CRF is reported by a majority of cancer patients at one time or another, the specific mechanisms involved in its pathophysiology remain poorly understood, and it is unclear whether it is a result of a combination of mechanisms or one centrally mediated disorder (Wang & Woodruff, 2015). Given that fatigue is a non-specific, multidimensional, and multifactorial experience, it is likely influenced by several factors that co-occur and co-vary depending on the unique characteristics of the patient (Bower, 2007). These may include complex interactions among physiologic factors (e.g., hormonal changes, sleep disorders, lack of exercise, drug side effects), psychosocial factors (e.g., depression, anxiety), and chronobiological factors (e.g., altered circadian rhythms; Liu et al., 2005; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). One of the key barriers of basic research into the potential mechanisms of CRF, is the inability to imitate the subjective and multifactorial nature of CRF in animal models (Stasi et al., 2003). The inability to model this syndrome has delayed the identification of underlying biological mechanisms or markers of fatigue, and has subsequently prevented the development of effective treatment options based on treating underlying causal factors.

In general, CRF has been attributed to dysregulation of basic mechanisms that can be categorized into either peripheral or central components (Ryan et al., 2007). Peripheral fatigue originates in the neuromuscular junctions and muscle tissues of the body and is associated with the inability of the peripheral muscles or joints to perform a task in response to signals from the brain (Ryan et al., 2007). Central fatigue originates in the central nervous system and refers to the difficulties associated with initiating or engaging in voluntary activities (Chaudhuri & Behan, 2004). These difficulties then manifest as problems completing mental and physical tasks where no cognitive or physical disabilities exist (Chaudhuri & Behan, 2004; Okada, Tanaka, Kuratsune,

Watanabe, & Sadato, 2004). These differences between peripheral and central fatigue may help to explain how patient perceptions of fatigue can vary from physical tiredness or exhaustion and a need for reduced activity, to reduced motivation or mental fatigue (Ahlberg et al., 2003; de Raaf, de Klerk, & van der Rijt, 2012).

Cytokine dysregulation. The proinflammatory cytokine hypothesis is one potential central fatigue mechanism to explain CRF. Cytokines are proteins that are produced by cells to facilitate communication between cells and can effect every organ in the body (Kurzrock, 2001). The theory that elevated levels of proinflammatory cytokines are implicated in the development and maintenance of CRF is based on the observation that patients undergoing treatment for cancer reported similar symptoms to those displayed in animals models of cytokine-induced sickness behavior (Cleeland et al., 2003). This "sickness behaviour" refers to the behavioral and physiological responses, including sleep disturbance, reduced activity and food intake, observed in animals after administration of inflammatory agents or specific proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor – alpha (TNF-α; Dantzer, 2001). It is possible that elevated levels of proinflammatory cytokines have been observed in cancer patients and survivors because they accumulate as a by-product of cellular damage and destruction, which occurs during tumor development and during cancer treatment (Ahlberg et al., 2003; Jager, Sleijfer, & van der Rijt, 2008). If present, there is the potential for these elevated levels of cytokines to contribute to other symptoms, such as depression, fever, and anemia that may then feedback and exacerbate fatigue symptoms (Kurzrock, 2001). Indeed, elevated levels of a number of circulating proinflammatory cytokines have been observed in patients with cancer and in those reporting higher levels of fatigue (Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007), though these associations have not been consistent.

Collado-Hidalgo and colleagues (2006) recruited fatigued and non-fatigued breast cancer survivors and collected serum samples. Fatigued breast cancer survivors were distinguishable from non-fatigued survivors by the presence of increased levels of IL-6 and TNF- α. Another study examining the presence of immune markers in breast cancer survivors reporting significant fatigue following treatment completion, found elevated levels of T-lymphocytes (Bower, Ganz, Aziz, Fahey, & Cole, 2003). In a sample of 200 breast cancer survivors between 3 months and 4 years post-treatment, women with CRF displayed higher levels of c-reactive protein (CRP) than those who were not fatigued (Alexander et al., 2009). Similar results were observed in two other studies where cancer survivors were characterized by higher levels of CRP (Alfano et al., 2012; Orre et al., 2009). Finally, a review of 20 studies investigating associations between CRF and proinflammatory biomarkers found that higher circulating levels of IL-6, IL-1 receptor antagonist, and neopterin were associated with CRF (Schubert et al., 2007).

Following this, studies investigating anti-inflammatory treatments as interventions for CRF have been shown to be beneficial for improving CRF. For example, one study investigating TNF-α agonists in 12 patients with advanced cancers undergoing chemotherapy found that treatment was associated with subsequent reduction in fatigue (Monk et al., 2006). Another study of a 12-week Iyengar yoga intervention for fatigued breast cancer survivors found that the intervention was associated with reduced inflammation-related gene expression (Bower et al., 2014).

Serotonin (5-HT) dysregulation. Another central fatigue hypothesis that may explain the origins of CRF is an increase in brain serotonin levels and/or an upregulation of serotonin receptors (Ryan et al., 2007). Serotonin, a neurotransmitter, is involved in a number of functions within the body including appetite, sleep, memory, learning, and mood, among many others.

Given that central serotonin levels have been implicated in both exercise-induced fatigue and chronic fatigue syndrome (Ryan et al., 2007), it is possible that serotonin dysregulation is present as a consequence of increased activity of proinflammatory cytokines that result from cancer and cancer treatments, that leads to alterations in serotonin metabolism and presented as fatigue (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010). There is evidence that proinflammatory cytokines, such as TNF-α, can influence serotonin metabolism, either by the existence of a feedback loop whereby TNF-α causes an increase in serotonin release into the synaptic space (Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002), or through increasing transporter function (Zhu, Blakely, & Hewlett, 2006). At the same time, elevated levels of TNF-α also lead to elevated levels of tryptophan, a precursor to serotonin. During cancer, this feedback loop between circulating proinflammatory cytokines and serotonin may become dysregulated as circulating levels of cytokines increase (Morrow et al., 2002). With increasing demands on the body during cancer, the brain may not be able to synthesize adequate levels of serotonin to overcome the increase in transporters, resulting in the symptoms observed (Morrow et al., 2002).

It follows that interventions to target and regulate serotonin levels or the expression of serotonin receptors should impact levels of fatigue if this hypothesis holds. However, studies of the use of selective serotonin-reuptake inhibitors in patients with CRF have not resulted in measurable improvements in fatigue (Morrow, 2003; Roscoe et al., 2005). Perhaps behavioral interventions to treat depression, which is also associated with serotonin dysregulation, may also have beneficial effects on fatigue (Tchekmedyian et al., 2003). These behavioural interventions could also be working through a variety of other pathways, however, and therefore do not directly support this mechanism.

Circadian rhythm disruption. Another potential mechanism by which cancer may be associated with fatigue is through circadian rhythm disruption. Circadian rhythms are endogenous physiological rhythms that follow an approximate 24-hour cycle to control several biological functions, such as sleep-wake patterns and hormone secretion such as melatonin, within the human body (Payne, 2011). This system is often referred to as the body's "biological clock" or "circadian clock" (Ryan et al., 2007) and its function is to "provide a temporal organization of physiological processes and behavior to promote effective adaptation to the environment" (Payne, 2011; p. 221). These rhythms are coordinated by a "master clock" that is located in the hypothalamic suprachiasmatic nucleus (SCN), a cluster of neurons located above the optic chiasm that can be entrained by environmental (e.g., alterations in light and dark) and psychological cues (e.g., stress, anxiety, and illness; Monteleone, Martiadis, & Maj, 2011; Ryan et al., 2007), and may also be affected by signal disruption or input from other areas of the brain (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010b).

Light is the most powerful zeitgeber, or "time giver", that can influence and entrain the master clock. In humans this occurs through retinal responses to light cues via the retino-hypothalamic tract. This pathway involves the activation of light sensitive retinal ganglion cells that contain the photopigment melanopsin, that then release glutamate to signal the SCN. These signals then activate or inhibit gene expression via complex feedback loops in the SCN. SCN output is then received by the paraventricular nucleus (PVN) of the hypothalamus which translates the SCN signals into hormonal and autonomic signals for peripheral organs and peripheral clocks (Monteleone et al., 2011). Alterations in any part of this system can result in the disruption of arousal and sleep patterns (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010a).

Several alterations in circadian function have been reported in patients with cancer (Ryan et al., 2007). These include changes in endocrine rhythms (e.g., cortisol, melatonin, prolactin secretion cycles), metabolic processes (e.g., body temperature, circulating protein levels), immune system function (e.g., increased levels of proinflammatory cytokines), and rest-activity patterns (Mormont & Levi, 1997). Common types of circadian rhythm alterations include diminished amplitude (e.g., flatter diurnal cortisol slope), phase shifts (e.g., delayed or altered rest-activity rhythms), period changes (e.g., alterations in the duration between peaks), and erratic peaks and troughs (Ryan et al., 2007). These can be categorized as disorders of timing (changes occurring at different times than usual), magnitude (smaller or larger changes than usual), or synchronization (some systems shifting while others stay the same so they become desynchronized; Lazuna & Farr, 2003). The causes of cancer-related circadian disruption may include a host of factors, including genetic, psychosocial, environmental, and behavioral influences, as well as the direct effects of the tumor on rhythm regulation (Mormont & Levi, 1997). Research examining the potential links between circadian rhythm disruption and fatigue has also focused on the role of circadian rhythm disruption in the dysregulation of the neuroendocrine system, discussed above (Ryan et al., 2007). To date, the most effective intervention to improve circadian dysregulation is systematic exposure to bright light (Dodson & Zee, 2010).

Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction. Disturbance of HPA-axis functioning is another potential mechanism that has been implicated in CRF, and is directly influenced by the circadian rhythm. That is, the major output of the SCN is to the paraventricular nucleus (PVN) of the hypothalamus which receives signals that are translated into hormonal and autonomic signals that are then released by the HPA-axis to affect peripheral organs

(Monteleone et al., 2011). The HPA-axis is the central regulatory system that controls the release of the stress hormone cortisol (Ryan et al., 2007). In order for cortisol to be released, first CRH is secreted from the PVN of the hypothalamus and acts with vasopressin to release adrenocorticotropic hormone (ACTH) from the anterior pituitary (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010). ACTH then stimulates the release of cortisol from the adrenal cortex. Once cortisol is released into the bloodstream, it can impact blood pressure, cardiovascular function, energy metabolism, and immune function (Ryan et al., 2007). Cortisol feeds back onto the HPA-axis by activating receptors on the hippocampus, hypothalamus, and pituitary to slow down production (Ryan et al., 2007). The HPA-axis is sensitive to the presence of proinflammatory cytokines, but cortisol also has a suppressive effect on cytokine production, meaning that elevated levels in one system leads to alterations in the circulating levels of the other (Ryan et al., 2007).

Typically, serum cortisol levels follow a diurnal pattern where the highest concentrations are present upon awakening in the morning and then slowly decline over the course of the day (Ryan et al., 2007). It is proposed that elevated levels of proinflammatory cytokines and chronic inflammation may reduce the synthesis and release of CRH (Shanks et al., 1998), that then results in lower or dysregulated release of cortisol from the adrenals, that may be experienced as feelings of fatigue. Additionally, given the direct influence of the circadian rhythm on HPA-axis activity, any alterations in that system would carry forward, and result in an alteration in the diurnal release of cortisol.

There is research evidence that HPA-axis function is altered in CRF, manifested by the presence of abnormal diurnal cortisol rhythms, both during active treatment and in the post-treatment period (Banasik, Williams, Haberman, Blank, & Bendel, 2011; Bower et al., 2005;

Schmidt et al., 2016; Schrepf et al., 2013; Tell, Mathews, & Janusek, 2014). Bower and colleagues (2005) recruited 27 fatigued and non-fatigued breast cancer survivors, had them participate in a standard laboratory stressor (i.e., the Trier Social Stress Test) and collected salivary cortisol. Fatigued survivors displayed blunted cortisol responses to the stressor compared with non-fatigued survivors. That is, the fatigued survivors did not display the expected increase in cortisol during stress that is typically displayed in healthy subjects (Dickerson & Kemeny, 2004). Interestingly, this study had also collected measures of autonomic function (i.e., blood pressure and heart rate) and found no difference in their expression between fatigued and non-fatigued individuals.

In another study examining the diurnal expression of cortisol in fatigued and non-fatigued breast cancer survivors, women with fatigue displayed flatter diurnal cortisol slopes than those who were not fatigued (Bower et al., 2005). The fatigued group also showed a less rapid decline in cortisol levels in the evening hours, accounting for the flatter overall slopes. Similar patterns of responding were observed in a sample of women recently diagnosed with breast cancer during active treatment (Tell et al., 2014).

Given that diurnal changes in cortisol have been shown to alter the number and function of immune cells, it is possible that neuroendocrine dysregulation (i.e., altered cortisol levels) may also play a role in proinflammatory cytokine production (Petrovsky, Mcnair, & Harrison, 1998). Low levels of circulating cortisol have been observed in patients with chronic fatigue syndrome as well as CRF (Cleare, 2003), so it is possible that the same mechanism that underlies that disorder is also responsible for similar symptoms experienced in CRF. Following this, interventions that normalize HPA function should be effective in treating CRF.

Models of CRF. The development of fatigue as a result of cancer and its treatments is likely due to a variety of complex interactions between a number of biological and psychophysiological mechanisms. In an attempt to elucidate the pathophysiology of CRF, there have been a number of models published in the literature that propose and outline complex interrelationships between the various mechanisms described above (Bower, 2007; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Morrow et al., 2002).

The model proposed by Morrow and colleagues (2002) places emphasis on the hypothesis that serotonin dysregulation is key to the development of CRF. Within this model, it is hypothesized that cancer and its treatments lead to an increase in proinflammatory cytokines (i.e., TNF-α, IL-1, IL-6) that interact with serotonin levels to alter the levels within the brain. They propose that TNF-α may stimulate an increase in the release of serotonin and lead to greater up-regulation of serotonin transporters. Concomitantly, it is proposed that elevated levels of TNF-α also lead to elevated levels of circulating tryptophan, a precursor to serotonin. The relationship between TNF-α and serotonin is then characterized as a complex regulatory feedback loop that becomes dysfunctional with increased levels of circulating cytokines. Finally, with increased demands on both the body and brain during cancer and treatment, it is possible that the brain may be unable to synthesize adequate levels of serotonin to overcome the increase in transporters, resulting in the symptoms observed. It is suggested that the association between depression and fatigue in patients with cancer can be explained by this common mechanism. Overall, this model is simple and provides a framework for future investigations. However, the relationships between variables, shown as simple arrows within the model, represent complex interrelationships that have not been fully elucidated.

A second model, proposed by Bower (2007) first suggests that cancer and its treatments activate proinflammatory cytokines that result in the development of fatigue through cytokine effects on the central nervous system. Chronic inflammation develops when long-term changes in immune homeostasis and neuroendocrine function are altered during cancer treatment. The interactions among individual differences (e.g., HPA-axis dysregulation, depression, cytokine gene polymorphisms) then increases the risk of chronic inflammation through HPA-axis dysregulation and depressive symptomatology. Unlike the previous model, this takes into account individual differences. Given that physical and mental manifestations of fatigue and the experience of fatigue can vary from person to person, by including individual differences as a potential pathway through which one may be more prone to developing fatigue, there is the potential to account for some of the variability of symptom expression with these between person differences. One of the limitations of this model is that it does not take into account a many of the other potential mechanisms, such as circadian disruption.

Miller and colleagues (2008) propose that an initial activation of the immune response is a result of various aspects of being diagnosed with and treated for cancer, including the biological effects of tissue damage and destruction, and the psychological effects of stress. This inflammatory response activates alterations in the sleep-wake cycle that can disrupt neuroendocrine system functioning (e.g., HPA-axis functioning) which feeds back into inflammatory processes by producing further release of proinflammatory cytokines. Unrestrained inflammation and the associated increased release of proinflammatory cytokines interact with the central nervous system (e.g., decreased serotonin and dopamine availability) to regulate behavior and produce symptoms such as depression, fatigue, and impaired sleep (Miller et al., 2008). This is among the most comprehensive models available to date.

The models of CRF available provide a solid foundation for understanding the potential mechanisms and have helped to guide research in uncovering the precise mechanisms involved in the development of CRF. To summarize these models, Figure 1.1 presents a modified version of the model presented by Miller and colleagues (2008) to incorporate the models developed by Morrow et al. (2002) and Bower et al. (2007), and also to address the potentially bi-directional relationships among these mechanisms.

Light Therapy

To date, light therapy represents the most successful clinical application of the resynchronization of circadian rhythms (Monteleone et al., 2011). The ability for light to influence circadian rhythms in humans was first documented in the 1980s. These early studies examined the impact of shifts in light-dark cycles on circadian rhythms, and the role of systematic exposure to light in supressing melatonin secretion and altering the phase of endogenous rhythms in delayed sleep-phase syndrome (Czeisler et al., 1981; Lewy, Wehr, Goodwin, Newsome, & Markey, 1980; Rosenthal et al., 1990). Since then, bright light therapy has demonstrated efficacy for a variety of circadian rhythm and fatigue disorders.

In a recent review of light therapy for sleep problems, van Maanen and colleagues (2016) reported that light therapy treatment resulted in small to medium effects for circadian rhythm sleep disorders, insomnia, sleep problems related to Alzheimer's disease/dementia, and other disorders associated with sleep and fatigue problems (i.e., chronic fatigue syndrome, traumatic brain injury), as well as sleep complaints including sleepiness, fatigue, and insomnia symptoms. It has also been used extensively for the treatment of seasonal and non-seasonal depression (Desan et al., 2007; Golden et al., 2005), delayed and advanced sleep phase syndromes (M.

Terman et al., 1995), jet lag syndrome (Boulos et al., 1995), and shift work syndrome (Eastman et al., 1995).

Mechanisms of light therapy. As discussed earlier, light has a direct influence on the human circadian rhythm through its role in the activation of the body's master clock, the SCN (Ryan et al., 2007). Environmental cues of the presence or absence of light are sent to the SCN via the retinohypothalamic pathway (Monteleone et al., 2011). These signals activate a cascade of events, including the production or inhibition of the release of proteins and clock genes that are temporally-related and connected via interdependent feedback loops. These neuromodulators then signal the release or inhibition of neurotransmitters in the brain and of hormones in a number of peripheral organs. Alterations in this system may manifest as behavioral symptoms, including the disruption of arousal and sleep patterns (Barsevick et al., 2010a). Given that dysregulation in this system underlies a multitude of disorders, it follows that the therapeutic use of light to correct the disruption of the circadian system should result in improvements in the behavioral symptoms that arise.

Research investigating the efficacy of light therapy for seasonal and non-seasonal depression has shown that bright light therapy has robust antidepressant effects (Terman & Terman, 2005). Normally, mood shows variations over the course of a 24-hour cycle, with lower mood in the evening compared to the morning (Boivin et al., 1997). This variation in mood over the course of the day has been found to be an interaction between circadian phase and the duration of time awake (Boivin et al., 1997). Therefore, it follows that if circadian rhythms play a role in mood within healthy subjects, it is likely involved in the maintenance of depression and other mood disorders. Indeed, abnormalities in the circadian rhythms of individuals with depression have been confirmed (Van Cauter & Turek, 1986), and examination of disturbances

in endogenous rhythms can distinguish those with depression from non-depressed individuals (Benca, Obermeyer, Thisted, & Gillin, 1992).

Among people suffering from seasonal-depression, poor mood can also be linked with circadian alterations. That is, their depressive symptoms and poor mood are the behavioral manifestation of a delay in endogenous rhythms that result from a later dawn in fall and winter months, producing a mismatch between the clock time and their sleep-wake cycle. Light therapy has the ability to repair this mismatch by providing a corrective phase advance and realigning the endogenous rhythm with the sleep wake cycle dictated by the clock. Indeed, the amount of improvement in mood among individuals with seasonal-depression treated with light therapy is directly correlated with the magnitude of the phase advance (Terman, Terman, Lo, & Cooper, 2001). That is, larger phase advances from exposure to morning light were associated with greater improvements in depression ratings. Given that CRF may result from alterations to the circadian system that are similar to those in seasonal affective disorder, but caused by cancer or cancer treatments (Ryan et al., 2007), it is possible that light therapy may act in similar ways on the circadian system to improve the symptoms that result from alterations in mood and sleep-wake disturbances.

Light exposure and cancer-related fatigue. In a review about the relationship between sleep and fatigue in cancer patients, Ancoli-Israel and colleagues (2001) highlighted a potential link between deteriorating health, reduced physical activity, and as a result, less exposure to sunlight. They suggest that with increased symptom burden, patients may begin a cycle of less activity and more time in bed, producing negative impacts on sleep quality. This reduction in sleep quality may then result in tiredness and further avoidance and reduction of physical activity, consequently further decreasing exposure to bright light. These factors combined could

lead to alterations in the circadian phase and a desynchronization of sleep-wake rhythms, producing further decrements in sleep quality and increased severity of fatigue.

In order to examine this potential association, Liu and colleagues (2005) recruited a sample of women scheduled to begin chemotherapy treatment for breast cancer to participate in a study to assess severity of fatigue and daily light exposure, as measured by a photometric transducer located in a wrist actigraph recorder. Overall, symptoms of fatigue were increased and mean light exposure duration and intensity were decreased over the course of the chemotherapy treatment. In addition, more fatigue and less vigor were associated with lower light intensity and shorter duration of bright light exposure. They hypothesized the presence of a negative feedback loop to explain these associations, wherein fatigue leads to lower levels of activity and more irregular sleep patterns that subsequently leads to less exposure to bright light (i.e., sunlight). The decreased exposure to bright light then leads to further circadian dysregulation, and more sleep-wake disturbances and fatigue. They suggest that increased exposure to light could break this cycle and prevent the deterioration of fatigue as a result.

To assess the potential for light therapy to impact circadian rhythmicity in breast cancer patients receiving active treatment, Neikrug and colleagues (2012) then recruited 39 women to undergo an intervention of early morning bright light therapy while wearing an actigraphy watch to track circadian rhythmicity. Early morning bright light exposure (30 minutes) was consistent with defence against circadian rhythm desynchronization that has been associated with cancer treatment (Savard et al., 2009). The exact mechanism underlying this finding is not known, though the authors suggest it may have been driven by improvements in sleep or fatigue as a result of the intervention. To better assess these potential hypotheses, two subsequent trials of light therapy were conducted.

Trials of light therapy for cancer-related fatigue. Based on this preliminary work, a randomized controlled trial investigated the impact of light therapy on self-reported fatigue and quality of life in 39 women with breast cancer undergoing active chemotherapy (Ancoli-Israel et al., 2012; Jeste et al., 2013). Patients completed baseline assessments of fatigue and quality of life prior to the start of chemotherapy, as well as at four time points over the course of a 4-cycle chemotherapy treatment regime: 1) chemotherapy treatment week of cycle 1; 2) recovery week of cycle 1; 3) chemotherapy treatment week of cycle 4; and 4) recovery week of cycle 4. During the entire chemotherapy treatment regime, patients were randomly assigned to use a light device that emitted either bright white light or dim red light for 30 minutes each morning upon awakening.

The group that received dim red light reported increased fatigue at both the treatment week of cycle 1 (p=.003) and the treatment week of cycle 4 (p<.001), relative to baseline (as would be expected in the normal course of chemotherapy), but no significant change from baseline at either of the recovery weeks. Conversely, the group that received bright white light did not report any significant change in fatigue from baseline values. With respect to the quality of life outcomes, the group that received dim red light showed decrements in self-reported quality of life at both the treatment week of cycle 1 (p=.004) and the treatment week of cycle 4 (p=.0004) relative to baseline values, while the group that received bright white light did not show any significant change from baseline (Jeste et al., 2013). Results of this trial suggest that morning bright light treatment helped prevent the typical worsening of fatigue and quality of life that occurs for many patients during chemotherapy treatment. Although the light treatment did not improve overall fatigue in this sample undergoing active treatment, the lack of deterioration in total fatigue during a period where symptoms typically worsen is encouraging.

A more recent study sought to determine the preliminary efficacy of bright light treatment for CRF among post-treatment survivors of breast cancer, gynecological cancer, and hematological malignancy (Redd et al., 2014). In the trial, 36 participants who scored ≤30 on the Functional Assessment of Chronic Illness Therapy fatigue scale (FACIT-F; where lower scores indicate more fatigue) were randomly assigned to receive a light therapy device that produced either bright white light or dim red light, and were instructed to use it every morning within 30 minutes of awakening for 4-weeks. At the end of the treatment period, no patients in the bright white light condition were clinically fatigued, whereas 55% of the patients in the dim red light condition still reported clinical fatigue. Furthermore, the effects of the bright white light treatment were maintained at 3-weeks post-intervention. Although these results show preliminary efficacy for light therapy to improve CRF in cancer patients and survivors, and provides some evidence that circadian rhythm dysregulation may play a role in symptoms of fatigue, the link between circadian dysregulation and CRF has not been definitively established. Likewise, the impact of light therapy on other important psychological and behavioral variables in CRF has not been investigated.

Rationale for Current Study

As discussed earlier, it is evident that cancer treatment can negatively impact circadian rhythms (Savard et al., 2009). It is also likely that this dysregulation persists into the post-treatment period (Roscoe et al., 2002; Ryan et al., 2007), resulting in behavioral alterations including fatigue and reduced sleep quality. It is through this pathway that light therapy is hypothesized to target underlying circadian dysregulation. More specifically, the application of a corrective phase advance via early morning bright light exposure, as is recommended for seasonal depression (Terman & Terman, 2005), would provide a corrective adjustment to the

circadian rhythm, allowing it to resynchronize with the sleep-wake cycle and other endogenous rhythms, potentially resulting in improvements in behavioral symptoms such as sleep quality and fatigue.

A secondary mechanism that is directly influenced by the central circadian rhythm and may also be impacted by a correction to the rhythm, is the HPA-axis and the diurnal release of cortisol. The disrupted output and phase of diurnal release of cortisol that can result from cancer or cancer treatments (Ryan et al., 2007) may also serve to maintain symptoms of fatigue in cancer survivors. Therefore, applying an adjustment to this rhythm via a corrective phase advance may result in subsequent reductions in symptoms associated with its dysregulation.

It is also possible that light therapy may improve symptoms of fatigue through a third pathway: by improving symptoms of depression. Given that fatigue often co-occurs with depression in individuals with cancer (Brown & Kroenke, 2009; Jacobsen et al., 2003) and that fatigue is a common symptom of depression (American Psychiatric Association, 2000), it is possible that improvement in mood through the use of light therapy could produce simultaneous reductions in fatigue. Combined, these hypotheses provide a unique perspective into a potential solution for symptoms of CRF though the proposal of a mechanism-driven intervention to target underlying dysregulation.

Therefore, given that light is an important regulator of mood, sleep-wake rhythms, and the diurnal release of hormones such as cortisol (Eismann, Lush, & Sephton, 2010), it is hypothesized that systematic exposure to light can regulate the functioning of these systems and help improve symptoms of CRF that are a result of dysregulation in one or more of these systems. Although other treatment strategies, such as exercise, mind-body interventions, and interventions that target sleep, have shown promising results for decreasing the impact of CRF

on some aspects of functioning, the effect sizes observed across interventions are typically small. Light therapy has been demonstrated as a safe, inexpensive, and-easy to-administer alternative for other fatigue-related disorders. As discussed, this form of therapy has demonstrated effectiveness in preventing the typical worsening of fatigue in patients undergoing active chemotherapy (Ancoli-Israel et al., 2012) and has shown preliminary efficacy in a sample of cancer survivors with post-treatment fatigue (Redd et al., 2014). However, the impact of light therapy on other psychological and behavioral variables and the mechanisms by which it improves symptoms of fatigue in cancer survivors with significant fatigue is yet to be determined. This study evaluated the effect a one-month treatment regime of early morning exposure to either bright white light (BWL) or dim red light (DRL) on self-reported fatigue, mood disturbance, depressive symptoms, sleep quality, and quality of life, as well as its impact on diurnal salivary cortisol rhythms in a sample of post-treatment cancer survivors with clinical levels of fatigue.

Aims

Primary aim. The primary aim of this study was to evaluate the impact of a one-month light therapy intervention on self-reported fatigue in post-treatment cancer survivors who met diagnostic criteria for CRF.

Secondary aim. The secondary aims of this study were to investigate the effects of light therapy on secondary measures of mood disturbance, depressive symptoms, sleep quality, and quality of life, as well as the impact of the intervention on diurnal cortisol rhythms.

Hypotheses

Primary hypothesis. Participants exposed to the BWL intervention would display greater improvements in self-reported fatigue, as measured by the Multidimensional Fatigue

Symptom Inventory – Short Form, after the one-month intervention, relative to those in the DRL condition.

Secondary hypotheses. Participants exposed to the BWL intervention condition would display greater improvements on subjective measures of mood disturbance, depressive symptoms, sleep quality, and quality of life after the one-month intervention period, relative to those in the DRL condition. In addition, exposure to BWL, and not DRL, would be associated with increased diurnal cortisol slope and lower evening cortisol levels relative to baseline.

Chapter 2. The LITE Study: Rationale and protocol for a randomized controlled trial of light therapy for cancer-related fatigue in cancer survivors

This chapter outlines the rationale and protocol for the blinded, randomized controlled trial of light therapy for post-treatment cancer-related fatigue. This protocol has been published in full and is presented as published in the journal *Contemporary Clinical Trials*. Permission from the journal to include the manuscript in this document has been included in the Appendix. The publication details are as follows:

Johnson, J. A., Garland, S. N., Carlson, L. E., Savard, J., Simpson, S. A., Ancoli-Israel, S., & Campbell, T. S. (2016). The LITE study: Rationale and protocol for a randomized controlled trial of light therapy for cancer-related fatigue in cancer survivors. *Contemporary Clinical Trials*, 166-173. doi: 10.1016/j.cct.2016.07.004.

To provide a more comprehensive examination of the complete protocol, items such as the demographics and health history forms, and questionnaire package have also been included as Appendices.

Abstract

Fatigue is a common and distressing symptom that can last for months or years in up to one-third of cancer survivors. Despite its prevalence, the nature and mechanisms of cancer-related fatigue are poorly understood and the available treatments may not provide sufficient relief. Fatigue has been identified as a significant contributor to decreased quality of life, making it an important target for intervention. One approach that may be a safe and inexpensive treatment is bright light therapy.

Methods: This study is a 4-week blinded randomized controlled trial. Subjects will be men and women who meet criteria for cancer-related fatigue and have completed cancer treatment. Subjects will be randomly assigned to receive a Litebook treatment device that produces either bright white light (treatment) or dim red light (active control). The devices will be used daily for 30 minutes upon waking for a period of four weeks. The primary outcome, fatigue, will be measured with the Multidimensional Fatigue Symptom Inventory-SF. Secondary outcomes include mood disturbance, sleep quality, quality of life, diurnal cortisol, and inflammatory biomarkers. Fatigue assessments will be completed weekly and secondary outcomes will be assessed at pre- and post-intervention.

Conclusions: The current research will examine the effect of light exposure on cancer-related fatigue and its potential psychological, behavioral, and biological mechanisms. If successful, this research would support the use of light therapy for the management of persistent fatigue in cancer survivors, expanding existing treatment options. It may also improve upon the current understanding of the mechanisms that underlie cancer-related fatigue.

Keywords: randomized controlled trial, light therapy, cancer-related fatigue, cancer, sleep, mood disturbance

Introduction

Cancer-related fatigue (CRF) is one of the most common and distressing symptoms reported by cancer patients and survivors (Wang et al., 2014). CRF has been reported by up to 80% of individuals who have received chemotherapy and/or radiotherapy and occurs across the range of cancer diagnoses (Hofman et al., 2007). It is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Berger et al., 2015). This type of fatigue is also not limited to the active phase of cancer. Symptoms of CRF have been reported before diagnosis, during treatment where symptoms typically worsen, and can persist long after treatment completion and into remission (Berger, Mitchell, Jacobsen, & Pirl, 2015; Gosain & Miller, 2013). Typically, patients anticipate that their levels of fatigue will return to normal following the conclusion of treatment, but approximately one-third of patients will continue to experience fatigue for months or years following treatment (Hofman et al., 2007; Wang et al., 2014).

Despite its prevalence, CRF remains relatively undertreated and the specific mechanisms involved in its pathophysiology remain poorly understood (Hofman et al., 2007). This is likely a result of the multifactorial nature of fatigue, in which symptoms are influenced by several factors that co-occur and co-vary along with the unique characteristics of the patient (Bower, 2007). These may include interactions among physiologic factors (e.g., sleep disorders, physical deconditioning, treatment side effects), psychosocial factors (e.g., depression, anxiety), and chronobiological factors (e.g., altered circadian rhythms; Berger et al., 2015). Treatments to manage CRF include those that are educational, non-pharmacological, and pharmacological

(Berger et al., 2015), though effect sizes are small (Jacobsen, Donovan, Vadaparampil, & Small, 2007).

Bright light therapy has demonstrated efficacy for a variety of circadian rhythm and fatigue disorders (Golden et al., 2005; Rastad, Ulfberg, & Lindberg, 2011; van Maanen et al., 2016). The proposed mechanism of action is that exposure to bright light in the morning leads to an advance of endogenous circadian rhythms that results in a realignment of these rhythms with the individual's sleep-wake cycle (Monteleone et al., 2011). It has been hypothesized that dysregulation in the endogenous rhythms of some cancer survivors may account for symptoms of fatigue (Ryan et al., 2007). It is therefore possible that by providing a corrective phase advance with early morning bright light exposure, rhythm dysregulation could be corrected resulting in a reduction of fatigue symptoms.

Bright light therapy has demonstrated effectiveness in preventing the typical worsening of fatigue in patients undergoing active chemotherapy (Ancoli-Israel et al., 2012) and has shown preliminary efficacy in a sample of cancer survivors with post-treatment fatigue (Redd et al., 2014). However, the impact of light therapy on other important psychological and behavioral variables and the mechanisms by which it improves symptoms of fatigue in cancer survivors is yet to be determined. Therefore, this study proposes to evaluate the effect a 4-week treatment regime of morning exposure to either bright white light (BWL) or dim red light (DRL) on fatigue, mood disturbance, sleep quality, quality of life, sleep patterns, diurnal cortisol, and inflammatory biomarkers in a sample of post-treatment cancer survivors with persistent fatigue. It is hypothesized that participants in the BWL condition will exhibit greater improvements on these outcomes at post-intervention than those in the DRL condition.

Materials and Methods

Trial Design

The present study is a 4-week blinded randomized controlled trial comparing the effects of morning exposure to either BWL or DRL on fatigue symptoms in a sample of cancer survivors with CRF (Figure 2.1). To capture weekly changes in fatigue symptoms, participants will be assessed in-person or over the phone at five time points. To assess how changes in insomnia symptoms are associated with changes in CRF over the study period, a self-report questionnaire of insomnia symptomatology will be administered either in-person or over the phone at three time points. The remaining assessments (mood disturbance, depressive symptoms, sleep quality, quality of life, credibility and expectancy, sleep diary, wrist actigraphy, diurnal cortisol, and inflammatory biomarkers) will be completed in-person at two time points. The complete assessment schedule for this study is outlined in Table 2.1. All study procedures have been reviewed and approved by the Conjoint Health Research Ethics Board of the University of Calgary and participants will be required to provide written informed consent before engaging in any research-related activity. The research design and reporting of this study will adhere to the recommendations of the CONSORT extension for non-pharmacological treatments (Boutron et al., 2008a, 2008b).

Participants

Participants will include English speaking men and women over the age of 18 years with stage 0-III, non-metastatic cancer, and treatment completion at least 3 months prior to participation in the study to minimize the effect of active treatment on the outcomes. Participants must meet the diagnostic criteria for CRF as outlined in the Diagnostic Interview Guide for Cancer-Related Fatigue (Cella et al., 1998). Exclusion criteria for this study includes: anemia,

active chemotherapy or radiotherapy (with the exception of ongoing hormonal or maintenance treatments), sleep disorders other than insomnia and hypersomnia (e.g., sleep apnea, restless legs syndrome), inability to maintain a regular sleep schedule (e.g., shift work), the presence of a comorbid DSM-IV-TR Axis I disorder (excluding major depression and anxiety; American Psychiatric Association, 2000), the presence of a medical condition that may impact levels of fatigue (e.g., autoimmune disorders, heart failure), the presence of an eye disease or eye surgery within the last two weeks, the presence of a condition contraindicated to the use of light therapy or the use of photosensitizing medications, current use of a light therapy device, pregnancy, and inability to travel for appointments. Participants will not be excluded for using psychotropic medication (e.g., antidepressants) provided that the dose has remained stable over the previous 6 weeks. They will also not be excluded for the use of hypnotic or sedative medications. Antidepressant and hypnotic use over the study period will be recorded and adjusted for if necessary.

Recruitment. A total of 124 participants will be recruited to participate in this study (see Figure 2.1 and sample size calculation for justification). To control for the seasonal changes in sunlight that occur in Calgary, Alberta, Canada, participants will be recruited through the fall and winter months (October to March). The primary means of recruitment will be through self-referral. Participants will be made aware of the study through: a) information pamphlets sent to southern Alberta cancer survivors identified through the Alberta Cancer Registry; b) posted announcements and pamphlets available in the main areas of the Tom Baker Cancer Center, located in Calgary, Alberta, Canada, its satellite locations, and community support groups; c) information provided to patients attending CRF education seminars held at the Tom Baker Cancer Center and University of Calgary; d) referral by Tom Baker Cancer Center oncologists,

psychiatrists, and nurses, as well as psychologists, social workers, and occupational therapists from the Department of Psychosocial Oncology; and e) information provided at community events. Potential participants will be able to obtain information about the research study on a study website or by contacting the researcher by phone or email.

Screening. Individuals interested in study participation will be contacted by phone to discuss the purpose, protocol, and randomized design of the study. If interested, the researcher will determine eligibility through a confidential screening process wherein they will administer the Diagnostic Interview Guide for Cancer-Related Fatigue (Cella et al., 1998), the Insomnia Screening Questionnaire (ISQ; Centre for Sleep and Human Performance Clinical Practice Guidelines Working Group, 2007), and specific questions about medical history, outlined in the inclusion and exclusion criteria. If the individual meets eligibility requirements, they will be invited to participate in the study and four in-person appointments will be scheduled (Table 2.1). Individuals that are not eligible to participate will receive resources specific to managing CRF either by email or mail, and will receive information about the light devices used in the study.

Equipment

The light therapy device used in this study is the Litebook Elite treatment device (The Litebook Company Ltd., Medicine Hat, Alberta, Canada). The Litebook is a small (5”x5”x1”), lightweight (11 oz.), portable battery-operated device that is designed to be placed on a table about 12-24 inches (approximately an arm’s length) from the patient’s face and offset at a 45-degree angle from the midline of the visual field. The Litebook used in the BWL treatment condition contains 25 white light-emitting diode (LED) lights that emit white light at 1250 lx (at 20 inches) and with a distribution of energy concentrated in the shorter wavelengths of visible light (peak between 464-466 nanometers). An identical-appearing Litebook device, used in the

DRL condition, contains 25 red LEDs that emit red light at <400 lx (at 20 inches) and have a distribution of energy that is concentrated in the longer wavelengths of visible light (peak between 632-633 nanometers). For safety purposes, neither the BWL nor DRL Litebook devices emit ultraviolet light. The devices are programmed to turn off after 30 minutes of continuous use. Participants will be instructed not to stare directly into the light beam, but instead allow light to enter the eye in a passive manner. Each Litebook has been modified to include an integrated logger device (HOBO State Data Logger, Onset Computer Corporation, Bourne, MA) that will monitor adherence by recording the date and duration that the light device is on.

Randomization Procedure

Participants will be assigned to one of two treatment conditions using a blocked randomized design with blocks of 4, 6, and 8 created by a random number generating computer program (Sealed Envelope, www.sealedenvelope.com) on a 1:1 allocation ratio. This randomization sequence will take place prior to the recruitment of participants by a research assistant not associated with the study. Using the randomization sequence, the research assistant will label the appropriate light device with each participant number, securing and concealing their allocation prior to beginning the study. The light devices will be stored in non-descriptive packaging without indication of the type of light to ensure that both the investigators and participants are blinded to the treatment condition. Participant numbers will be assigned in the order that they are enrolled in the study.

Measures

The primary outcome measure in this study is the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF; Stein, Jacobsen, Blanchard, & Thors, 2004). The secondary outcomes include: the Profile of Mood States – Short Form (POMS-SF; Shacham, 1983), the

Centre for Epidemiological Studies – Depression scale (CES-D; Radloff, 1977), the Insomnia Severity Index (ISI; Bastien, Vallieres, & Morin, 2001; Morin, Belleville, Bélanger, & Ivers, 2011; Morin, 1993), the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989), the Functional Assessment of Cancer Therapy- General (FACT-G; Cella et al., 1993) and Fatigue (FACT-F; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000), the Consensus Sleep Diary (Carney et al., 2012), wrist actigraphy, salivary cortisol, and inflammatory biomarkers. A brief description of each measure can be found in either Table 2.2 or in the following section. The assessment schedule for all outcomes is outlined in Table 2.1.

Biological samples.

Salivary cortisol. Salivary cortisol will be measured for a period of three consecutive days during both week 0 and week 4, on weekdays when possible. Participants will be provided with 12 labelled, color-coded salivettes (SARSTEDT AG & Co., Germany) and asked to provide four samples per day, over a period of 3 days. Sampling will take place: 1) immediately upon waking, 2) 12:00pm, 3) 5:00pm, and 4) before bed. Participants will be asked to refrain from providing a sample for 30 minutes after eating or drinking. In order to ensure enough saliva is collected, participants will be asked to keep the cotton swab in their mouth for at least 5 minutes and then record the time that they completed the sample on the provided tracking sheet. Samples will be stored in a freezer until they can be returned to the researcher. All samples will be stored in a freezer at -80°C until study completion.

Whole saliva samples will be shipped for processing at an outside laboratory (TUD Biopsychology Laboratory, Dresden, Germany). The cortisol values will be determined using a commercial chemiluminescence immunoassay (CLIA, IBL International, Hamburg, Germany)

that will be conducted according to manufacturer protocols. The intra- and inter-assay coefficients of variation for this process are expected to be less than 8%. The cortisol values will be log-transformed to account for non-normal distribution prior to analysis.

Inflammatory biomarkers. Inflammatory biomarkers will be measured during week 0 and week 4 via serum samples that will be collected at Calgary Laboratory Services located in the Tom Baker Cancer Center. Participants will be instructed to arrive at the laboratory early in the morning to provide a serum sample, and will be asked to refrain from eating or drinking anything other than water prior to providing the sample if possible. It will be recommended that serum samples are collected in the morning after an overnight fast to attenuate the influence of circadian patterns and the presence of glucocorticoids (Zhou, Fragala, McElhaney, & Kuchel, 2010). Prior to providing the sample, participants will complete a questionnaire that will assess their consumption of food, alcohol, medications, and cigarettes in the last 24-hours. This questionnaire will be collected by the lab technician and returned to the researcher along with a form outlining the time and date of the serum collection and processing.

Laboratory technicians will be instructed to collect one 3mL sample of serum in a red top vacutainer tube and record the time and date of the sample. Once the sample is collected, it will be stored in a fridge for 60 minutes to allow time to clot after which it will be centrifuged at 1000 x g for 10 minutes at 4°C. The technician will then aliquot approximately 0.5 mL of serum from the middle of the sample into the microcentrifuge tube and place it in the storage container and then into the freezer at -70°C. The samples will be filtered and then analyzed in duplicate using bead-based multiplexing technology (addressable laser bead immunoassay, ALBIA; Eve Technologies Corporation, Calgary, Alberta, Canada). Previous reports have identified a number of inflammatory biomarkers that have been associated with fatigue in cancer patients and

survivors (Bower, 2007; Collado-Hidalgo et al., 2006). In order to examine the link between the identified biomarkers and fatigue in this sample, the following parameters will be assayed from the serum samples collected at week 0 and week 4: interleukin (IL)-1β, IL-1ra, soluble IL-6 receptor (sIL-6R), IL-6, tumor necrosis factor alpha (TNF-α), soluble TNF-RI, soluble TNF-RII, and C-reactive protein (CRP).

Procedure

Eligible participants will meet with the researcher at the Behavioral Medicine Laboratory at the University of Calgary. During the first appointment (week 0a), the study procedures will be explained in detail, written consent will be obtained, and the demographics and medical history form will be completed. Then, participants will receive equipment and instructions for procedures to be completed during the week, including: 1) how to track their sleep patterns for a period of 7 days using the provided sleep diary; 2) how to properly care for the actigraph watch that they will wear 24-hours a day for 7 days; 3) how to collect saliva samples over a period of 3 days; and 4) how to provide a serum sample. They will also receive parking passes for all of their remaining appointments.

One week later, the participant will return to the Behavioral Medicine Lab for their second appointment (week 0b) wherein they will return the actigraphy watch, sleep diary, and the saliva tubes and tracking sheet, and complete the questionnaire package. Once the questionnaire package is complete, the participant will be provided with a Litebook Elite treatment device (either BWL or DRL) according to their randomization assignment, along with instructions for its use and a log to track its use. The researcher will demonstrate how to operate a sample device without turning it on. The participant will be instructed to use the device within 30 minutes of waking for a duration of 30 minutes each morning for a period of 28 days,

beginning the following morning. Participants will receive no information regarding the differences between the devices. They will be informed that they will have the opportunity to use the device that they were not assigned to after they have completed the protocol. There will be no restrictions or schedule for waking times during the study. The participant will be instructed to contact the research assistant if they have any technical issues with the light device. Participants will be contacted on a weekly basis to verbally complete the fatigue assessment (MFSI-SF) over the phone, with an additional assessment of insomnia symptoms (ISI) completed during week 2. After each weekly assessment, the researcher will remind the participant to continue to use the device daily for 30 minutes.

At the end of week 3, the participant will return to the Behavioral Medicine Laboratory for their third appointment to complete their weekly fatigue assessment. At this time, they will also be provided with a sleep diary and actigraphy watch to track their sleep patterns for a period of 7 days, another 12 saliva tubes and tracking sheet to collect saliva samples for a period of 3 days, and another requisition form to have their serum collected within the week. Each of these tasks will take place during the final week of the intervention, as close to the final day of light use as possible.

Participants will return to the Behavioral Medicine Laboratory for their fourth appointment at the end of week 4 to return their light device, light use diary, sleep diary, actigraphy watch, and saliva samples. At this time, they will complete the questionnaire package. Then, the researcher will conduct a debriefing session wherein they will discuss the study hypotheses in detail with the participant and reveal the intervention conditions. The participant will be given the opportunity to use the light device that they were not assigned to and will also receive an information booklet specific to managing CRF.

Data Entry and Analysis

Upon completion of the study protocol, saliva and serum samples will be organized and coded to be processed at outside laboratories. Outcome measure data will be entered and checked by research assistants who are blind to intervention allocations. Missing data points will be replaced through multiple imputation techniques. The intervention allocations will only be revealed once all of the data has been entered and the outcome data are calculated.

All data analyses will be carried out using SPSS for Windows Version 24.0. Tests will be performed with a two-sided alternative hypothesis, at a critical significance level of 5%, unless multiple comparisons are used, in which case a statistical correction will be applied. To ensure the appropriateness of the analysis, the distributional normality of the data will be confirmed. To verify whether the groups are comparable on continuous and categorical demographic variables and all outcomes variables, t-tests and Pearson chi-squared tests will be conducted. If between-group differences exist at baseline, such differences will be adjusted for statistically in subsequent analyses. Variables that will be investigated as potential covariates include: age, sex, time since last treatment, and baseline depression scores (CES-D).

Primary Aim. Linear mixed models with random intercept and random linear and quadratic time effects on the five weekly assessments of fatigue using the MFSI-SF, will be used to test the hypothesis that BWL, relative to DRL, treatment will result in greater improvements in self-reported fatigue in cancer survivors.

Secondary Aims. In order to test whether BWL or DRL treatments are associated with greater improvements in subjective measures of mood disturbance, sleep quality, quality of life, and both subjective and objective sleep parameters as measured by sleep diaries and actigraphy, a repeated measures analysis of variance (ANOVA) will be performed. For each outcome

measure, a 2(Group) x 2(Time) repeated measures ANOVA will be performed. The two time points (week 0 and week 4) will be the within-subjects variable and the treatment conditions (BWL and DRL) will be the between-subjects variable. Post-hoc analyses will be conducted to examine the simple main effects for treatment if a significant interaction is detected. Analyses will follow the intent-to-treat principle. Similar analyses will be conducted to examine changes in inflammatory biomarker expression from week 0 to week 4 with age, sex, smoking status, time of sample collection, and medication use included as covariates. To investigate changes in diurnal cortisol rhythms, the slope of diurnal changes in cortisol levels from week 0 to week 4 will be calculated by regressing cortisol values on time of sample for each sampling day. Given that raw cortisol values typically display non-normal distributions, data will be log transformed prior to calculating slopes. Mean cortisol values and area under the curve with respect to ground (AUC_G; as outlined in Fekedulegn et al., 2007) will also be calculated using the transformed values for each sampling day. Multi-level modeling will be employed to determine whether group (BWL or DRL) was a significant predictor of cortisol slope after controlling for relevant confounds. Analyses will also examine whether group was a significant predictor of mean cortisol or AUC_G. Finally, exploratory analyses will also examine the role of adherence to the intervention and the role of credibility and expectancy on treatment outcomes.

Sample Size and Analytic Approach

As discussed, BWL has been shown to prevent a worsening of fatigue during chemotherapy (Ancoli-Israel et al., 2012), and has shown preliminary efficacy (d=0.98) in improving fatigue levels in a similar but smaller sample (Redd et al., 2014). For this study, the primary outcome of self-reported fatigue, as measured by the MFSI-SF, will be analyzed using linear mixed models analyses. However, no precedent has been set for the effectiveness of BWL

on measures of sleep quality, mood, or biological measures in post-treatment cancer survivors. Bright white light has also not been demonstrated to be more beneficial than other wavelengths of light, such as DRL, when the ICD-10 CRF criteria have been applied or when the MFSI-SF has been used. For these reasons, an estimated medium effect size of 0.25, according to Cohen (1992), will be used on the MFSI-SF. Using a two-tailed test and a 5% significance level, 28 participants in each group (56 total) would provide adequate power (80%) to detect a medium effect (Hedeker, Gibbons, & Waternaux, 1999). In order to examine the secondary hypotheses using the analyses outlined above (using a two-tailed test and a 5% significance level), an estimated 49 participants in each group (98 total) would provide adequate power (80%) to reject the null hypothesis and account for a 0.5 correlation between pre-and post-intervention assessments. With an estimated attrition rate of 20%, the number of participants required becomes 62 per group (124 total).

To obtain an adequate sample size for this trial (BWL: n=62; DRL: n=62), approximately 433 patients presenting with symptoms of fatigue will need to be screened for eligibility based on the following assumptions: approximately 40% of patients screened (n=173) will be eligible to participate; 80% of these (n=138) are expected to consent to participate; 90% who consent to participate will likely complete baseline assessments and begin the intervention protocol (n=124); 80% who began the intervention (BWL: n=49; DRL: n=49) will remain to complete post-intervention assessments. This results in a total sample size of 98. Refer to Figure 2.1 for flowchart.

Discussion

A large majority of cancer patients will experience fatigue at some point along the cancer continuum (Berger et al., 2015). A systematic review of 40 studies revealed that the prevalence

of fatigue related to cancer can range from 46% to 96% depending on the patient group assessed, the method of assessment, and the treatment received (Prue et al., 2006). Importantly, the impact of CRF on a patient's quality of life and ability to perform daily activities has been reported as more problematic than other cancer-related symptoms such as pain, depression, and nausea (Curt et al., 2000; Wang et al., 2014), making it an important target for treatment. Patients have reported that fatigue prevents them from leading a normal life and impacts their ability to maintain their daily routine (Curt et al., 2000). CRF is also reported to significantly impact emotional well-being (e.g., loss of emotional control, feelings of isolation and solitude), negatively affect social functioning (e.g., maintenance of interpersonal relationships, spending time with friends), make it more difficult to perform typical cognitive tasks (e.g., remembering things, maintaining temporal order), disrupt employment and financial status (e.g., lost work days, change in conditions of employment), and increase burden on caregivers (e.g., lost work days; Curt et al., 2000). Although the residual symptoms of cancer and its treatments, such as fatigue, can have a profound negative impact on quality of life and functioning, these symptoms are often not monitored as closely during follow-up compared to during active cancer treatment (Shi et al., 2011), and the treatment options available to them may not provide sufficient relief (Jacobsen et al., 2007).

Given the success of light therapy in treating other fatigue related disorders, research has begun to examine whether these results extend to cancer populations. In a trial investigating the impact of light therapy on fatigue and quality of life in 39 women with breast cancer undergoing active chemotherapy (Ancoli-Israel et al., 2012; Jeste et al., 2013), results suggest that morning bright light treatment helped prevent the typical worsening of fatigue and quality of life during chemotherapy treatment. Although the light treatment did not improve overall fatigue in this

sample, the lack of deterioration in total fatigue during a period where symptoms typically worsen is encouraging. A more recent study sought to determine the effect of bright light treatment on CRF among 36 post-treatment survivors (Redd et al., 2014). At the end of the treatment period, patients who had received bright white light therapy were no longer clinically fatigued (as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue subscale), whereas 55% of the patients in the active control condition continued to report clinical fatigue. Also, the effects of the bright white light treatment were maintained 3-weeks post-intervention. Though these results show preliminary efficacy for light therapy to improve CRF in cancer survivors, the finding requires replication in a larger sample and the physiological mechanisms behind this treatment need to be investigated.

Despite a novel intervention and a strong methodology, the following limitations of this study deserve mention. First, there is no follow-up period after the week 4 assessment, therefore it will not be possible to evaluate any potential long-term effects of light therapy treatment on patient self-reported outcomes or biological measures. Second, it is possible that benefits may be experienced simply as a result of the implementation of a daily routine (i.e., using the light every morning upon awakening), as a result of raising patients' awareness to increase their exposure to natural daylight, or due to the passage of time. Third, there is the potential for poor adherence to the treatment that may not be detectable by the researcher despite our efforts to include both subjective and objective monitoring. Participants will be asked to use the light therapy device for 30 minutes upon awakening in the morning; therefore, it is possible that they may encounter interruptions associated with their morning routine that prevents adherence to the treatment regime, and subsequently prevents them from receiving an adequate dose. This will be mitigated

by incorporating weekly reminders to prompt the participant to continue to use the device for the required duration upon awakening each morning throughout the treatment period.

The proposed study also has a number of key strengths. First, the population recruited will not be limited by tumor location, stage, or cancer treatments received, increasing the generalizability of results. Second, the blinding of participants, researchers, and outcome assessors from the treatment allocations and randomization schedule removes potential bias from outcome measurement and may also prevent attrition that could be associated with expectation specific to the condition assigned to. Finally, the present study has been designed to assess a number of potential mechanisms that may serve to maintain fatigue symptoms, such as increased proinflammatory cytokines, circadian rhythm disruption, and hypothalamic-pituitary-adrenal-axis dysregulation, and the impact of light therapy on the alterations of these systems. A number of models propose and outline complex interrelationships between various mechanisms to elucidate the pathophysiology of CRF (Bower, 2007; Miller et al., 2008; Morrow et al., 2002); however, there is a lack of consensus regarding the model that best describes the interplay between these mechanisms. Therefore, results of this trial may address key gaps in the literature regarding the mechanisms that underlie CRF and the pathways through which it is improved.

Conclusions

The available treatments for CRF may not be suitable or provide benefits for all patients, and inadequate treatment is associated with overall reduction in quality of life. The current research will investigate the role of light exposure in CRF and its potential psychological, behavioral, and biological mechanisms. If successful, the results of this study may provide support for light therapy as a safe, non-pharmacological alternative for the management of fatigue in cancer survivors, signifying a transformation and paradigm shift in treatment approach.

Furthermore, the current lack of understanding of the mechanisms surrounding CRF represents a critical barrier to progress in treatment. As a result of the inclusion of various biological and sleep measurements, this research may also improve upon the current understanding of the mechanisms associated with CRF, potentially altering existing models and informing clinical practice.

Acknowledgements

The authors would like to acknowledge the Canadian Cancer Society Research Institute - Innovation grant (Grant #: 2012-701425) for funding this trial. J.A. Johnson acknowledges the following funding sources: Alberta Cancer Foundation, Lloyd & Florence Cooper Memorial Fund, Killam Trust, and Alberta Innovates-Health Solutions.

Chapter 3: A blinded randomized controlled trial of light therapy for cancer-related fatigue in cancer survivors

The following chapter is a summary of the results of the randomized controlled trial that completed data collection in March 2015. More specifically, the manuscript outlines the results of recruitment, participant flow through the study, adherence to the light therapy intervention, the primary outcome of fatigue and associated subscales, and the secondary outcomes of mood disturbance, depressive symptoms, sleep quality, and quality of life. Overall, the trial was relatively successful, with a total sample of 81 participants and a minimal dropout rate. The study's limitations and suggestions for future directions are discussed.

This manuscript has not yet been submitted for publication and has not yet been reviewed by all co-authors at the time of submission. Submission to the Journal of Clinical Oncology is forthcoming.

Abstract

Purpose: To examine the impact of a 4-week light therapy intervention on symptoms of fatigue in cancer survivors with clinical levels of fatigue. Secondary outcomes include mood disturbance, depressive symptomatology, sleep quality, and quality of life.

Method: This 4-week blinded randomized controlled trial recruited cancer survivors who met ICD-10 criteria for cancer-related fatigue. Subjects were randomly assigned to receive a light therapy device that produced either bright white light (BWL; treatment) or dim red light (DRL; active control). The devices were used daily for 30 minutes upon waking for 28 days. The primary outcome, fatigue, was assessed weekly with the Multidimensional Fatigue Symptom Inventory-Short Form. Secondary outcomes assessed pre- and post-intervention included mood (Profile of Mood States), depressive symptoms (Centre for Epidemiological Studies Depression Scale), sleep quality (Pittsburgh Sleep Quality Index), and quality of life (Functional Assessment of Cancer Therapy General and Fatigue scales).

Results: A total of 81 participants were randomly assigned to receive BWL (n=42) or DRL (n=39). Linear mixed models analyses revealed a significant time-group interaction for fatigue symptoms, wherein the BWL condition reported a greater reduction in total fatigue score than those in the DRL condition (between group effect size d=.30). There were also significant improvements over time for both groups on measures of mood disturbance, depressive symptoms, sleep quality, and quality of life over the one-month intervention period.

Conclusion: Greater improvements in fatigue were observed in those receiving early morning exposure to BWL compared to DRL. These findings, along with previous reports of light therapy interventions for cancer-related fatigue, support the use of light therapy as a treatment to improve fatigue symptoms in cancer survivors.

Keywords: randomized controlled trial, cancer, oncology, cancer-related fatigue, light therapy, mood disturbance

Background

Cancer-related fatigue (CRF) is one of the most prevalent and distressing symptoms experienced in the months and years following cancer treatment, with up to one third of survivors affected (Wang et al., 2014). It has been defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Berger et al., 2015). Unfortunately, CRF remains under-recognized and under-treated (Curt et al., 2000; Hofman et al., 2007), and the treatments available may not provide adequate relief (Jacobsen et al., 2007).

Bright light therapy is a recommended treatment for seasonal depression (Rastad et al., 2011) and other mood disorders (Golden et al., 2005), and has recently gained attention as a non-pharmacological treatment for sleep disorders (van Maanen et al., 2016). A primary advantage of this treatment approach is that it is safe, easy-to-access, and has relatively low behavioral demand compared with other treatments, such as exercise and cognitive-behavioral therapy (Matthews, Schmiege, Cook, Berger, & Aloia, 2012; Sprod et al., 2015). Specific to cancer, bright light therapy was shown to prevent the worsening of fatigue during chemotherapy in an RCT of women with breast cancer (Ancoli-Israel et al., 2012), and preliminary efficacy was demonstrated for improving symptoms of fatigue in cancer survivors (Redd et al., 2014). Although the mechanisms that underlie CRF are not well established, it is likely multi-factorial, with factors such as treatment side effects, sleep problems, hypothalamic-pituitary-adrenal axis dysregulation, and mood disturbance interacting with individual characteristics to produce the reported symptoms (Berger, Mitchell, Jacobsen, & Pirl, 2015; Bower, 2007). Given that circadian rhythm dysregulation may underlie several of the mentioned factors, it is possible that

light therapy could target this dysregulation by providing a corrective phase advance to the endogenous circadian rhythms (Monteleone et al., 2011). This corrective shift would realign endogenous rhythms with the individuals' sleep-wake cycle and synchronize their output (Monteleone et al., 2011) to subsequently reduce behavioral and psychological symptoms, such as fatigue.

To date, there have been no trials investigating the impact of light therapy in cancer survivors who meet explicit CRF diagnostic criteria and there has been limited examination of its impact on related physical and psychological outcomes in this population. The primary aim of this study was to assess the impact of a 4-week intervention of early morning light exposure on symptoms of CRF among cancer survivors with clinical levels of fatigue. The secondary aim was to investigate the impact of the intervention on mood disturbance, depressive symptomatology, sleep quality, and quality of life. It was hypothesized that exposure to bright white light (BWL; treatment condition) would produce greater improvements on these outcomes relative to dim red light (DRL; active comparator).

Method

The trial design for this study was outlined in greater detail elsewhere (Johnson et al., 2016). Ethics approval was obtained from the Conjoint Health Research Ethics Board of the University of Calgary and all participants provided written informed consent before engaging in any research-related activities.

Participants

Participants were recruited from Calgary, Alberta, Canada and surrounding areas. To control for seasonal changes in daylight, participants were recruited during the fall and winter months only. Adults with non-metastatic disease who completed treatment at least three months

prior to enrollment were eligible. Participants were required to meet the diagnostic criteria for CRF outlined in the International Classification of Diseases – 10th Revision (ICD-10; Cella, Peterman, Passik, Jacobsen, & Breitbart, 1998). Individuals receiving ongoing hormonal or maintenance treatments and/or using psychotropic medications were eligible provided their dose had remained stable for the previous 6 weeks. Individuals were ineligible if they screened positive for the presence of another sleep or psychiatric condition, if they had another medical condition that could influence fatigue levels, the presence of an eye disease, recent eye surgery, or the use of photosensitizing medications, or if they were currently employed as a shift worker. The primary outcome was assessed weekly (five assessments), while the full battery of assessments was completed at baseline and after the 4-week intervention.

Blinding and Random Assignment

Individuals interested in study participation discussed the randomized design of the trial with the researcher during the informed consent process. Participants were told they would be assigned to receive one of two types of light devices, but were not provided with any details regarding the differences between them. Prior to recruitment, participant numbers were assigned to either BWL or DRL using a blocked randomized design (blocks of 4, 6, and 8) created by a computer-based random number generator on a 1:1 allocation ratio. A research assistant not associated with the study used the randomization sequence to label the appropriate light device with each participant number, securing and concealing their allocation prior to beginning the study. The light devices were stored in non-descriptive packaging without indication of the type of light enclosed to ensure that both the investigators and participants were blind to condition. Participant numbers were assigned in the order that they were enrolled.

Intervention

The light therapy device used in this study was the Litebook Elite (The Litebook Company Ltd., Medicine Hat, AB). The Litebook is a small (5in. x 5in. x 1in.) and lightweight (11 oz.) device that is designed to be placed 12-24 inches from the user's face and offset at a 45-degree angle from the visual midline. The BWL device contained 25 white light-emitting diode (LED) lights that emitted white-blue light at 1250 lx, within the shorter wavelengths of visible light (~465 nanometers). An identical device was used in the DRL condition but contained 25 red LEDs that emitted red light at <400 lx, within the longer wavelengths of visible light (~633 nanometers). The devices were programmed to turn off after 30 minutes of continuous use. Participants were asked to use the device every morning for 30 minutes, within 30 minutes of waking, for a period of 4 weeks (28 days). Participants and researchers were blind to condition and were not made aware of the intervention assignment until they had completed the trial.

Measures

Primary outcome.

The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF; Stein et al., 2004) is a 30-item comprehensive measure designed to assess the physical and psychological aspects of fatigue. This questionnaire has five subscales: general, physical, emotional, mental, and vigor. Change over time and between groups were assessed for the total score and each subscale.

Secondary outcomes.

Mood disturbance. The 37-item Profile of Mood States-Short Form (POMS-SF; Shacham, 1983) assesses six affective dimensions of mood. Higher scores indicate greater mood disturbance.

Symptoms of depression. The Center for Epidemiological Studies – Depression scale (CES-D; Radloff, 1977) is a 20-item measure developed to identify current depressive symptomatology related to major or clinical depression in adults and adolescents. A cut-score of ≥16 is indicative of greater depressive symptom severity (Radloff, 1977).

Sleep quality. The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) is a 19-item self-report scale designed to assess sleep quality and disturbances over a one-month time period in clinical populations. Higher scores indicate more sleep disturbance and a total score greater than 5 is indicative of "poor sleep" (Buysse et al., 1989).

Quality of life. The Functional Assessment of Cancer Therapy- General (FACT-G; Cella et al., 1993) is a 27-item general quality of life measure that contains questions specific to cancer, its treatments, and symptoms. The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F; Yellen et al., 1997) is a 13-item scale that assesses the specific concerns of individuals with fatigue. Higher scores on both scales indicate better quality of life. A score >30 on the FACIT-F is considered within a normal range for levels of fatigue (Cella, 2013).

Credibility and expectancy. The Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000) is a 6-item scale that can be divided into two distinct factors and was used to assess participants' attitudes towards the treatment's credibility and expectancy for improvement in fatigue symptoms. This questionnaire was administered both before and after the intervention.

Adherence. Participants were provided with a tracking sheet to log daily use of the light device, including: 1) the number of minutes between waking and turning on the device; 2) the number of minutes the device was used per day; 3) the number of minutes spent away from the device while it was on; and 4) the activities engaged in while using the device. Each Litebook was also modified to include an integrated logger device (HOBO State Data Logger, Onset

Computer Corporation, Bourne, MA) that recorded the date and duration that the light device was on.

Sample Size

The sample size for this study was calculated to be 28 participants in each group (56 total) to provide adequate power (80%) to detect a medium effect on the primary outcome (Hedeker et al., 1999). To examine the secondary outcomes, an estimated 49 participants in each group (98 total) would provide adequate power (80%). An estimated attrition rate of 20% increased the total number of participants required to 62 per group (124 total). The full calculation is provided in the published protocol (Johnson et al., 2016).

Statistical Methods

To assess the primary outcome of fatigue (MFSI-SF), linear mixed models with random intercepts and slopes and with time as a continuous variable were used to analyze the total score and five subscales. For the model, the random effects were subject, intercept, and slope, and the fixed effects were time (baseline, weeks 1 through 4), group (BWL or DRL), and the time x group interaction, along with a priori covariates of age, sex, time since last treatment, baseline depression score (CES-D), and baseline credibility and expectancy (CEQ). These variables were selected theoretically given previous, findings that age, sex, and depression have been associated with fatigue (Prue et al., 2006). Furthermore, time since last treatment was included as it was anticipated there may be differences between participants who had recently completed treatment and those who were several years post-treatment (Wang et al., 2014). To adjust for anticipatory effects of the intervention and expectation, CEQ scores were also included as covariates. This resulted in a tightly controlled model that would isolate the effects of the intervention itself on

outcomes. The restricted maximum likelihood estimate (REML) method was used to estimate the model parameters and SEs. The covariance structure was set to unstructured.

To assess the secondary outcomes, generalized estimating equations were implemented instead of the planned RM-ANOVAs as the sample size was smaller than anticipated. For each of these models, the fixed effects were time (baseline and week 4), group, and time x group interaction, along with the covariates age, sex, time since last treatment, and baseline score on the outcome measure. The REML method was used to estimate the model parameters and SEs. The covariance structure was set to compound symmetry for all models. The significance level was set at $p<.05$. Effect sizes (*d*) were calculated for both groups from baseline to post-intervention for all outcomes using estimated marginal means and standard errors from the analysis output. All data analyses were carried out with IBM SPSS v.24 (SPSS, Chicago, IL).

Results

Participants

Between October 2013 to March 2014, and between October 2014 to March 2015, 252 people were assessed for eligibility and 81 participants were eligible and randomly assigned. Figure 3.1 outlines participant flow through the study, along with reasons for ineligibility, refusal, and withdrawal. Table 3.1 outlines participant demographics and disease characteristics.

Adherence

In total, 76 participants returned their light use tracking sheets and 76 logger devices recorded complete data. The participants who did not return their tracking sheets noted that they forgot to complete the form (n=3) or dropped out of the study and did not provide a sheet (n=2). The logger devices that did not produce usable data either malfunctioned (n=3) or the participant withdrew and did not have complete data (n=2). The outcomes for the adherence measures for

participants with compete data are presented in Table 3.2. Overall, participants reported using the light devices for an average of 30 minutes per day (SD=0.6), within 30 minutes of waking (SD=23.2). There were no differences between the groups on any of the adherence outcomes. Activities during light use included: reading, eating/drinking, computer use, watching TV, applying makeup, or sitting silently. No adverse events were reported.

Primary Outcome

The adjusted mean scores on the MFSI-SF for both groups at each time point are reported in Table 3.3 and are represented graphically in Figure 3.2. The random intercept and random slope linear mixed model analysis revealed a significant slope for age, $t(71.30)=-2.315$, $p=.023$, baseline CES-D score, $t(71.335)=9.541$, $p<.001$, and for the time x group interaction, $t(75.728)=-2.161$, $p=.034$ (Table 3.4). They also showed that for every year increase in age, a decrease of approximately 0.29 on overall fatigue score (SE=0.12) was predicted across all time points. In addition, every one-point increase in baseline CES-D total score was associated with a 1.17-point increase on total fatigue score (SE=0.12), so greater depressive symptomatology was associated with overall greater levels of fatigue across all time points. Finally, after adjusting for age, sex, time since last treatment, baseline depression score, and baseline credibility and expectancy, participants in the BWL condition reported a 1.49-point greater reduction in total fatigue score (SE=.69) after each week of light use than those in the DRL condition, amounting to a 17% greater reduction in the BWL group, than DRL, after 4 weeks. Upon examination of the adjusted means, a pattern appears wherein both groups improved for the first two weeks of light use, but the BWL condition continued to improve into week 4, whereas the DRL saw no further improvement. These improvements are quantified by large within-group effect sizes, while the between group effect size at week 4 was $d=.30$, a small but significant effect. There were

improvements on all MFSI-SF subscale scores over time for both groups, with no time x group interactions.

Secondary Outcomes

***Mood disturbance*.** There was a significant main effect of time (p<.001), with both groups improving on POMS total score from baseline to post-intervention (Table 3.5; Figure 3.3). There were no differences between the groups.

***Symptoms of depression*.** There was a significant main effect of time (p<.001) on CES-D total score, with both groups displaying lower scores over time (Table 3.5; Figure 3.4). It is noteworthy that both groups had a mean score above the clinical cut-off (≥16; Radloff, 1977) at the beginning of the trial and improved to non-clinical levels (>16) at the end of week 4.

***Sleep quality*.** Baseline total scores for both groups were above the cut score for significant sleep disturbance (>5). The PQSI total score was significantly improved over time for both groups (p<.001), though both groups remained above the clinical cut-off of total score greater than 5, distinguishing "poor sleep" (Table 3.5; Figure 3.5).

***Quality of life*.** Exposure to both types of light improved overall quality of life from baseline to post-treatment (p<.001; Table 3.5; Figure 3.6). The FACIT-F also showed improvement over time for both groups, but no differences were observed between groups from baseline to post-treatment. Both groups had lower than normal baseline FACIT-F scores (<30 total score; Cella, 2013) where lower scores indicate more fatigue, but showed clinically meaningful change (4-point increase) and had values considered within normal limits at the end of the study period (>30 total score).

***Credibility and expectancy*.** Results revealed significant main effects of time (p<.001) and group (p=.020) for expectancy (Table 3.5). That is, both groups showed decreases in

expectation over time from baseline levels, and the DRL group reporting a lower overall mean expectancy score (M=13.99, SE=.75) than the BWL group (M=16.09, SE=.77) collapsing across time. There were no significant effects for credibility. Change in MFSI-SF total score from baseline to post-intervention was not correlated with baseline expectancy, r=-.113, p=.325, but was correlated with baseline credibility, r=-.239, p=.034.

Discussion

This is the first blinded, randomized controlled trial to examine the use of light therapy in cancer survivors who met diagnostic criteria for CRF. The results support our hypothesis that a one-month intervention of BWL improves symptoms of fatigue in cancer survivors, relative to an active comparator (DRL). Both groups also showed improvements in mood disturbance, depressive symptoms, sleep quality, and quality of life, reflected by large effect sizes and clinically meaningful change.

The light therapy intervention was found to be acceptable to participants in both groups, as evidenced by the high rates of adherence and the low dropout rate. The short duration and period of use likely account for this, but it may also be explained by design features including blinding, monitoring of device use, and a motivated participant group who were largely self-referred. Light therapy has the potential to fill the treatment gap that exists as a result of under-treatment as it is relatively inexpensive and easy to access which may benefit those who are underserved, and it is easy-to-use with low burden and behavioral demand relative to exercise, cognitive-behavioral therapy, or sleep interventions.

One unexpected result was the pre-post improvements across fatigue and all secondary outcomes in the DRL group, with medium to large within-group effects. The causes for this are

speculative, but may include placebo effects, change in daily routine, self-monitoring, or a real therapeutic effect of the DRL. Regardless, this interesting finding merits follow-up research.

This trial was well-designed and has several strengths. First, the sample was not limited by cancer type, stage, or treatments received, increasing the generalizability of the findings. Second, participants, researchers, and outcome assessors were blind to condition allocation and the randomization schedule removing potential bias from the measurement of outcomes and interactions with participants. Third, participants were required to meet diagnostic criteria for CRF, ensuring the target symptom was present and at a level where meaningful change could be detected. Nevertheless, this also increased the challenge of recruitment. Although the trial was sufficiently powered for the primary outcome, the analyses conducted on the secondary outcomes were underpowered as a result of the small sample size and therefore may not provide a comprehensive summary of the intervention's impact. Additionally, maintenance and long-term effects of the intervention were not measured. Future research would benefit from the inclusion of a longer intervention period and the incorporation of follow-up assessments to examine the durability of treatment effects.

These results are somewhat consistent with those reported by Redd and colleagues (2014). However, the primary outcome used to assess fatigue in that trial (FACIT-F) did not produce similar results in the present study. This may be accounted for by the differences in statistical procedures between trials, but could also be explained by the multidimensional nature of the MFSI-SF and its ability to detect changes across a more diverse range of symptoms when blinding and diagnostic criteria are applied. Regardless, the overall conclusions between trials are similar and complementary in nature; that is, BWL therapy helps to reduce CRF.

Conclusion

Overall, these results in combination with previous trials of light therapy during and after cancer treatment support the use of light therapy for the improvement of fatigue and other psychological symptoms in those affected by cancer, providing another option for those who have not experienced relief with current treatments.

Chapter 4: The impact of light therapy on diurnal salivary cortisol rhythms of cancer survivors with clinical fatigue

Abstract

Background: Altered diurnal patterns of cortisol output have been observed in cancer survivors and have been linked with persistent fatigue. A corrective phase advance via exposure to morning bright light may target underlying circadian dysregulation that modulates the hypothalamic-pituitary-adrenal axis and the diurnal release of cortisol, a mechanism that may serve to maintain symptoms of fatigue post-treatment. This research examines the impact of a light therapy intervention on the diurnal cortisol rhythms of fatigued cancer survivors.

Method: Post-treatment adult cancer survivors who met diagnostic criteria for cancer-related fatigue were recruited. Participants were randomly assigned to receive either bright white light (BWL) or dim red light (DRL) and used the device daily for 30 minutes, for a period of four weeks. Assessments of fatigue, depressive symptoms, and salivary cortisol were collected at baseline and post-intervention. Cortisol was sampled four times per day (waking, noon, 5pm, evening) for three days at baseline and again during the final week. Cortisol output at each sampling time, diurnal slopes, and total cortisol output (AUCg) were calculated at baseline and post-intervention for both groups.

Results: Seventy-seven participants were randomized to receive BWL (n=40) or DRL (n=37). After the one-month intervention, LMM analyses revealed no significant differences in cortisol slope or total cortisol output over time or between groups. Cortisol output at waking trended toward increases for both groups over time (d=-.16, p=.069), an increased at the noon sampling time for both groups (d=-.27, p=.001). A significant interaction (p=.003) at the 5pm sampling time was characterized by significantly lower cortisol output in the BWL condition (d=.35), and an increase in cortisol output in the DRL condition (d=-.17). Changes in fatigue and depression scores were not associated with any of the cortisol outcomes.

Discussion: The light therapy intervention was associated with some measured change in the diurnal release of cortisol, though there may not have been a measurable level of dysregulation to begin with. It is unclear how or whether these changes are associated with changes in fatigue. Additional research examining these associations is warranted.

Keywords: salivary cortisol, diurnal cortisol rhythms, cancer, cancer-related fatigue

Background

The hypothalamic-pituitary-adrenal axis (HPA-axis) is the central regulatory system that controls the release of the stress hormone cortisol (Ryan et al., 2007). The typical diurnal pattern of cortisol secretion is characterized by high levels at the time of waking, peaking within 30 to 45 minutes of waking, and then gradually decreasing over the course of the day with the lowest concentrations observed in the evening (Tsigos & Chrousos, 2002). This endogenous rhythm is directly influenced by the suprachiasmatic nucleus, a cluster of neurons in control of the body's circadian rhythms, that is largely influenced by exposure to light (Monteleone et al., 2011). Dysregulation in this system has been associated with disruptions in sleep-wake patterns, daytime dysfunction, lower daytime activity levels, worse quality of life, and increased levels of fatigue (Payne, 2011).

Previous reports suggest that the HPA-axis and diurnal patterns of cortisol may be disrupted by cancer and its treatments (Ryan et al., 2007), resulting in reduced quality of life (Bower et al., 2005). Cancer-related fatigue (CRF), the most common and distressing symptom reported by cancer survivors (Berger et al., 2015), has been linked to alterations in typical diurnal cortisol rhythms (Bower et al., 2005; Schmidt et al., 2016; Tell et al., 2014). Specifically, flatter diurnal cortisol slopes and a less rapid decline in cortisol in the evening hours were observed in long-term breast cancer survivors with significant fatigue, relative to healthy controls (Bower et al., 2005). Similarly, a recent study of diurnal cortisol in breast cancer patients reported that high levels of evening cortisol and more overall cortisol output was associated with physical fatigue, independent of depressive symptoms (Schmidt et al., 2016). Reports indicate small to moderate effect sizes among current recommended treatment for CRF (e.g., exercise and psychosocial interventions; Cramp & Byron-Daniel, 2009; Kangas, Bovbjerg, & Montgomery, 2008), which

may be a result of a lack of mechanism-driven interventions (Berger et al., 2015). Given that dysregulation in diurnal cortisol rhythmicity has been observed in cancer survivors with fatigue and that correction of this dysregulation has been associated with reduced symptoms of fatigue (Banasik et al., 2011; Schrepf et al., 2013), research investigating treatments that target the disruption in the normal diurnal cortisol rhythm and HPA-axis functioning in cancer survivors may provide insight into the mechanisms of this disorder, and also result in more effective treatments.

Light therapy is a treatment modality that has been used to target circadian rhythm dysregulation that manifests as insomnia (van Maanen et al., 2016) and mood disorders (Golden et al., 2005). Exposure to bright light has also been shown to directly impact cortisol levels in a sample of healthy subjects by significantly reducing plasma cortisol levels, with no change associated with dim light exposure (Jung et al., 2010). Given that early morning exposure to bright white light was found to improve symptoms of fatigue relative to an active comparator in a sample of cancer survivors with persistent fatigue (Redd et al., 2014), it is possible that the mechanism associated with this change can be explained by alterations to diurnal cortisol patterns and output. The proposed mechanism of action is that early morning exposure to bright light provides a corrective phase advance to target dysregulation of the circadian rhythm (Monteleone et al., 2011), manifested as disrupted diurnal cortisol output. This phase advance of the circadian system allows for a realignment and harmonization of underlying rhythms, including those of the HPA-axis and the individuals' sleep-wake cycle (Monteleone et al., 2011), to subsequently reduce behavioral and psychological symptoms.

The aim of the present analysis was to examine cortisol rhythms in a sample of cancer survivors who met diagnostic criteria for fatigue and investigate whether their rhythms could be

characterized by more dysregulated patterns of output (i.e., flatter slopes). Furthermore, we wanted to determine whether light therapy could impact patterns of diurnal cortisol output, and examine whether changes in fatigue were associated with changes in cortisol output. We hypothesized that exposure to early morning bright white light would result in steeper diurnal cortisol slopes following the 4-week intervention. Furthermore, we hypothesized that treatment with BWL would result in lower evening cortisol values at post-intervention and lower overall total cortisol output.

Method

This research is a secondary analysis of a blinded randomized controlled trial of light therapy for CRF in cancer survivors. The complete protocol for this trial is outlined in greater detail elsewhere (Johnson et al., 2016). All participants were required to provide informed written consent before engaging in any research related activity. Ethics approval for this study was obtained from the Conjoint Health Research Ethics Board of the University of Calgary.

Participants

Participants were recruited from Calgary, Alberta, Canada and surrounding areas. To control for seasonal changes in hours of daylight, participants were recruited during the fall and winter months only. Adults with non-metastatic disease and treatment completion at least three months prior to enrollment were eligible. Participants were required to meet the diagnostic criteria for CRF outlined in the International Classification of Diseases – 10th Revision (ICD-10; Cella et al., 1998). Individuals receiving ongoing hormonal or maintenance treatments and/or using psychotropic medications were eligible provided their dose had remained stable for the previous 6 weeks. Individuals were ineligible if they screened positive for the presence of another sleep or psychiatric condition (e.g., sleep apnea, restless legs syndrome, bipolar

disorder), if they had been diagnosed with an ongoing medical condition that could influence fatigue levels (e.g., anemia, autoimmune disorder, heart failure), the presence of an eye disease, recent eye surgery, or the use of photosensitizing medications, or if their employment required shift work. For this analysis, participants who were currently taking corticosteroids or immune modulating medications were also excluded.

Procedure

At baseline, participants provided demographic and medical history information, and completed a questionnaire package that included the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and the Center for Epidemiological Studies – Depression Scale (CES-D). During the baseline week, participants were provided with a salivary collection kit to collect samples at home and returned the samples to the researcher at the end of the week. Following the baseline period, participants were randomized to receive one of two types of light devices to take home, bright white light (BWL) or dim red light (DRL), and were asked to use the device daily for 30 minutes, within 30 minutes of waking for a period of 4 weeks (28 days). During the final week of light use (week 4), participants were provided with a second salivary collection kit and returned it to the researcher on the final day of the study. At the end of the study, participants returned the light device and completed the self-report questionnaires again.

Intervention

The light therapy device used in this study was the Litebook Elite treatment device (The Litebook Company Ltd., Medicine Hat, AB). The Litebook is a small (5in. x 5in. x 1in.), lightweight (11 oz.) device that is designed to be placed on a table 12-24 inches from the user's face and offset at a 45-degree angle from the midline of the visual field. The Litebook in the BWL treatment condition contained 25 white light-emitting diode (LED) lights that emitted

white light at 1250 lx and with a distribution of energy concentrated in the shorter wavelengths of visible light (peak between 464-466 nanometers). An identical-appearing Litebook device used in the DRL condition contained 25 red LEDs that emitted red light at <400 lx with a distribution of energy concentrated in the longer wavelengths of visible light (peak between 632-633 nanometers). The devices were programmed to turn off after 30 minutes of continuous use. Each Litebook was modified to include an integrated logger device (HOBO State Data Logger, Onset Computer Corporation, Bourne, MA) that recorded the date and duration that the light device was on. Participants were also required to record their daily use of the device on a tracking sheet provided to them upon receiving the device.

Measures

Fatigue. The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF; Stein et al., 2004) is a 30-item comprehensive measure designed to assess the physical and psychological aspects of fatigue.

Symptoms of depression. The Center for Epidemiological Studies – Depression scale (CES-D; Radloff, 1977) is a 20-item measure developed to identify current depressive symptomatology related to major or clinical depression in adults and adolescents. A score ≥16 is indicative of clinical levels of depressive symptomatology (Radloff, 1977).

Salivary cortisol measurement and processing. Participants collected saliva samples using salivette collection vials (SARSTEDT AG & Co., Germany) at four time points (waking, noon, 5pm, evening) over a period of three consecutive days at baseline and again during the final week of light use, as close to the end of the week as possible. Participants were asked to collect the samples on weekdays only and to avoid eating, drinking, or brushing teeth at least 30 minutes prior to collection. Color coded, time stamped tubes and tracking sheets were provided

to increase compliance. Participants were asked to track the time that each sample was actually completed and store the sample in the fridge or freezer once complete.

All salivettes were stored in a freezer at -80C until they were shipped for processing at an outside laboratory (TUD Biopsychology Laboratory, Dresden, Germany). The cortisol values were determined using a commercial chemiluminescence immunoassay (CLIA, IBL International, Hamburg, Germany) conducted according to manufacturer protocols. The samples were processed in single (i.e., not in duplicate). The intra-assay coefficients of variation for this process were expected to be less than 8%. Cortisol concentrations were calculated in nmol/L.

Data Reduction Strategy

Prior to analysis, data were screened for sampling time outliers. As outlined in Schrepf et al. (2013), sampling time ranges were determined to allow the maximum number of participants to be included, but also to maintain homogeneity within each sample time. The following sampling ranges were specified: 0400 to 0930 for waking sample, 1100 to 1330 for noon sample, 1600 to 1830 for 5pm sample, and 2030 to 0100 for evening sample. Cortisol values that fell outside of these ranges were removed as well as cortisol values that were greater than 4 standard deviations above the mean cortisol level of each sampling time. Upon removal of all outliers, mean cortisol values were calculated for each time point. To adjust for the non-normal distributions of the raw cortisol values, all values were transformed using a natural log transformation and the transformed values were used for all analyses.

Statistical Analyses

To investigate changes in fatigue (MFSI-SF total scores) and depressive symptoms (CES-D total scores), linear mixed models (LMMs; SPSS MIXED procedure), adjusting for baseline values and with fixed slopes and intercepts were used to determine whether time, group, or time

x group interaction effects were present. The covariates of age and sex were included in each model to account for age-related changes in fatigue (Cella, Lai, Chang, Peterman, & Slavin, 2002) and also sex differences in depressive symptoms (Piccinelli & Wilkinson, 2000). The number of months since last treatment was also included as a covariate to account for differences that may exist between those who have recently completed treatment and those who may be several years post-treatment (Wang et al., 2014). The change score for both outcomes was calculated by subtracting raw post-intervention total scores by raw baseline total scores.

To investigate changes in diurnal cortisol rhythms, three separate analyses were conducted. First, the slope of diurnal changes in cortisol levels were calculated by regressing cortisol values on time. Smaller, more negative slope values represent a larger decline in cortisol levels over the course of the day, while larger, less negative slope values (closer to zero) reflect flatter diurnal rhythms. A LMM with fixed slopes and intercepts was used to determine whether group (BWL or DRL) was a significant predictor of cortisol slope and whether cortisol slope changed from baseline to post-intervention. A follow-up LMM analysis including change in MFSI-SF total score and change in CES-D total score into the models as covariates was conducted to determine whether change on these outcomes predicted change in cortisol slope. A second LMM analysis of cortisol output at each sampling time was also conducted to examine change over time at each time point and differences between groups. Finally, overall diurnal cortisol secretion was calculated as the area under the curve with respect to the ground (AUCg) based on the trapezoidal formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). A LMM analysis was conducted to estimate change in total cortisol output over time and between groups.

The covariates of age, BMI, cancer type, and time since last treatment were included in each model as they have been previously identified factors that can affect circulating levels of cortisol (Abercrombie et al., 2004; Bower et al., 2005; Deuschle et al., 1997). The covariance structure was set to autoregressive (AR1) and all data analyses were conducted using SPSS version 24.0.

Results

Overall, data from 77 participants were eligible for inclusion in the analysis. Of the 81 recruited for the full trial, three were excluded for current corticosteroid use, and one was excluded for current use of Herceptin (an immune modulating medication; Figure 4.1). Participant characteristics are outlined in Table 4.1. A total of 2,013 (93.7%) cortisol samples were available for analysis. After screening for outliers, a total of 19 (1%) of samples were removed and another 109 (5.4%) were removed for collection outside of the specified sampling time windows. Adherence to the light therapy intervention was excellent, with participants reporting 26.7 (*SD*=2.2) days of light use and an average of 30.1 (*SD*=0.6) minutes per day.

Analyses revealed a significant time effect for both MFSI-SF total score and CES-D total score, indicating that both the BWL and DRL groups improved on symptoms of fatigue and depression after the intervention (Table 4.2). There were no significant differences between groups, and a trend toward a time x group interaction for MFSI-SF total score was observed (p=.055), with the BWL trending to greater improvements than the DRL group (for a more comprehensive summary of the impact of the intervention on MFSI-SF total and subscale scores, as well as CES-D total scores, see Chapter 3).

Linear mixed model analysis of cortisol slopes revealed no significant effects of time (p=.188) or group (p=.797), and no significant time x group interaction (p=.929; Table 4.2) in

this subsample of participants. Therefore, the cortisol slopes were found to be no different from baseline to post-intervention, and did not differ significantly between groups. Neither change in MFSI-SF nor change in CES-D were associated with cortisol slopes.

Analyses comparing change in cortisol output at each time point revealed a trend towards increased waking cortisol over time for both groups, $F(1, 72.14)=3.40$, $p=.069$, $d=-.16$ (Figure 4.2). There was also a significant increase in output observed in noon samples from baseline to post-intervention for both groups, $F(1, 70.91)=11.99$, $p=.001$, $d=-.27$. A significant time x group interaction was observed for the 5pm sample, $F(1, 70.82)=9.69$, $p=.003$, with participants in the BWL condition showing lower cortisol concentrations from baseline to post-treatment ($d=.35$), relative to the DRL group that exhibited a slight increase over the same period ($d=-.17$; Figure 4.2). Finally, there were no observed time ($p=.731$), group ($p=.115$), or time x group effects ($p=.967$) for the evening cortisol sample. When change in MFSI-SF score and change in CES-D score were added to the models, they were not significant predictors of cortisol output.

The LMM analysis of AUCg revealed no significant time, $F(1, 66.85)=2.93$, $p=.092$, or group effects, $F(1, 68.94)=.705$, $p=.404$, and no time x group interaction, $F(1, 66.76)=.120$, $p=.730$. That is, there were no significant differences in total cortisol output between groups or when comparing baseline and post-intervention values. When change in MFSI-SF total score and change in CES-D total score were included in the model, they were not associated with AUCg.

Discussion

This is the first trial to investigate the impact of a light therapy intervention on diurnal cortisol rhythms among cancer survivors with clinical levels of fatigue. Light therapy was not associated with change in diurnal cortisol slope or total cortisol output from baseline to post-intervention, and these measures did not differ between light therapy conditions. Furthermore,

change in fatigue and depressive symptoms over the intervention were not associated with change in cortisol slope or total cortisol output. Examination of cortisol output at each sampling point revealed increases in waking and noon cortisol after the light therapy intervention for both conditions, though the waking increase was trending towards a significant time x group interaction. There was also a significant decrease in the 5pm output for participants in the BWL group and an increase at the same sampling time for those in the DRL group. No differences in evening samples were observed either over time or between groups.

It was anticipated that light therapy would be associated with an increase in diurnal slope and lower overall total cortisol output (AUCg) in the BWL group, but results did not support these hypotheses. Although two previous studies investigating cortisol dysregulation in breast cancer reported that flatter slopes were associated with greater fatigue (Bower et al., 2005; Tell et al., 2014), other research has not supported this association (Schmidt et al., 2016). Additionally, research in breast cancer patients and survivors (Bower et al., 2005; Schmidt et al., 2016) and ovarian cancer patients (Schrepf et al., 2013), has reported consistent associations between nocturnal cortisol levels and fatigue, namely, greater symptoms of fatigue associated with higher evening cortisol levels. Although the same improvements were not detected in this study, the decrease in late afternoon cortisol output (5pm sample) in the BWL group after the intervention is compelling as it indicates that changes were occurring in the direction that supports steeper slopes.

Interestingly, another trial investigating the impact of a yoga intervention on symptoms of fatigue and diurnal cortisol rhythms among cancer survivors, reported a similar pattern with 5pm salivary cortisol significantly decreasing after a yoga intervention (Banasik et al., 2011). Perhaps this decrease in late afternoon cortisol levels precedes changes in nocturnal cortisol, and

with a longer intervention period, could carry over into the evening period. The inconsistencies observed across the mentioned studies may be accounted for by differences in the sample characteristics, fatigue measures, statistical analyses, data reduction techniques, and cortisol sampling methods. It may also be the case that the sample in the current study did not have dysregulated cortisol rhythms at the outset. Comparison of raw values and untransformed slopes indicate that this sample may display cortisol levels that are similar to those of controls (Abercrombie et al., 2004), but it is difficult to make comparisons of cortisol values across studies. Regardless, further research examining the impact of light therapy on the diurnal release of cortisol during and after cancer treatment is warranted.

The following limitations deserve mention. First, the full protocol for this trial was relatively burdensome and required participants to provide four saliva samples for three consecutive days at both the beginning and end of the trial. Although we attempted to improve adherence to the protocol by color coding and time-stamping all salivettes, and providing a detailed tracking sheet for participants to record the time of the sample, it is possible that some samples were collected on the wrong day or at a time different than what was listed. We attempted to alleviate this problem by specifying acceptable sampling ranges and removing values that were collected outside of this range in the data reduction procedure.

Second, it is possible that several variables known to impact diurnal cortisol rhythms but not taken into account in this analysis may factor into the results observed. For example, disease characteristics (e.g., tumor stage or disease severity), some health conditions (e.g., mood disorders), and use of specific medications (e.g., use of NSAIDs), have been shown to impact circulating cortisol (Gerber et al., 2011; Schmidt et al., 2015; Weinrib et al., 2010). It is possible

that undiagnosed health conditions or medications not accounted for could unintentionally impact our results.

Third, this analysis did not incorporate day-to-day variations in sleep and napping behaviors. A recent study of cortisol rhythms in women with breast cancer (Tell et al., 2014) reported that prior day naps, greater sleep disturbance, and longer sleep latency were all associated with patterns of cortisol secretion the following day. Therefore, future research should seek to measure and incorporate sleep and napping behaviors into analyses of diurnal cortisol to further investigate these associations. Finally, it is possible that changes in diurnal cortisol rhythms may require a longer intervention period to be detected. Given that the duration of this intervention was only 28 days and that cortisol was collected up to 6 days before the end of the intervention period, it is possible that a longer duration of light use is required to observe proposed changes to the underlying endogenous rhythms. For example, the yoga intervention described above which found changes in cortisol levels had an intervention period of 8 weeks (Banasik et al., 2011). Research investigating the long-term outcomes of light therapy on CRF and its underlying mechanisms are required to achieve a thorough understanding of its impact.

Conclusion

A one-month light therapy intervention for CRF appears to have some impact on diurnal cortisol rhythms in cancer survivors with persistent fatigue, though more global measures of rhythmicity, such as slope and AUCg were not impacted. Further, there were no observed associations among diurnal salivary cortisol output and changes in reported fatigue. Light therapy may have the potential to impact CRF through circadian rhythm entrainment, but the sample in this study likely did not display enough dysregulation for the intervention's influence

to be fully captured. Further evaluation of this hypothesis is required in a CRF sample that displays a greater degree of dysregulation in the diurnal cortisol rhythm.

Chapter 5: Discussion

Discussion

This document has outlined the background of the impact of cancer and CRF on survivors' quality of life, the treatments available to manage CRF, the potential underlying mechanisms that serve to maintain symptoms of fatigue in cancer survivors, and the rationale for a trial of light therapy to impact fatigue by targeting these underlying mechanisms. The protocol for a blinded randomized controlled trial to investigate the impact of a light therapy intervention on symptoms of fatigue in cancer survivors was then presented as a manuscript, recently published in *Contemporary Clinical Trials*. Next, the results of the completed trial were presented and included analyses that investigated the primary outcome of fatigue and secondary outcomes of mood disturbance, depressive symptoms, sleep quality, and quality of life, along with adherence to the intervention. Following this, a third manuscript describing the impact of the light therapy intervention on diurnal salivary cortisol rhythms was presented. Finally, the following section will provide a summary of all the results, compare and extend them to related research, discuss the strengths and limitations of the trial, and also provide suggestions for future research.

Summary of Results

This was the first blinded randomized controlled trial to investigate the impact of light therapy on symptoms of fatigue, mood disturbance, sleep quality, and quality of life in cancer survivors with post-treatment CRF. It is also the first to investigate the impact of this intervention on the diurnal salivary cortisol rhythms. The primary hypothesis was that early morning exposure to BWL would be associated with greater improvements on symptoms of fatigue, relative to those in the DRL condition. Secondary hypotheses posited that BWL treatment would also be associated with greater improvements in mood disturbance, depressive

symptoms, sleep quality, and quality of life when compared to DRL treatment. Finally, it was hypothesized that BWL would be associated with a steeper cortisol slope, lower total cortisol output, and lower evening cortisol levels after the one-month intervention compared to DRL, and that steeper diurnal cortisol rhythms pre-to-post intervention would be associated with improved fatigue.

The primary results confirmed our hypothesis, in that early morning exposure to BWL resulted in greater improvements in symptoms of fatigue relative to DRL treatment after a one-month intervention period, adjusting for age, sex, months since last cancer treatment, baseline depression score, and credibility/expectancy scores. More specifically, both groups reported improvements in symptoms of fatigue up to the second week of light use. After that, the BWL condition continued to report decreases in fatigue until the conclusion of the intervention, while the DRL group showed no further improvement after the second week, though the treatment effects were maintained until the final week. Increasing age was associated with lower fatigue, and higher depression scores were associated with more fatigue. Although the between-groups effect size of fatigue scores was relatively small at the final week (d=.30), the within-group effect sizes were large (d range 0.93 to 1.20), indicating that compared to baseline, participants in the BWL group showed substantial improvements. This magnitude of improvement over time in the BWL condition is promising and provides support for the use of light therapy for improving symptoms of fatigue during the post-treatment period.

Analyses investigating change on the subscales of the MFSI-SF (i.e., general, physical, mental, emotional, and vigor) were conducted to determine whether light therapy had any differential effects on specific facets of fatigue measured by the MFSI-SF. Given that some patients report, for example, more symptoms of physical versus mental fatigue (de Raaf et al.,

2012), this analysis would provide insight into the potential mechanisms of light therapy by revealing its impact on specific symptoms. Indeed, both groups improved over time on all of the fatigue subscales. There was also a trend towards a significant interaction on the subscale of physical fatigue (p=.063), wherein the BWL condition had greater overall improvements on the physical dimension of fatigue than those in the DRL group. Physical fatigue was captured by items that inquired about feelings of heaviness and weakness in the arms and legs and in the body in general. This finding may have important implications for the role of light therapy as an introductory treatment option to improve physical symptoms prior to engaging in more intensive therapies, such as exercise interventions.

The analyses to determine the impact of light therapy on the secondary outcomes of mood disturbance, depressive symptoms, sleep quality, and quality of life did not support our hypothesis that greater improvements would be observed in the BWL condition relative to the DRL condition. That is, participants in both groups reported improved mood disturbance, reductions in depression symptoms, improvements in sleep quality, and improved quality of life. Although the improvements in the DRL condition were not expected or directly hypothesized, they are not surprising and have a number of potential explanations. First, it is possible that the red lights may provide enough of a therapeutic dose of light to produce the benefits observed on these outcomes. This is plausible given that even dim light has been shown to have an effect on the circadian system (Brainard et al., 1988). Furthermore, it is noteworthy that although the DRL produced light at an intensity (<400lx) and at a wavelength (~650 nm) that the circadian system is not as sensitive to (Thapan, Arendt, & Skene, 2001), the intensity of the lights used in this trial were greater than those used in previous trials of light therapy specific to cancer patients and

survivors (<50lx; Ancoli-Israel et al., 2012; Redd et al., 2014), which failed to find any therapeutic effect of the DRL condition.

Second, the change in daily routine, monitoring of symptoms, and potential placebo effects may have played a role in improvements. Anecdotally, several participants had mentioned that the use of the device allowed them to take extra time in the morning and enjoy 30 minutes to themselves. It is possible that factors associated with improved self-care and greater awareness of symptoms were associated with change in both groups. A compelling enquiry into the placebo response in blinded randomized trials of medications for fatigue in patients with advanced cancer reported that up to 56% of patients reported a placebo response to treatment (De La Cruz, Hui, Parsons, & Bruera, 2010). In that report, greater placebo responses were associated with worse physical well-being and overall worse quality of life. Given the severity of symptoms in this sample, it is possible that the placebo responses account for a portion of the improvements observed over time in both groups.

Third, the analyses to compare change over time and differences between groups may have been underpowered to detect interaction effects. The study was initially powered on the primary outcome of fatigue, but a secondary power analysis was conducted to ensure interaction effects could be detected in secondary outcomes. In order to detect these effects, we would have required 124 people in the trial. However, after a challenging recruitment period, the final sample size recruited was not large enough to meet the power requirements for secondary outcomes. Therefore, it is possible that these effects may have been present but were too small to detect with the current sample size, hence suffering from Type II error. Regardless, it is encouraging that change over time on all of the outcomes were present and warrants further

investigation into the impact of light therapy on psychological and psychosocial outcomes in cancer survivors in general.

Most of the full RCT sample (77 of 81) were included in an analysis of diurnal cortisol rhythms to examine whether the light therapy intervention had an impact on circulating levels of cortisol and patterns of their diurnal output. There were no significant differences detected over time or across groups for diurnal cortisol slopes after the light therapy intervention. That is, the pattern of release of cortisol over the course of the day was not significantly altered by the intervention as measured by the slope of cortisol output. There were however differences in cortisol output either over time or between groups at specific sampling times throughout the day. Namely, there was a trend towards increased morning cortisol output for both groups and a significant increase in noon cortisol output for both groups during the final week of the study. There was a significant decrease in cortisol output observed at the 5pm sampling time for the BWL group, and an increase at the same time for the DRL condition. Furthermore, there were no differences between groups or over time in evening cortisol output and no differences observed over time or between groups in total cortisol output, as measured by area under the curve.

Although these results did not support our hypotheses, they provide interesting insights into how light therapy may work to improve the diurnal expression of cortisol in fatigued cancer survivors. It is possible that the one-month intervention period was not long enough to produce the expected change in cortisol output. However, with the observed increase in morning and noon cortisol output and decrease in late afternoon output, it is conceivable that these changes may have been more pronounced with an extended intervention period, potentially producing the hypothesized pattern of results. Therefore, longer exposure to the intervention and a longer period of cortisol sampling should be examined to investigate these findings further and to gain a

better understanding of how light may impact the circadian variations in cortisol rhythms of fatigued cancer survivors. It may also be the case that the sample in the current study did not have dysregulated cortisol rhythms at the outset. The slopes analysis was conducted with log transformed cortisol values, making it difficult to compare with available norms. Upon examination of the raw values against sampling norms and a recalculation of slope using these values, it is apparent that participants displayed cortisol values that may be consistent with those of a normal sample (Abercrombie et al., 2004). In order to gain a better understanding of the potential impact of light therapy on diurnal cortisol rhythms in CRF, future research should ensure baseline dysregulation in the rhythm is present or consider statistical comparisons among those with greater dysregulation.

Credibility and expectancy were measured both before and after the intervention to assess how participants' attitudes towards the light therapy's credibility and expectancy to improve their symptoms of fatigue impacted the outcomes – a proxy to measure the potential placebo effect of favorable change associated with expectancy. Further, we wanted to survey how participant perception of light therapy changed after the intervention and used these measures as an auxiliary measure of acceptability. To reiterate, the expectancy factor focused on affectively-based beliefs about the light device. That is, how much improvement in fatigue symptoms the participant thinks will occur, how much they really feel that the therapy will help them reduce their fatigue symptoms, and how much improvement in fatigue symptoms they feel will occur by the end of the treatment period. The credibility aspect of the measure focused on cognitively-based beliefs about the intervention. That is, how logical the treatment offered seems, how successful the patient thinks this treatment will be at reducing symptoms of fatigue, and how confident the patient would be in recommending the treatment to a friend with similar problems.

The tense of the wording was changed at the post-intervention assessment to capture attitudes towards the intervention once they had completed the protocol.

Overall, participants in both groups reported a decrease in expectancy scores over time, and the DRL group reported a lower overall mean score on expectancy than those in the BWL condition. That is, both groups did not feel that their symptoms had been reduced to the degree they had anticipated at the start of the trial, with participants in the DRL condition emphasizing this by reporting lower overall scores at both times, seeming to indicate some disappointment with their results. Interestingly, there were no differences in credibility relative to baseline, indicating that the participants in both conditions were confident in the intervention and still believed that it was credible and logical even after their expectations had decreased. It is possible that participants' expectations were high to begin with but lowered after only small changes in fatigue symptoms were felt at the end of the study, yet they still believed that further improvements may have been possible with a longer intervention period, or perhaps for people other than themselves. Taken together, it is likely that participants found the intervention to acceptable in that it was logical and had the potential to help, even though their expectations of treatment effect were not met at the end of the four weeks.

To examine adherence to the treatment, the self-report and objective measures of light use were summarized. In previous trials of light therapy specific to cancer, a dropout rate of 33% was observed in a sample of women undergoing chemotherapy for breast cancer (Ancoli-Israel et al., 2012; Jeste et al., 2013) and attrition was not reported in a more recent RCT of a light therapy intervention on symptoms of fatigue in a heterogeneous sample of cancer survivors (Redd et al., 2014). Given that there is no precedent for standard attrition in a light therapy intervention study, the present trial was powered on an expected attrition rate of 20%. Upon

conclusion of the trial, only two participants had dropped out (2.5%), both for reasons external to the trial. Participants in both groups used the devices for just under the recommended number of days (26 of 28 days), used the devices within 30 minutes of waking, and for the recommended 30 minutes per day. There were no differences between the groups on any of these measures, and there were no differences between the self-report and objective measures of use. These rates of adherence are much higher than those reported in a trial of light therapy for seasonal depression (59%; Michalak, Murray, Wilkinson, Dowrick, & Lam, 2007) and among those of cognitive behavioral therapy CRF (32-52%; Matthews et al., 2012) and exercise (32%; Shang et al., 2012).

The high adherence rates may be due to a number of factors. First, the protocol was relatively manageable, with light use suggested for only 30 minutes per day in the morning, and for a short period of only 4 weeks. It is unclear whether similar rates of adherence would be observed during a longer intervention period or if a longer exposure period (i.e., one hour) were required. Second, several design features of the study, including blinding of conditions and monitoring of device use, may have motivated participants to adhere. Finally, the participants recruited for this study were required to meet clinical diagnostic criteria for CRF, meaning that symptom severity was at the highest levels. Additionally, a majority of the participants were years into the post-treatment period and still experiencing significant, clinically meaningful levels of fatigue, so they were highly motivated to find relief. These two factors in combination likely had a large impact on adherence. The high expectancy and credibility ratings of this novel treatment at the outset support this notion.

Links with Previous Research

There are a limited number of research studies investigating the impact of light therapy on fatigue related to cancer (Ancoli-Israel et al., 2012; Jeste et al., 2013; Redd et al., 2014). The

results of this trial are consistent in some respects with those previously reported. For example, Redd and colleagues (2014) reported improvements in symptoms of fatigue (d=0.98) in a sample of 36 cancer survivors with clinical levels of fatigue (FACIT-F <30 at trial start) after exposure to a 4-week early morning BWL intervention, when compared to DRL. The primary outcome used to assess fatigue in that trial (FACIT-F), when used in our study, did not result in the same significant time x group interaction, but instead improvements over time in both groups. As the same devices were used (Litebook), it is more likely that these differences may be accounted for by differences in statistical techniques to examine change on the FACIT-F between trials, but could also be explained by the multidimensional nature of the MFSI-SF and its ability to detect changes across a more diverse range of symptoms when blinding and diagnostic criteria are applied. It is noteworthy that participants in that study were not blind to condition and were made aware of the differences between the light devices prior to beginning the treatment. Regardless, the overall conclusions between trials are similar and complementary in nature, and together support the recommendation of light therapy for CRF in cancer survivors.

Only a select number of studies have examined diurnal cortisol rhythms in cancer patients and survivors (Bower et al., 2005; Schmidt et al., 2016; Schrepf et al., 2013; Tell et al., 2014), and only one has examined changes in cortisol rhythms before and after an intervention in cancer survivors (Banasik et al., 2011). These studies have revealed links between flattened cortisol slopes and increased symptoms of fatigue (Bower et al., 2005; Tell et al., 2014), and that steeper cortisol slope has been associated with less fatigue (Bower et al., 2005; Schrepf et al., 2013). Furthermore, higher evening cortisol levels were associated with increased levels of fatigue (Schmidt et al., 2016) and reductions in evening cortisol levels were associated with decreased fatigue (Schrepf et al., 2013). The results of this trial did not support the hypothesis

that change in slope (i.e., steeper slopes) would occur after the light therapy intervention, and that change in slope would be associated with change in fatigue. Although our hypothesis was not supported, other research has reported results consistent with ours, wherein diurnal slope was not consistently associated with fatigue (Schmidt et al., 2016) and change in slope was not observed after an intervention to target fatigue (Banasik et al., 2011).

Interestingly, although we did not observe any difference in evening cortisol output over time or across groups as hypothesized, the decreased cortisol output in the late afternoon sample of the BWL group is consistent with results observed at the same time point in a group of breast cancer survivors exposed to a yoga intervention to target fatigue (Banasik et al., 2011). It is possible that this late afternoon decrease in cortisol output could precede decreases that occur later on into the evening hours, and that with a longer intervention or sampling period these changes may have been detected. The differences in reported results across studies may be a result of a number of factors including patient groups (e.g., breast cancer patients only versus more heterogeneous samples), data reduction strategies (e.g., the use of mean cortisol values versus inter- and intra-individual variations), fatigue measures, and sampling methodology and processing; therefore, further research is required to gain a better understanding of the factors that can modulate change in cortisol rhythms.

Benefits and Future Directions of Light Therapy

Given the high adherence rates and high credibility ratings observed in this study, and the relatively low cost and ease of administration of the therapy, light therapy could fill the current treatment gap that exists for CRF. First, the improvements observed in this study resulted in relatively large effect sizes from baseline to post-intervention on the fatigue and psychological outcomes. Although these improvements may not have been as large as participants had initially

expected, this intervention may fill a unique position as a "booster" intervention to get people to a point, either with regards to energy level, mood, motivation, or self-efficacy to manage symptoms of fatigue, where they are prepared to "step-up" to a more intense and efficacious treatment, such as exercise. This may be especially true given the finding that physical fatigue was improved to a somewhat greater degree among participants in the BWL condition, relative to those in the DRL condition. The implementation of light therapy as a treatment starting point is conceivable given that light therapy is an easy-to-use and much more approachable option for people who may not have found relief with other treatment options, or who have yet to attempt any of the available options as they may seem too difficult or behaviorally demanding.

Second, it is possible that through the proposed mechanisms described earlier, light therapy could be added as a supplement to other treatments and provide additional or more rapid relief of symptoms than stand-alone therapies. Research examining the combination of light therapy with, for example, moderate intensity exercise would provide information regarding its potential as an adjuvant therapy. Third, given that light therapy has a low risk of negative side effects and does not produce residual effects or result in tolerance as observed with many medications, it is a safe and natural option that may be preferred over long-term medication use. Fourth, light therapy is relatively inexpensive and easy to purchase, potentially allowing individuals who are low-income or residing in rural locations to access treatment without the barriers that exist for other treatments.

In the systematic review by van Maanen (2016), light intensity was found to be a significant moderator of effect in studies of light therapy for sleep problems. As light intensity was not found to be important for other types of sleep problems, what may be more important is the wavelength. In this trial, we compared low intensity, long wavelength light to high intensity,

short wavelength light, and found differences on some of outcomes. Given that this information is often not reported in studies of light therapy, it is unclear what dose (intensity and wavelength) are ideal for treating fatigue. Future research may seek to compare differing intensities, wavelengths, durations, and treatment schedules to determine optimal dosage and scheduling.

On a similar note, the use of light boxes that are larger in size have been recommended over those that are smaller as they provide a large field of light to cover the visual field to ensure maximal light exposure (Eastman, 2011). However, the devices used in this trial were small, lightweight, battery operated, and portable. Although the field of light produced by the Litebook is small compared to larger, stationary devices, the light produced is direct and participants can recognize when they are outside of the device's field of range. Traditional light devices typically require an individual to remain seated for an extended period of time, preventing them from undertaking other tasks simultaneously. Given that the protocol for this trial required participants to use the device within 30 minutes of waking, typically when they were preparing to begin their day, these devices allowed them to switch tasks or move locations with little effort, something not possible with the larger, traditional devices. The size and portability of devices in this study also likely influenced adherence, as participants were not required to remain stationary during their morning routine. These factors help improve the generalizability of these findings as several of the participants in this study were able to incorporate the use of the device in their everyday, sometimes very busy, morning routine with no measurable impact to adherence.

Strengths

One of the key strengths of this trial is the design. First, the use of the randomized design ensured participant preference did not differentially influence treatment effects, especially given that light therapy has become more popular and more familiar among the general population.

The use of the block randomized design also ensured that had the allocation schedule been accidentally revealed at any point, the researcher would not have knowledge of the previous or subsequent participant assignment. The use of an active comparator provided a unique exploration into the role of self-monitoring, placebo effects, and change in routine. Had this trial used a standard control or waitlist condition as the comparator, it is unlikely that the impact of these extraneous variables would be apparent and the true effects of the light therapy unknown. Future trials investigating light therapy for any outcome should implement the use of an appropriate active comparator, but may also consider implementing a third usual care condition for reference. Finally, this trial was designed with multiple levels of blinding, including on the level of the participant, researcher, outcome assessor, and data entry assistant. The use of blinding removed potential bias from the reporting of symptoms and outcome measures, researcher-participant interactions, and data entry. Overall, the use of these design features provides an important framework interpreting the results.

The sample recruited for this study was not limited by sex, age, cancer type, stage, or cancer treatments received. Although the overall characteristics of the sample were relatively homogeneous (i.e., white, educated women with breast cancer), this afforded us with the ability to recruit a large enough sample to detect a signal on the primary outcome of fatigue. It is also noteworthy that this was the first trial to implement the requirement of clinical levels of fatigue, as measured by the ICD-10 structured interview for CRF. The inclusion of this criteria ensured that the target symptom was present and at a level where meaningful change could be detected. Although the trade-off with the added challenge to recruitment was not ideal, this strengthens the study's conclusions.

The location that this study took place afforded us with the unique challenge of accounting for extreme changes in the number of daylight hours that occurs between seasons. On the summer solstice (June 21) there are just over 16.5 hours of daylight in Calgary, AB, compared to only 7.9 hours on the winter solstice (December 21) – amounting to an 8.6-hour difference. Though it is unclear whether seasonality plays a role in symptoms of CRF, the role of seasonal changes in daylight on depressive symptoms has been well documented (Harmatz et al., 2000). Given the links between fatigue and depression and the potential role for seasonality to impact our outcomes of interest, it was important to account for these associations. In order to do this, we restricted recruitment to the fall and winter months to control for seasonal changes in daylight. That is, participants were only recruited between the months of October and March (3 months pre- and post-solstice), allowing us to recruit participants during both increases and decreases in daylight, but also avoiding periods when daylight hours are at a peak. Again, the trade-off with the added challenge to recruitment was not ideal, but we believe that this was an important variable to account for.

Finally, one of the most important strengths of this research is the focus on examining a number of potential underlying mechanisms that may be associated with CRF and that may also be impacted by light therapy. As previously discussed, the mechanisms of fatigue are not well-understood and a gap exists in the literature where mechanism-driven interventions that target underlying dysregulation are not being tested. This trial was designed to quantify this dysregulation and determine whether exposure to light can produce change on outcomes such as depressive symptoms, sleep quality, and diurnal cortisol rhythms, among others, that may serve to modulate symptoms of fatigue.

Limitations and Challenges

Although this trial was well designed, there are several key limitations to address. First, there was no follow-up period after completion of the four-week light therapy treatment, so we do not know whether these changes can be maintained. The primary goal of this study was to determine whether light therapy could produce change on the primary outcome of fatigue relative to an active comparator; as such, it was not our intention to examine the long-term impact of this intervention. As a result, we cannot speculate as to whether these improvements can be maintained beyond the treatment period. Redd and colleagues (2014) included a 3-week post-intervention assessment that revealed maintenance of effects in the BWL condition. Future research should look to extend the treatment period beyond four-weeks, and monitor change at 3- and 6-month post-intervention to determine whether treatment effects are enduring, or whether recurring or long-term treatment schedules should be implemented.

Recruitment of this sample posed several challenges. First, it was difficult to spread the message of the existence of the trial and reach those who may be struggling with fatigue. Initial recruitment methods, including advertising in the cancer center and at local events, were not very fruitful as the group we were targeting did not regularly attend those venues. Fortunately, we addressed this relatively early on and found alternative recruitment methods, including media releases and the use of mail outs through the Alberta Cancer Registry, to reach participants in their homes. Second, the strict inclusion and exclusion criteria provided a further challenge to recruitment as 41% of people screened did not meet criteria for inclusion. The most common reasons for this were barriers to transportation/distance, current cancer treatment, stage IV or metastatic disease, and the presence of a sleep disorder. Third, the protocol for this trial was somewhat burdensome, requiring participants to drive and attend a number of in-person

appointments during difficult winter conditions, to track and record complex behaviors (e.g., sleep diaries), and provide time sensitive biological samples, with some required on consecutive days at multiple times throughout the day. Further, the intervention required the addition of an activity to the morning routine, which for several of the participants was considered burdensome.

Regardless of these challenges, we were able to recruit a sample large enough to detect a signal on the primary outcome of interest. Conversely, the secondary outcomes were not powered to detect interaction effects, preventing us from gaining a more comprehensive understanding of the impact of the intervention. Future research with this population should use recruitment methods that directly target individuals (i.e., mailing lists) and may benefit from data collection techniques that reduce burden including at-home visits, online questionnaires, and even hiring a private phlebotomist to conduct blood draws.

Although discussed in greater detail previously, there were also several limitations associated with the cortisol collection and analysis. First, it is important to highlight again the high demand procedure for collection of cortisol samples over consecutive days. To try and reduce this burden, a number of aids, including color-coded tubes and tracking sheets, were provided to participants, along with detailed instructions. However, it is possible that any number of these samples may have been collected on the wrong day or at the wrong time, which may potentially skew some of the values observed in this trial. To offset this potential problem, the collection over a period of three consecutive days may provide results more reflective of the subject's usual diurnal pattern. Second, there are a number of extraneous, confounding variables that can impact levels of circulating cortisol that have been identified in the literature but were not included here, such disease grade, tumor characteristics, smoking status, use of antidepressants, and exercise, among others (Hansen, Garde, & Persson, 2008). It was not

possible to measure all of these variables, or to adjust for them in the analyses. Therefore, it is possible that these variables may differentially impact the results without our knowledge; therefore, the results should be interpreted with caution. Finally, there are a wide variety of data reduction strategies and data analysis techniques available to examine change in cortisol rhythms over time. It is possible that a different approach to analysis would provide a more comprehensive representation of change in cortisol rhythms over time in this study.

Conclusion

Light therapy has the potential to impact symptoms of fatigue through circadian rhythm entrainment, improvement in sleep quality and timing, improvements in depressive symptoms, and potentially through alterations to the diurnal release of diurnal cortisol rhythms. The results of this blinded randomized controlled trial of light therapy for CRF, in combination with previous trials of light therapy during and after cancer treatment, support the use of this intervention for the improvement of fatigue and other psychological symptoms in those affected by cancer. The results also provide insight into some of the potential mechanisms of CRF, and the means through which light therapy may impact underlying dysregulation to improve the behavioral symptoms that result from cancer and its treatments. Future research is necessary to determine the optimal treatment duration, dose, wavelength, and intensity of light required to improve symptoms of fatigue in this population.

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Table 2.1.

Outcome assessment schedule

	Screen	Baseline		Intervention			
		Week 0a	Week 0b	Week 1	Week 2	Week 3	Week 4
CRF interview guide	Phone						
Inclusion/exclusion criteria and medical history	Phone						
Sleep disorder screen (ISQ)	Phone						
Consent form		X					
Demographics form		X					
Fatigue scale (MFSI-SF)			X	Phone	Phone	X	X
Questionnaire package (POMS-SF, CES-D, PSQI, FACT-G, FACT-F, CEQ)			X				X
Insomnia scale (ISI)			X		Phone		X
Sleep diary		X					X
Wrist actigraphy		X					X
Salivary cortisol		X					X
Serum collection		X					X

Note. "X" indicates that the assessment will be completed by self-report during in-person appointment; "Phone" indicates that the assessment will be completed over the phone.

Abbreviations: CES-D = Center for Epidemiological Studies – Depression Scale; CEQ = Credibility Expectancy Questionnaire; CRF = cancer-related fatigue; FACT-F = Functional Assessment of Cancer Therapy – Fatigue; FACT-G = Functional Assessment of Cancer Therapy – General; ISI = Insomnia Screening Questionnaire; ISQ = Insomnia Screening Questionnaire; MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form; POMS-SF = Profile of Mood States – Short Form; PSQI = Pittsburgh Sleep Quality Index

Table 2.2.

Primary and secondary outcome measures

Measure	Description	Reliability and Validity
Screening		
Diagnostic Interview Guide for Cancer-Related Fatigue (Cella et al., 1998)	A 14-item structured interview derived from the ICD-10 diagnostic criteria for CRF (Cella et al., 1998). Participants must meet at least 6 of the 11 criteria.	Cronbach's alpha coefficient of 0.82, 100% sensitivity, and 86% specificity (Van Belle et al., 2005).
Medical history screen	A guide to screen for the presence of medical disorders that may be associated with fatigue or conditions that may increase risk of negative side effects associated with light exposure.	N/A
Insomnia Screening Questionnaire (ISQ) (Centre for Sleep and Human Performance Clinical Practice Guidelines Working Group, 2007)	A 17-item questionnaire used to screen for primary sleep disorders on six domains (insomnia, psychiatric disorders, circadian rhythm disorder, movement disorders, parasomnias, and sleep disordered breathing).	N/A
Primary outcome		
The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) (Stein et al., 2004)	A 30-item measure of the physical and psychological aspects of fatigue, including five subscales (general, physical, emotional, mental, and vigor) and a total score. Higher scores indicate greater fatigue.	The internal consistency ranges from .87 to .92 with test-retest reliabilities ranging from .51 to .70.
Secondary outcomes		
Profile of Mood States-Short Form (POMS-SF) (Shacham, 1983)	A 37-item scale that assesses six affective dimensions of mood (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment). Higher scores indicate greater mood disturbance.	Good internal consistency, Cronbach's alpha ranging from .80 to .91.

Center for Epidemiological Studies – Depression scale (CES-D) (Radloff, 1977)	A 20-item measure to identify current depressive symptomatology related to major or clinical depression (depressed mood, feelings of guilt, worthlessness and helplessness, psychomotor retardation, loss of appetite, and sleep difficulties). Higher scores represent greater depressive symptomatology.	A score ≥16 is indicative of "significant" or "mild" depressive symptomatology.
Insomnia Severity Index (ISI) (Bastien et al., 2001; Morin, 1993; Morin et al., 2011)	A 7-item measure designed to assess severity of sleep-onset and sleep maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, impairment attributed to the sleep problem, noticeability of difficulties to others, and degree of distress elicited. Higher scores indicate more severe symptoms of insomnia.	Cut-off scores: 0-7 (no clinically significant insomnia), 8-14 (subthreshold insomnia), 15-28 (presence of clinically significant insomnia) (M.-H. Savard, Savard, Simard, & Ivers, 2005). Validated for use with cancer populations. Cronbach's alpha = 0.90 (M.-H. Savard et al., 2005).
Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989)	A 19-item scale that assesses sleep quality and disturbances in clinical populations. It is composed of seven "component" scores (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction), and a global score. Higher scores indicate worse sleep quality.	A global score >5 yields a diagnostic sensitivity of 89.6% and specificity of 86.5% in good and poor sleepers. The component scores have an overall Cronbach's alpha of .83.
Functional Assessment of Cancer Therapy- General (FACT-G) (Cella et al., 1993)	A 27-item general quality of life measure that contains questions specific to cancer, its treatments, and symptoms with four subscales (physical well-being, social well-being, emotional well-being, and functional well-being). Higher scores indicate better quality of life.	Good test-retest reliability (r = 0.82 to 0.92) and is sensitive to change over time (Yellen et al., 1997).
Functional Assessment of Cancer Therapy- Fatigue subscale (FACT-F) (Yellen et al., 1997)	A 13-item subscale that assesses the specific concerns of individuals with fatigue. Lower scores indicate greater fatigue.	Good test-retest reliability (r = 0.90) and adequate internal consistency (alphas = 0.93 and 0.95) (Yellen et al., 1997).

Credibility/Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000)	Used to assess participants' attitudes towards treatment credibility and expectancy for improvement in symptoms. The credibility factor focuses on cognitively-based beliefs about the treatment while the expectancy factor focuses on affectively-based beliefs.	High internal consistency (Cronbach's alpha between 0.84 and 0.85) and good test-retest reliability ($r_{expectancy}$ = 0.53 to 0.85, and $r_{credibility}$ = 0.62 to 0.78) (Devilly & Borkovec, 2000).
Consensus Sleep Diary (Carney et al., 2012)	The log will be used to calculate changes in subjective reports of: SOL, NWAK, WASO, TST, TIB, SE, napping frequency and duration, and subjective sleep quality. It will also track nap duration and sleeping medication use.	N/A
Wrist actigraphy	A watch-like wrist actigraph (Motionlogger Micro Sleep Watch, Ambulatory Monitoring, Inc., Ardsley, NY) to be worn on the non-dominant wrist 24-hours a day to record daily levels and patterns of sleep/wake activity. The parameters derived will include mean daily activity patterns, as well as the following indices of sleep: SOL, NWAK, WASO, TST, and SE.	The use of actigraphy has been demonstrated sensitive to treatment effects, while being less costly and intrusive than polysomnography (Vallières & Morin, 2003)
Adherence	A daily log will track: 1) number of minutes between waking and turning on the device; 2) number of minutes the device is on each day; 3) number of minutes spent away from the device while it is on; and 4) activities engaged in while using the device. Data from an integrated logger will also provide an objective measure of minutes of device use per day.	N/A

Note. Abbreviations: CRF = cancer-related fatigue; ICD-10 = International Classification of Diseases – 10th Revision; NWAK = number of awakenings; SE = sleep efficiency; SOL = sleep onset latency; TIB = time in bed; TST = total sleep time; WASO = wake after sleep onset

Table 3.1

Demographics and clinical characteristics of sample

Demographic or Clinical Characteristic	Intervention Group					Total (N=81)	
	BWL (n=42)		DRL (n=39)				
	No.	%	No.	%	P	No.	%
Sex					.269		
Women	38	90.5	32	82.1		70	86.4
Men	4	9.5	7	17.9		11	13.6
Age, years					.127		
Mean	56.6		60.0			58.2	
SD	10.5		9.3			10.0	
Range	30-81		41-76			30-81	
Race/ethnicity					.642		
White	39	92.9	37	94.9		76	93.8
Asian	2	4.8	2	5.2		4	5.0
First Nations	1	2.4				1	1.2
Marital status					.041		
Partnered	34	81.0	24	61.5		58	71.6
Single	6	14.3	6	15.4		12	14.8
Divorced			6	15.4		6	7.4
Widowed	2	4.8	3	7.7		5	6.2
Education, years					.146		
Mean	15.4		16.5			15.9	
SD	3.0		3.7			3.3	
Range	9-20		12-28			9-28	
Employment					.285		
Full-time	18	42.9	14	35.9		32	39.5
Part-time	8	19.0	4	10.3		12	14.8
Retired	9	21.4	16	41.0		25	30.9
Disability	6	14.3	3	7.7		9	11.1
Homemaker	1	2.4	2	5.1		3	3.7

Cancer type					.671		
Breast	28	66.7	23	59.0		51	63.0
Gynecological	6	14.3	4	10.3		10	12.3
Colorectal	5	11.9	5	12.8		10	12.3
Lung	1	2.4	3	7.7		4	4.9
Prostate	1	2.4	1	2.6		2	2.5
Bone	1	2.4				1	1.2
Bladder			1	2.6		1	1.2
Head & Neck			1	2.6		1	1.2
Testicular			1	2.6		1	1.2
Months since diagnosis					.154		
Mean		24.2		31.8			27.8
SD		17.5		29.1			23.9
Range		6-102		11-162			6-162
Months since final tx					.203		
Mean		16.8		23.4			20.0
SD		16.3		28.7			23.2
Range		4-94		3-160			3-160
Previous treatments							
Surgery	40	95.2	36	92.3	.584	76	93.8
Chemotherapy	28	66.7	35	89.7	.013	63	77.8
Radiation	30	71.4	27	69.2	.829	57	70.4
Hormone therapy	14	33.3	14	35.9	.808	28	34.6
Current treatments							
Hormonal	14	33.3	17	43.6	.343	31	38.3
Antidepressants	11	26.2	11	28.2	.839	22	27.2
Hypnotic/Sedative	10	23.8	7	17.9	.517	17	21.0

Note. Abbreviations: BWL = bright white light; DRL = dim red light; tx = treatment

Table 3.2

Light device use by intervention group

	Intervention Group			
	BWL	DRL		Total
	Mean (SD)	Mean (SD)	p	Mean (SD)
Tracking sheet	n=39	n=37		N=76
Total time on (mins)	30.2 (0.6)	30.1 (0.7)	.74	30.1 (0.6)
Time to turn on (mins)	33.0 (26.3)	26.8 (19.3)	.25	30.0 (23.2)
Time spent away (mins)	0.2 (0.4)	0.3 (0.7)	.62	0.3 (0.5)
Days used	26.6 (2.3)	26.9 (2.0)	.58	26.7 (2.2)
Logger device	n=41	n=35		N=76
Total time on (mins)	29.5 (2.6)	29.2 (2.4)	.52	29.4 (2.5)
Days used	26.4 (2.2)	26.9 (2.1)	.34	26.6 (2.1)

Note. Abbreviations: BWL = bright white light; DRL = dim red light

Table 3.3

Adjusted means and SEs for MFSI-SF total score and subscales

	Assessment Time					
	Baseline	Week 1	Week 2	Week 3	Week 4	Effect Size (Cohen's d)
Outcome	EMM (SE)	EMM (SE)	EMM (SE)	EMM (SE)	EMM (SE)	Baseline to Week 4
Total Score						
BWL	29.43 (2.57)	21.91 (2.57)	15.70 (2.58)	12.86 (2.59)	9.48 (2.58)	1.20
DRL	29.28 (2.54)	19.48 (2.55)	15.61 (2.55)	14.98 (2.55)	14.45 (2.55)	0.93
General						
BWL	14.10 (1.04)	12.08 (1.04)	10.52 (1.04)	8.84 (1.04)	7.65 (1.04)	0.96
DRL	15.08 (1.02)	13.12 (1.02)	11.46 (1.02)	10.75 (1.02)	10.23 (1.02)	0.76
Physical						
BWL	8.06 (0.76)	7.23 (0.76)	5.84 (0.77)	5.18 (0.77)	4.22 (0.77)	0.77
DRL	7.44 (0.75)	6.39 (0.76)	5.92 (0.76)	5.28 (0.76)	5.02 (0.76)	0.51
Emotional						
BWL	7.80 (0.73)	7.10 (0.73)	5.77 (0.73)	5.32 (0.74)	4.58 (0.73)	0.68
DRL	6.62 (0.72)	5.18 (0.72)	4.74 (0.72)	4.39 (0.72)	4.57 (0.72)	0.46
Mental						
BWL	8.33 (0.78)	5.90 (0.78)	5.19 (0.79)	4.67 (0.79)	4.56 (0.79)	0.74
DRL	8.45 (0.77)	6.02 (0.77)	5.65 (0.77)	5.60 (0.77)	5.57 (0.77)	0.60
Vigor						
BWL	8.87 (0.74)	10.41 (0.74)	11.62 (0.74)	11.17 (0.75)	11.54 (0.74)	-0.56
DRL	8.32 (0.73)	11.24 (0.73)	12.16 (0.73)	11.04 (0.73)	10.94 (0.73)	-0.57

Note. Abbreviations: BWL = bright white light; DRL = dim red light; EMM = estimated marginal mean; MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form; SE = standard error

Table 3.4

Fatigue outcomes using Linear Mixed Models with random slopes and intercepts

	Estimates of Fixed Effects				
Outcome	Estimate	SE	t(df)	p	95% CI
MFSI-SF Total Score					
Intercept	23.27	9.31	2.50(71.94)	.015	[4.71, 41.82]
Time	-3.41	0.49	-6.92(75.28)	<.001	[-4.39, -2.43]
Group[a]	1.46	2.54	0.58(71.85)	.567	[-3.60, 6.53]
Age	-0.29	0.12	-2.32(71.30)	.023	[-.53, -.04]
Sex (Female)	4.82	3.54	1.36(71.30)	.177	[-2.23, 11.88]
Months since last treatment	-0.06	0.05	-1.14(71.34)	.258	[-.16, .05]
Baseline CES-D score	1.17	0.12	9.54(71.40)	<.001	[.92, 1.41]
Baseline credibility score	-0.32	0.40	-0.80(71.82)	.429	[-1.11, .48]
Baseline expectancy score	0.28	0.31	0.91(71.82)	.364	[-.33, .90]
Time x Group[a]	-1.49	0.69	-2.16(75.73)	.034	[-2.85, -.11]
MFSI-SF General					
Time	-1.21	0.22	-5.83(76.20)	<.001	[-1.62, -.80]
Group[a]	-0.72	1.09	-0.66(73.21)	.510	[-2.90, 1.46]
Age	-0.16	0.05	-3.01(71.77)	.004	[-.26, -.05]
Baseline CES-D score	0.20	0.05	3.89(71.85)	<.001	[.20, .30]
Time x Group[a]	-0.40	0.29	-1.39(76.58)	.170	[-.98, .18]
MFSI-SF Physical					
Time	-0.60	0.14	-4.28(75.57)	<.001	[-.88, -.32]
Group[a]	1.01	0.96	1.05(75.57)	.298	[-.91, 2.93]
Age	0.01	0.34	0.29(71.03)	.772	[-.06, .08]
Baseline CES-D score	0.13	0.04	3.66(70.35)	<.001	[.06, .20]
Time x Group[a]	-0.37	0.20	-1.89(75.74)	.063	[-.76, .02]
MFSI-SF Emotional					
Time	-0.49	0.14	-3.52(75.30)	.001	[-.77, -.21]
Group[a]	1.58	0.79	2.01(69.94)	.049	[.01, 3.15]
Age	-0.01	0.04	-0.19(71.85)	.852	[-.08, .07]
Baseline CES-D score	0.30	0.04	8.40(71.85)	<.001	[.23, .37]
Time x Group[a]	-0.33	0.19	-1.68(75.66)	.097	[-.72, .06]
MFSI-SF Mental					
Time	-0.62	0.13	-4.74(76.85)	<.001	[-.88, -.36]
Group[a]	-0.02	0.92	-0.02(74.32)	.986	[-1.85, 1.82]
Age	-0.06	0.04	-1.38(71.98)	.172	[-.14, .03]
Baseline CES-D score	0.22	0.04	5.48(71.82)	<.001	[.14, .31]
Time x Group[a]	-0.26	0.18	-1.41(77.12)	.162	[-.62, .11]

Note. BWL: n=42; DRL: n=39; The Vigor subscale could not converge so it is not reported

[a]Reference group is BWL

Abbreviations: BWL = bright white light; CES-D = Centre for Epidemiological Studies – Depression; DRL = dim red light; EMM = estimated marginal mean; MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form; SE = standard error

Table 3.5

Sleep and psychological outcomes using Generalized Estimating Equations

	Assessment Time					Generalized Estimating Equations (type III tests of fixed effects)					
	Baseline		Week 4		Effect Size (Cohen's d)	Time Effect		Group Effect		Time-Group Interaction	
Outcome	EMM	SE	EMM	SE	Baseline to Week 4	F (df)	p	F (df)	p	F (df)	p
POMS-SF						121.12		1.09		2.51	
Total score						(1,79.58)	<.001	(1,75.68)	.299	(1,79.58)	.117
BWL	30.37	1.75	9.47	1.77	1.83						
DRL	29.34	1.76	13.70	1.78	1.42						
CES-D						45.56		.030		.806	
Total score						(1,79.53)	<.001	(1,75.37)	.864	(1,79.53)	.372
BWL	16.83	.81	10.74	.82	1.15						
DRL	16.23	.82	11.57	.82	0.91						
PSQI						34.98		2.79		1.84	
Total score						(1,79.09)	<.001	(1,74.73)	.099	(1,79.10)	.179
BWL	9.83	.31	7.73	.31	1.04						
DRL	9.88	.30	8.59	.31	0.67						
FACT-G						29.79		.123		.211	
Total score						(1,78.66)	<.001	(1,75.25)	.727	(1,78.66)	.647
BWL	77.08	1.03	82.65	1.05	-0.84						
DRL	77.18	1.03	81.89	1.05	-0.72						
FACIT-F						84.15		.000		.001	
Total score						(1,79.56)	<.001	(1,75.96)	.989	(1,79.56)	.972
BWL	27.67	.99	35.83	1.00	-1.27						
DRL	27.71	.99	35.81	1.00	-1.31						

CEQ-Cred						1.55		1.65		.621	
Total score						(1,79.44)	.216	(1,75.53)	.203	(1,79.44)	.433
BWL	20.37	.61	20.11	.61	0.07						
DRL	20.13	.61	18.99	.61	0.30						
CEQ-Exp						22.80		5.70		3.21	
Total score						(1,78.42)	<.001	(1,74.53)	.020	(1,78.42)	.077
BWL	17.50	1.01	14.68	1.02	0.43						
DRL	17.09	1.01	10.89	1.02	0.98						

Note. BWL: n=42; DRL: n=39; covariates include age, sex, time since last cancer treatment, and baseline score

Abbreviations: BWL = bright white light; CES-D = Centre for Epidemiological Studies – Depression; CEQ-Cred = Credibility Expectancy Questionnaire – Credibility; CEQ-Exp = Credibility Expectancy Questionnaire – Expectancy; DRL = dim red light; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-G = Functional Assessment of Cancer Therapy – General; POMS-SF = Profile of Mood States – Short Form; PSQI = Pittsburgh Sleep Quality Index

Table 4.1

Demographics and clinical characteristics of sample

Demographic or Clinical Characteristic	Intervention Group				Total (N=77)	
	BWL (n=40)		DRL (n=37)			
	No.	%	No.	%	No.	%
Sex						
Women	36	90.0	30	81.1	66	85.7
Men	4	10.0	7	18.9	11	14.3
Age, years						
Mean	56.8		59.5		58.1	
SD	10.7		9.1		10.0	
Range	30-81		41-76		30-81	
BMI						
Mean	27.0		28.1		27.5	
SD	4.1		6.35		5.3	
Range	18-45		20-40		18-45	
Race/ethnicity						
White	37	92.5	35	94.6	72	93.5
Asian	2	5.0	2	5.4	4	5.2
First Nations	1	2.5			1	1.3
Marital status						
Partnered	32	80.0	23	62.2	55	71.4
Single	6	15.0	6	16.2	12	15.6
Divorced			5	13.5	5	6.5
Widowed	2	5.0	3	8.1	5	6.5
Education, years						
Mean	15.3		16.6		15.9	
SD	2.9		3.7		3.3	

Employment						
Full-time	17	42.5	14	37.8	31	40.3
Part-time	8	20.0	4	10.8	12	15.6
Retired	9	22.5	15	40.5	24	31.2
Disability	5	12.5	2	5.4	7	9.1
Homemaker	1	2.5	2	5.4	3	3.9
Cancer type						
Breast	26	65.0	21	56.8	47	61.0
Gynecological	6	15.0	4	10.8	10	13.0
Colorectal	5	12.5	5	13.5	10	13.0
Lung	1	2.5	3	8.1	4	5.2
Prostate	1	2.5	1	2.7	2	2.6
Bone	1	2.5			1	1.3
Bladder			1	2.7	1	1.3
Head & Neck			1	2.7	1	1.3
Testicular			1	2.7	1	1.3
Months since diagnosis						
Mean	24.0		32.4		28.0	
SD	17.9		29.6		24.5	
Range	6-102		12-162		6-162	
Months since final tx						
Mean	16.7		23.9		20.2	
SD	16.6		29.3		23.7	
Range	4-94		3-160		3-160	
Previous treatments						
Surgery	38	95.0	34	91.9	72	93.5
Chemotherapy	26	65.0	33	89.2	59	76.6
Radiation	29	72.5	25	67.6	54	70.1
Hormone therapy	12	30.0	13	35.1	25	32.5
Current treatments						
Antidepressants	10	25.0	11	29.7	21	27.3

Note. BMI = body mass index; BWL = bright white light; DRL = dim red light; tx = treatment

Table 4.2

Estimated marginal means and SEs for psychological outcomes and log transformed cortisol slopes at baseline and post-intervention

	Assessment Time				
	Baseline	Post-Intervention	Time Effect	Group Effect	Time-Group Interaction
Outcome	EMM (SE)	EMM (SE)	F(df)	F(df)	F(df)
MFSI-SF Total[a]			157.68** (1, 75.45)	1.92 (1, 70.61)	3.81* (1, 75.45)
BWL	28.58 (1.54)	8.48 (1.55)			
DRL	27.81 (1.54)	13.13 (1.55)			
CES-D Total[b]			43.41** (1, 75.53)	.003 (1, 71.27)	.869 (1, 75.53)
BWL	16.93 (0.84)	10.68 (0.84)			
DRL	16.19 (0.84)	11.49 (0.85)			
Log cortisol slope[c]			1.77 (1, 74.45)	.067 (1, 70.64)	.008 (1, 74.48)
BWL	-1.07	-1.02			
DRL	-1.09	-1.04			

Note. The natural log transformation was performed on mean values of cortisol prior to calculating slopes.

[a] adjusting for age, sex, time since last treatment, baseline MFSI-SF score, baseline CES-D score

[b] adjusting for age, sex, time since last treatment, baseline CES-D score

[c] adjusting for age, sex, body mass index, time since last treatment, type of cancer

*p=.055

**p<.001

Abbreviations: BWL = bright white light; CES-D = Center for Epidemiological Studies – Depression Scale; DRL = dim red light;

MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form

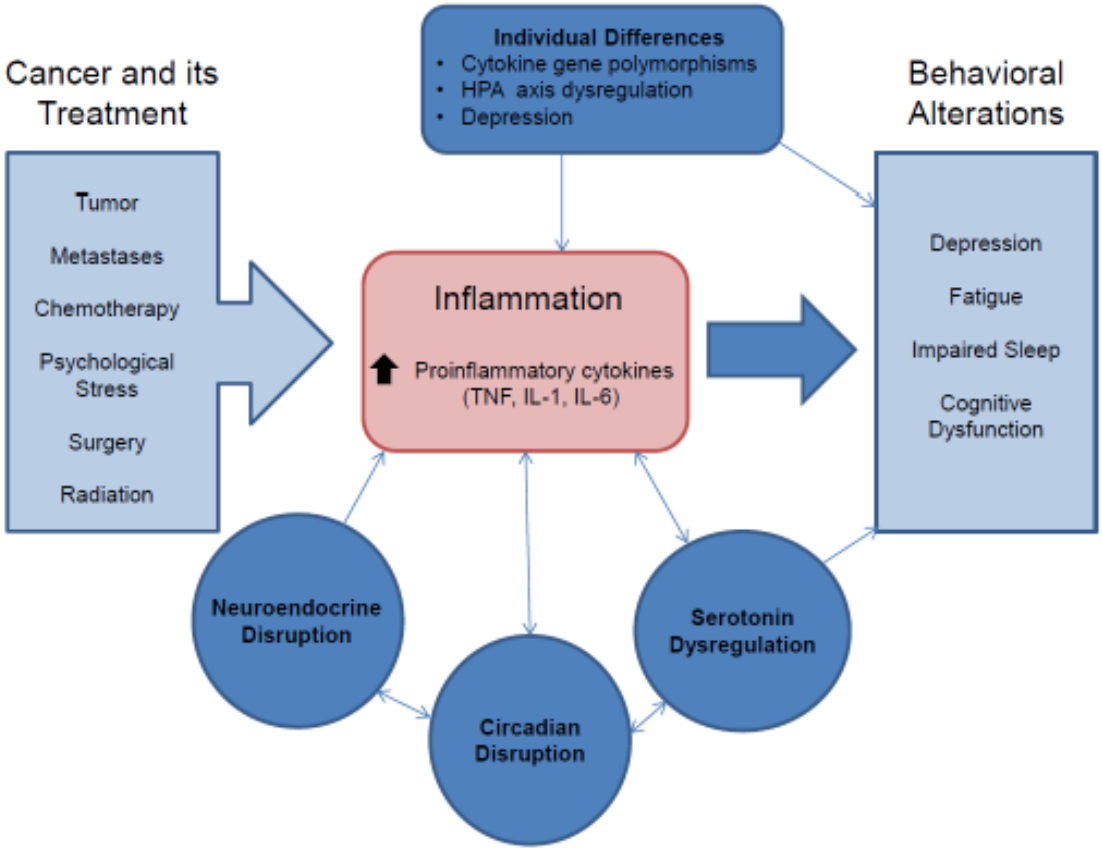

Figure 1.1. A revised model of cancer-related fatigue

Abbreviations: HPA = hypothalamic-pituitary-adrenal; IL = interleukin; TNF = tumor necrosis factor

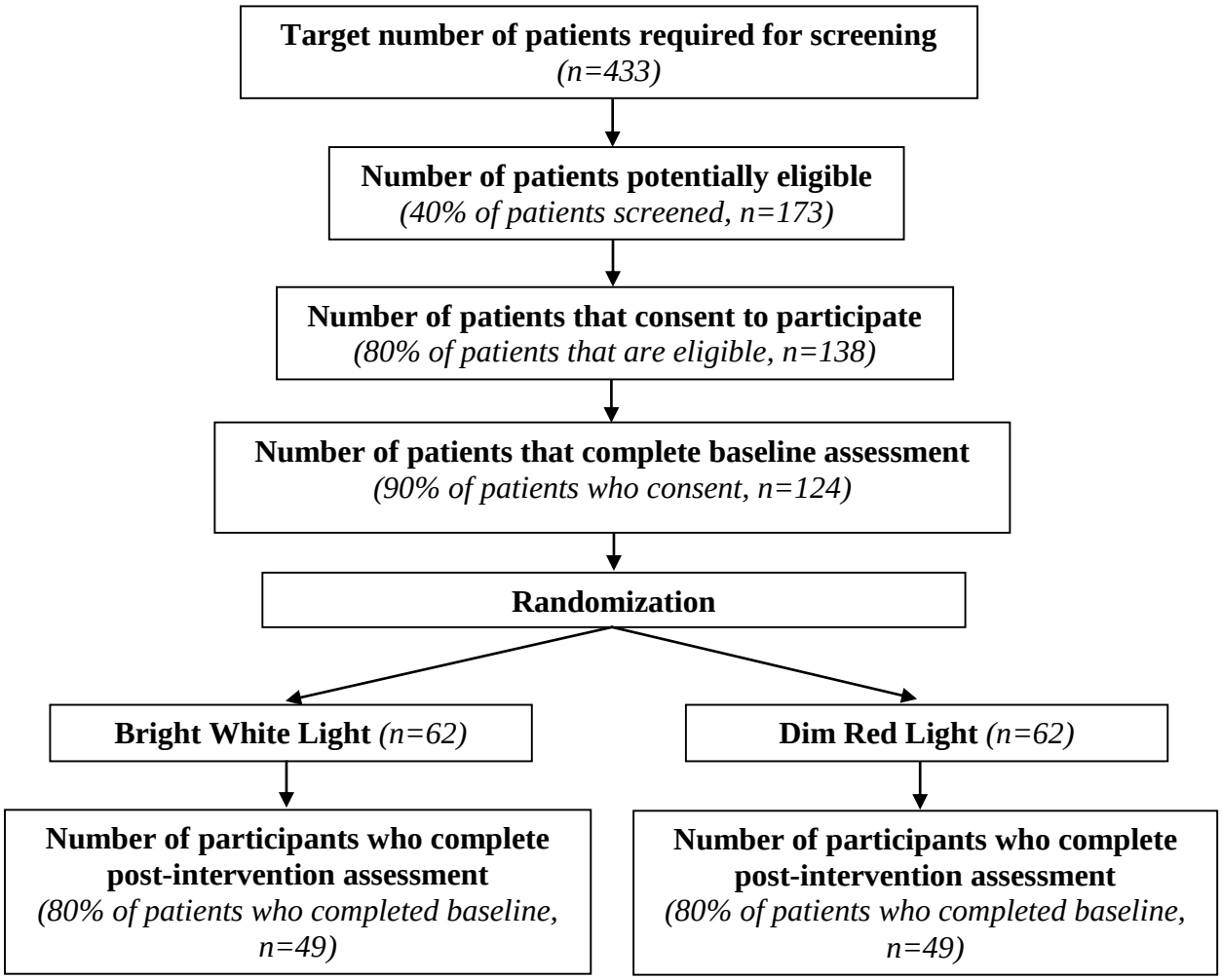

Figure 2.1. Recruitment flowchart.

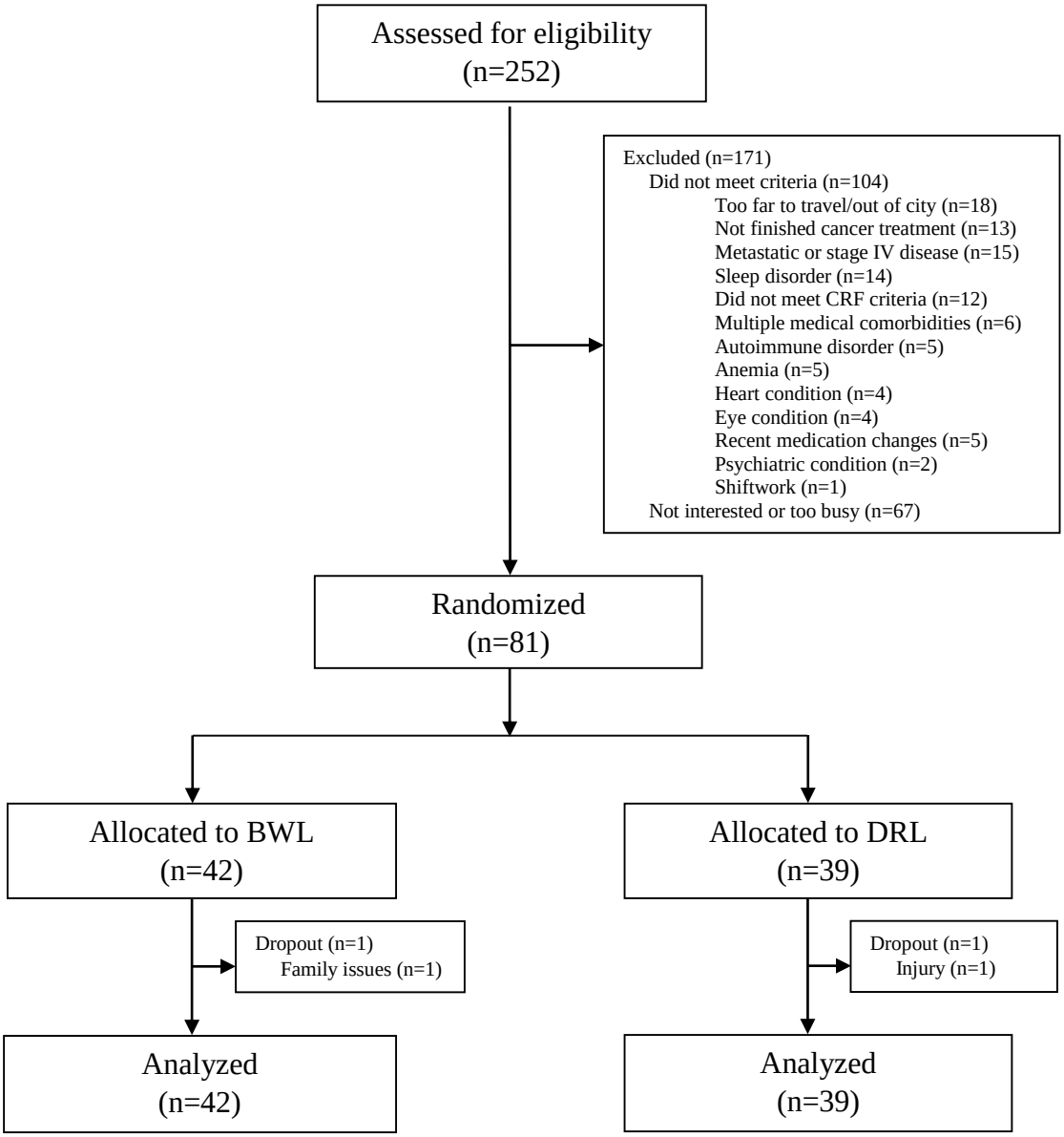

Figure 3.1. Participant flow through study.

Abbreviations: BWL = bright white light; CRF = cancer-related fatigue; DRL = dim red light

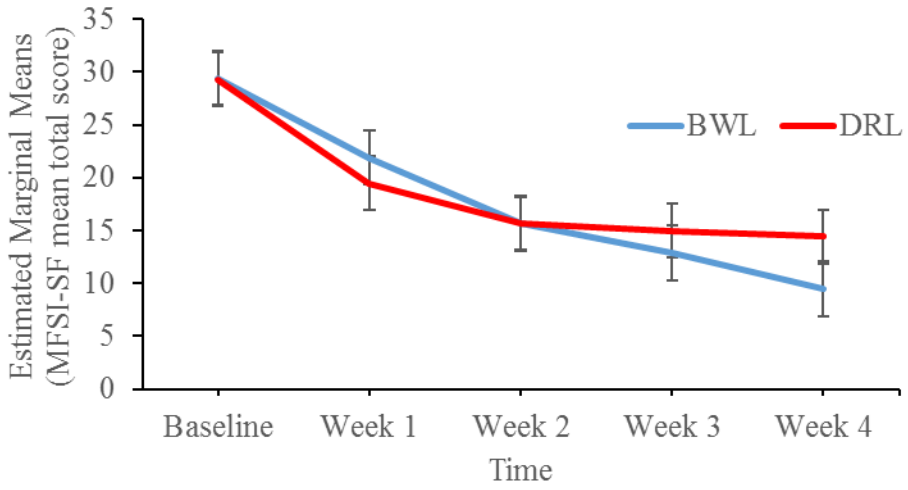

Figure 3.2. Adjusted means and standard errors for mean fatigue total scores for BWL and DRL from baseline to the end of the 4-week light therapy intervention

Abbreviations: BWL = bright white light; DRL = dim red light; MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form

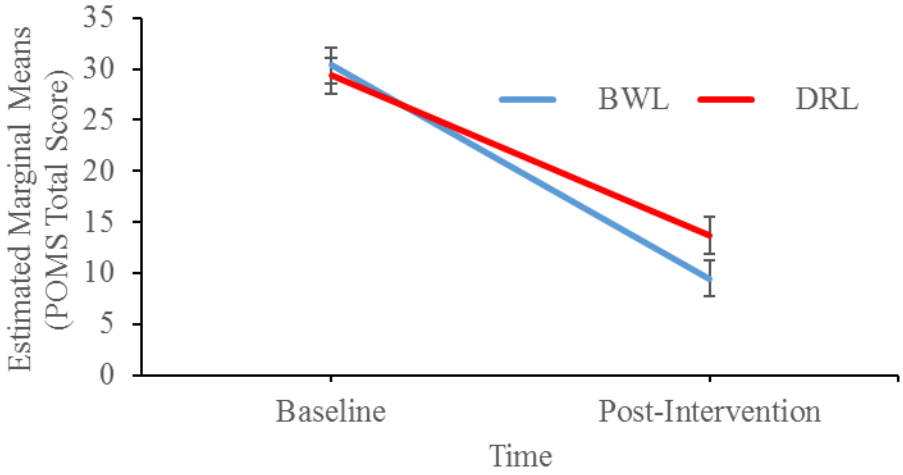

Figure 3.3. Adjusted means and standard errors for mean mood disturbance total scores for BWL and DRL at baseline and post-intervention.

Abbreviations: BWL = bright white light; DRL = dim red light; POMS = Profile of Mood States

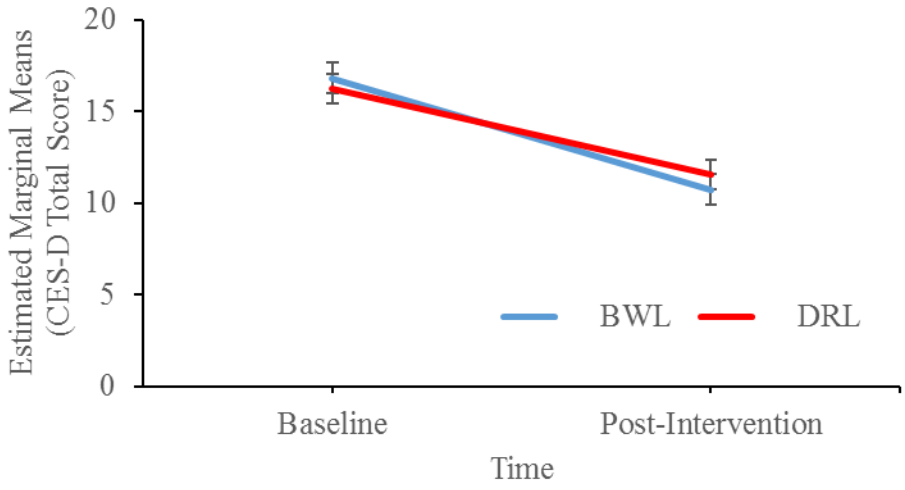

Figure 3.4. Adjusted means and standard errors for mean depression total scores for BWL and DRL at baseline and post-intervention.

Abbreviations: BWL = bright white light; CES-D = Centre for Epidemiological Studies – Depression scale; DRL = dim red light

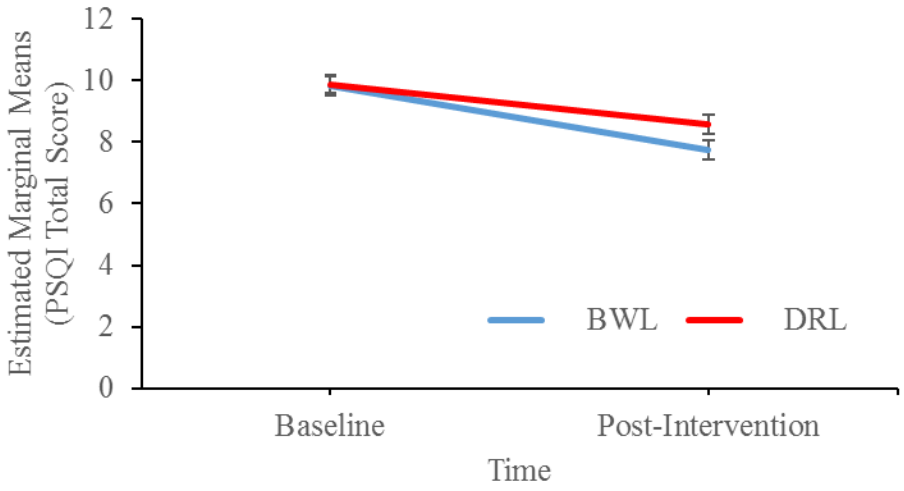

Figure 3.5. Adjusted means and standard errors for mean sleep quality total scores for BWL and DRL at baseline and post-intervention.

Abbreviations: BWL = bright white light; DRL = dim red light; PSQI = Pittsburgh Sleep Quality Index

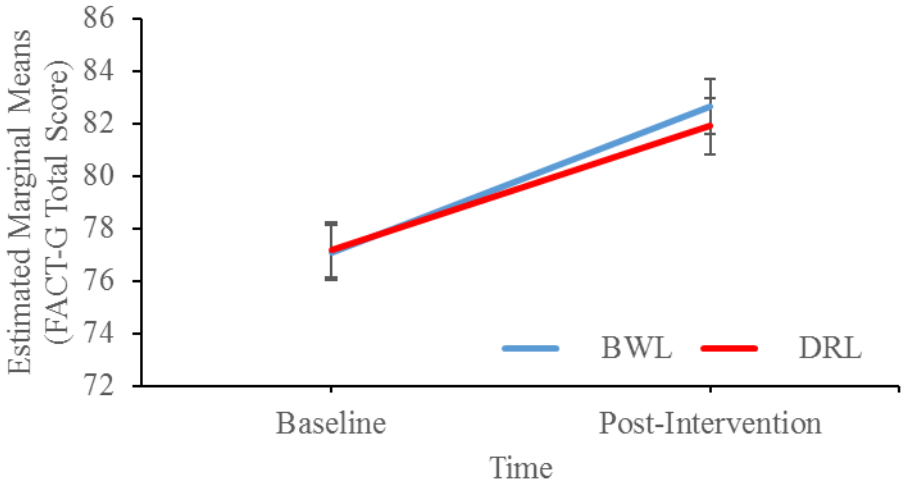

Figure 3.6. Adjusted means and standard errors for mean quality of life total scores for BWL and DRL at baseline and post-intervention.

Abbreviations: BWL = bright white light; DRL = dim red light; FACT-G = Functional Assessment of Cancer Therapy – General

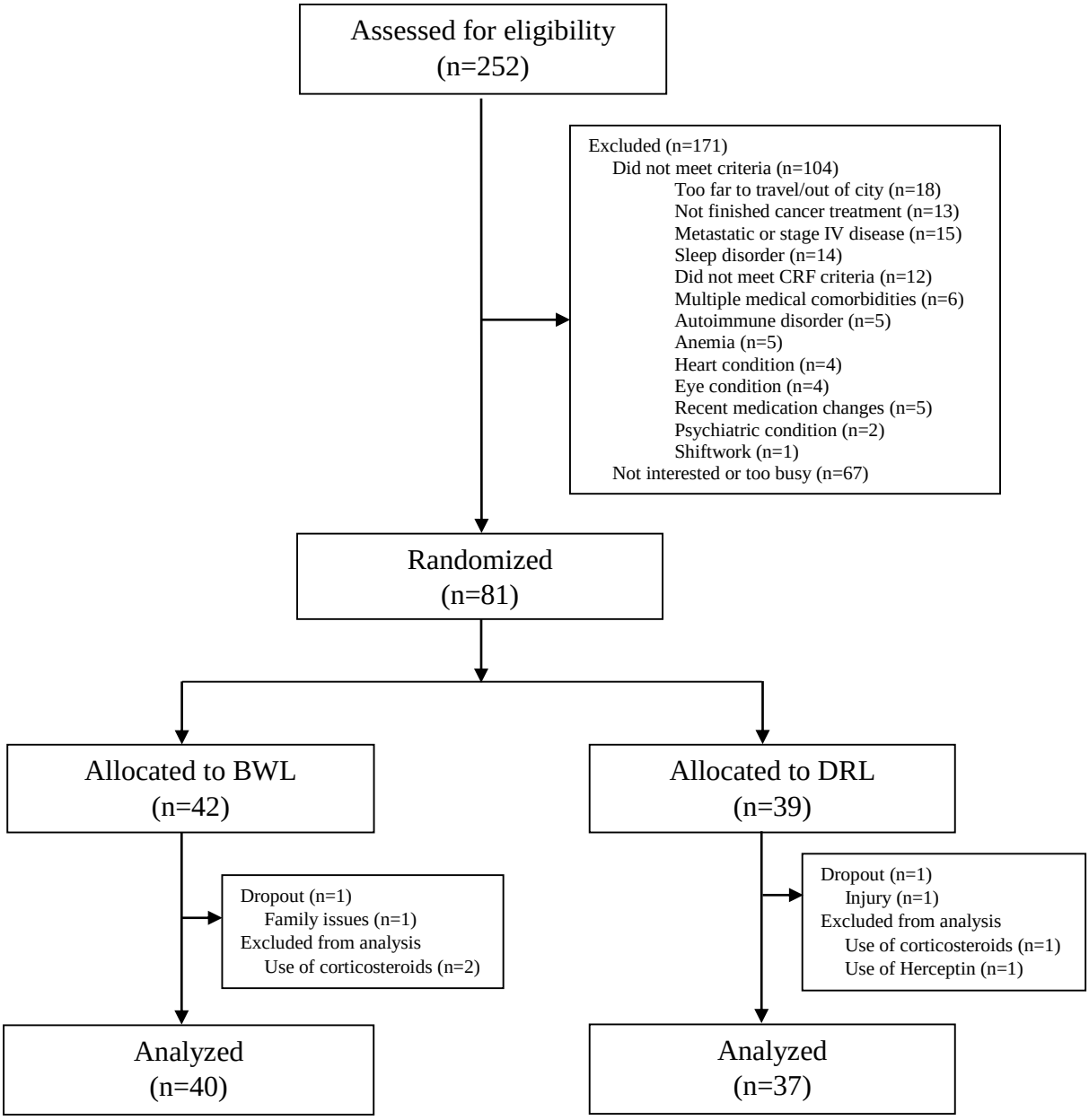

Figure 4.1. Participant flow chart for cortisol analysis.

Abbreviations: BWL = bright white light; CRF = cancer-related fatigue; DRL = dim red light

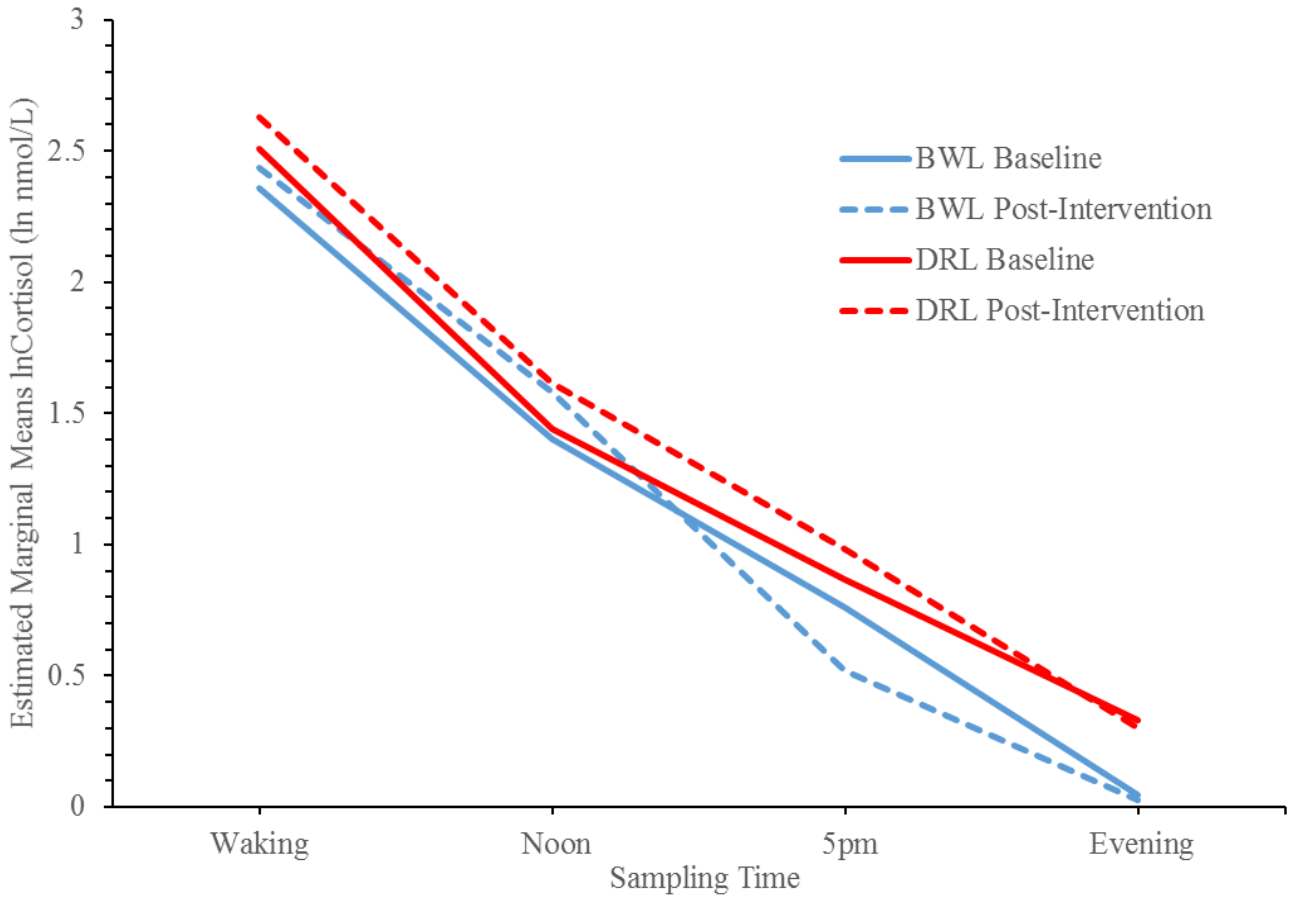

Figure 4.2. Estimated marginal means of natural log transformed cortisol output at each sampling time point for baseline and post-intervention measurements. Means are adjusted for age, body mass index, months since last treatment, and type of cancer.

Abbreviations: BWL = bright white light; DRL = dim red light

Appendices

Appendix A. Screening questionnaires

ID # _____

Date: _____ Assessed by: _____

Name: _____

Phone Number: _____ Alternate: _____

Email Address: _____

How did you hear about study? _____

ID # _____

Year of Birth: _____ Do you live in Calgary (area)? _____

Can you read and speak English? _____

Cancer Diagnosis and stage: _____

Metastatic cancer? _____

Date of last cancer treatment? _____

Are you on hormone treatments? _____

Name: _____

Dosage: _____

Name: _____

Dosage: _____

Are you anemic? _____

Are you pregnant? _____

Do you have a sleep disorder? (e.g., sleep apnea)? _____

Do you have an abnormal sleep schedule (shift work)? _____

Do you have any other medical conditions that may impact your levels of fatigue?
_____

Are you on any medications that make you photosensitive (e.g. ___)?

_____

Do you have any vision problems? (e.g. cataracts, macular degeneration)_____

Have you had eye surgery in the last 2 months? _____

Have you ever been diagnosed with a psychiatric disorder? _____

Details: _____

Are you currently on any medications? _____

Has your dose remained stable over the past 6 months? _____

ID # _____

Diagnostic Interview Guide for Cancer-Related Fatigue

NOTE: Capitalized text represents instructions to the interviewer. Text in quotations represents statements to be read verbatim to the respondent.

	Circle one	
1. "Over the past month, has there been at least a 2 week period when you had significant fatigue, a lack of energy, or an increased need to rest every day or nearly every day?"	Yes	No

IF NO, STOP HERE. IF YES, CONTINUE.

"For each of the following questions, focus on the worst 2 weeks in the past month (or else the past 2 weeks if you felt equally fatigued for the entire month)."

2. "Did you feel weak all over or heavy all over? (every day or nearly every day)?"	Yes	No
3. "Did you have trouble concentrating or paying attention? (every day or nearly everyday?)"	Yes	No
4. "What about losing interest or desire to do the things you usually do? (every day or nearly everyday?)"	Yes	No
5. "How were you sleeping? Did you have trouble falling asleep, staying asleep or waking too early? Or did you find yourself sleeping too much compared to what you usually sleep? (every night or nearly every night?)"	Yes	No
6. "Have you found that you usually don't feel rested or refreshed after you have slept? (every day or nearly everyday?)"	Yes	No
7. "Did you have to struggle or push yourself to do anything? (every day or nearly everyday?)"	Yes	No
8. "Did you find yourself feeling sad, frustrated or irritable because you felt fatigued? (every day or nearly everyday?)"	Yes	No
9. "Did you have difficulty finishing something you had started to do because of feeling fatigued? (every day or nearly everyday?)"	Yes	No
10. "Did you have trouble remembering things? For example, did you have trouble remembering where your keys were or what someone had told you a little while ago?	Yes	No

(every day or nearly everyday?)"

11. "Did you find yourself feeling sick or unwell for several hours after you had done something that took some effort (every time or nearly every time)?"	Yes	No

IF LESS THAN 6 ITEMS INCLUDING #1 ARE MARKED YES, STOP HERE

12. "Has fatigue made it hard for you to do your work, take care of things at home, or get along with other people?"	Yes	No

IF #12 IS NO, STOP HERE

13. IS THERE EVIDENCE FROM THE HISTORY, PHYSICAL EXAMINATION OR LABORATOY FINDINGS THAT THE SYMPOMS ARE A CONCEQUENCE OF CANCER OR CANCER THERAPY?	Yes	No

IF #13 IS NO, STOP HERE

14. ARE THE SYMPTOMS PRIMARILY A CONSEQUENCE OF CO-MORBID PSYCHIATRIC DISORDERS SUCH AS MAJOR DEPRESSION, SOMATIZATION DISORDER, OR DELIRIUM?	Yes	No

IF #14 IS YES, PATIENT <u>DOES NOT MEET CRITERIA</u> FOR CANCER-RELTED FATIGUE

IF #14 IS NO, PATIENT <u>MEETS CRITERIA</u> FOR CANCER RELATED FATIGUE

ID # _____

Insomnia Screening Questionnaire

The Insomnia Screening Questionnaire is a tool that can be used to assist in the diagnosis of a primary sleep disorder.

Over the past month:	**Circle the best answer**				
	Never	**Rarely**	**Occasionally**	**Most nights/days**	**Always**
1. Do you have trouble falling asleep?	1	2	**3**	**4**	**5**
2. Do you have trouble staying asleep?	1	2	**3**	**4**	**5**
3. Do you wake up un-refreshed?	1	2	**3**	**4**	**5**
4. Do you take anything to help you sleep?	1	2	**3**	**4**	**5**
5. Do you use alcohol to help you sleep?	1	2	**3**	**4**	**5**
6. Do you have any medical condition that disrupts your sleep?	1	2	**3**	**4**	**5**
7. Have you lost interests in hobbies or activities?	1	2	3	**4**	**5**
8. Do you feel sad, irritable or hopeless?	1	2	3	**4**	**5**
9. Do you feel nervous or worried?	1	2	3	**4**	**5**
10. Do you think something is wrong with your body?	1	2	3	**4**	**5**
11. Are you a shift worker or is your sleep schedule irregular?	1	2	3	**4**	**5**
12. Are your legs restless and/or uncomfortable before bed?	1	2	3	**4**	**5**
13. Have you been told that you are restless or that you kick your legs in your sleep?	1	2	3	**4**	**5**
14. Do you have any unusual behaviors or movements during sleep?	1	**2**	**3**	**4**	**5**

Over the past month:	Circle the best answer				
	Never	**Rarely**	**Occasionally**	**Most nights/days**	**Always**
15. Do you snore?	1	2	3	**4**	**5**
16. Has anyone ever told you that you stop breathing, gasp, snort or choke in your sleep?	1	2	3	**4**	**5**
17. Do you have difficulty staying awake during the day?	1	2	3	4	5

Diagnostic Domains

1. Insomnia: Q1-6
2. Psychiatric Disorders: Q7-10
3. Circadian Rhythm Disorder: Q11
4. Movement Disorders: Q12-13
5. Parasomnias: Q14
6: Sleep Disordered Breathing: Q15-17

Guidelines for Interpretation

1. Patients who answer 3, 4 or 5 on any question likely suffer from insomnia, If they answer 3, 4, or 5 to two or more items and have significant daytime impairment the insomnia requires further evaluation and management.

2. Patients who answer 4 or 5 on questions 6-9 should be further screened for psychiatric disorders.

3. Patients who answer 4 or 5 on question 11 likely have a circadian rhythm sleep disorder. Further questioning about shift work or a preference for a delayed sleep phase should be done.

4. An answer of 4 or 5 on either item is significant and likely contributing to the patient's disturbed sleep. Question 12 refers to restless legs syndrome and question 13 refers to periodic limb movement disorder.

5. An answer of 2-5 on question 14 should raise concern especially if the event or movement is violent or potentially injurious to themselves or a bed partner.

6. Answering 4 or 5 on questions 15 or 16 alone requires further clinical evaluation for sleep apnea.

ID # _____

Are they eligible? Y or N

If no:

Thank them for their time and inform them that they are not eligible to participate

Offer other resources:
- "The Energy to Fight Fatigue" Class at TBCC
- Offer to email or mail fatigue booklet

If yes:

Describe the study

Is this something you would be interested in?

Invite to participate in study

Set up dates to meet (make sure they can make it for all dates)

Will you be driving?

Do you need transit passes?

Give directions (email?)

Give them your contact information
- Phone: [redacted]
- Email: [redacted]

Would they like to be contacted by phone or email?

Appendix B. Demographics and medical history questionnaires

ID:_____

Demographics and Medical History Questionnaire

Date of Birth (mm/dd/yy): ____/____/____ **Sex:** ☐ Male ☐ Female

Marital Status:
- ☐ Single
- ☐ Married
- ☐ Common-Law
- ☐ Divorced
- ☐ Widowed

Employment:
- ☐ Full-time
- ☐ Part-time
- ☐ Homemaker
- ☐ Unemployed
- ☐ Retired
- ☐ Disability

Race/Ethnicity:
- ☐ White
- ☐ Chinese
- ☐ Black
- ☐ Filipino
- ☐ Latin American
- ☐ Japanese
- ☐ South Asian (Ex. East Indian, Sri Lankan, etc.)
- ☐ West Asian (Ex. Iranian, Afghan, etc.)
- ☐ Aboriginal (N. American Indian, Metis, Inuit)
- ☐ Arab
- ☐ Korean
- ☐ Other: _____

Years of Education: _____
(Including elementary, secondary, high school, technical, and university)

Date of Diagnosis (mm/dd/yy): _____/_____/_____

Type of Cancer and Stage: _____

Treatments previously received: (mark all that apply)
- ☐ Surgery
- ☐ Chemotherapy
- ☐ Radiation
- ☐ Hormones (please Indicate: □ Past or □ Present)

Date of last treatment: (mm/dd/yy): _____/_____/_____

Medications:

Please list all of the medications and dosage that you are currently taking (**excluding** vitamins, dietary supplements and herbs).

1. e.g. Ativan, 1 mg, before bed	6.
2.	7.
3.	8.
4.	9.
5.	10.

ID:_____

If applicable, please indicate how often you participate in the activities listed below.

Choose only **one of the time periods** by indicating with a ☑.

Alcohol Consumption (beer, wine, liquor)

Amount of drinks_____ per/ Day ☐ Week ☐ Month ☐

Caffeine Consumption (coffee, tea, soft drinks, chocolate, etc.)

Number of times_____ per/ Day ☐ Week ☐ Month ☐

Nicotine Consumption (cigarettes, cigars, pipe, chewing tobacco, etc.)

Number of times_____ per/ Day ☐ Week ☐ Month ☐

Physical Activity (sports, exercise, vigorous work activities, etc.)

Minutes of activity_____ per/ Day ☐ Week ☐ Month ☐

Vitamins, Dietary Supplements & Herbs

Please indicate with a ☑ the **Vitamins, Dietary Supplements, and Herbs** you take **4 or more times a week**.

☐ Vitamin A	☐ Vitamin B6	☐ Vitamin B12	☐ Vitamin C
☐ Vitamin D	☐ Vitamin E	☐ Beta-carotene	☐ Calcium
☐ Co-enzyme Q10	☐ Folic Acid	☐ Selenium	☐ Zinc
☐ Multi-vitamin	☐ Shark Cartilage	☐ Garlic	☐ Green Tea
☐ Ginger	☐ Fish Oils	☐ Valerian	☐ Ginseng
☐ St. John's wort	☐ Glucosamine	☐ Ginkgo biloba	☐ Echinacea
☐ Essiac	☐ Melatonin	☐ Other:	

ID:_____

Other Complementary Therapies

Please indicate with a ☑, which complementary therapies you have used in the past month and indicate the frequency of use.

☐ **Meditation**
Times used last month _____

☐ **Yoga**
Times used last month _____

☐ **Acupuncture / Acupressure**
Times used last month _____

☐ **Massage therapy**
Times used last month _____

☐ **Chiropractic**
Times used last month _____

☐ **Homeopathy**
Times used last month _____

☐ **Relaxation Techniques**
Times used last month _____

☐ **Prayer**
Times used last month _____

☐ **Spiritual Healing (Reiki, Distance)**
Times used last month _____

☐ **Naturopathy**
Times used last month _____

☐ **Reflexology**
Times used last month _____

☐ **Other:**
Times used last month _____

Psychological Therapies

Please indicate with a ☑, which psychological therapies you have used in the past month and indicate the frequency of use.

☐ **Individual Psychotherapy**
Times used last month _____

☐ **Individual Behaviour Therapy**
Times used last month _____

☐ **Group Psychotherapy**
Times used last month _____

☐ **Couple/Family Psychotherapy**
Times used last month _____

☐ **Hypnosis**
Times used last month _____

☐ **Self-help Books**
Times used last month _____

☐ **Other:**
Times used last month _____

ID:_____

Medical History

Condition		Date of Diagnosis	Treatments/Medication (Include Name & Dose)
Heart Disease	NO YES		
Diabetes	NO YES		
Vascular Disorders (Stroke)	NO YES		
Head Injury	NO YES		
Epilepsy	NO YES		
Thyroid Disease	NO YES		
Autoimmune Disease	NO YES		
Other:	NO YES		

ID:_____

Psychiatric History

Condition		Date of Diagnosis	Treatments/Medication (Include Name & Dose)
Mood Disorder	NO YES		
Anxiety Disorder	NO YES		
Psychotic Disorder	NO YES		
Substance Abuse	NO YES		
Other:	NO YES		

Appendix C. Questionnaire package

The LITE Study

Questionnaire Package

Participant ID: _____

Date: _____

Baseline or Post-Treatment

ID:_____

The Multidimensional Fatigue Symptom Inventory-Short Form

Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes **how true each statement has been for you in the PAST SEVEN DAYS.**

	Not at All	A Little	Moderately	Quite a Bit	Extremely
1. I have trouble remembering things	0	1	2	3	4
2. My muscles ache	0	1	2	3	4
3. I feel upset	0	1	2	3	4
4. My legs feel weak	0	1	2	3	4
5. I feel cheerful	0	1	2	3	4
6. My head feels heavy	0	1	2	3	4
7. I feel lively	0	1	2	3	4
8. I feel nervous	0	1	2	3	4
9. I feel relaxed	0	1	2	3	4
10. I feel pooped	0	1	2	3	4
11. I am confused	0	1	2	3	4
12. I am worn out	0	1	2	3	4
13. I feel sad	0	1	2	3	4
14. I feel fatigued	0	1	2	3	4
15. I have trouble paying attention	0	1	2	3	4
16. My arms feel weak	0	1	2	3	4
17. I feel sluggish	0	1	2	3	4
18. I feel run down	0	1	2	3	4
19. I ache all over	0	1	2	3	4

ID:_____

	Not at All	A Little	Moderately	Quite a Bit	Extremely
20. I am unable to concentrate	0	1	2	3	4
21. I feel depressed	0	1	2	3	4
22. I feel refreshed	0	1	2	3	4
23. I feel tense	0	1	2	3	4
24. I feel energetic	0	1	2	3	4
25. I make more mistakes than usual	0	1	2	3	4
26. My body feels heavy all over	0	1	2	3	4
27. I am forgetful	0	1	2	3	4
28. I feel tired	0	1	2	3	4
29. I feel calm	0	1	2	3	4
30. I am distressed	0	1	2	3	4

ID:_____

Profile of Mood States-Short Form

Below is a list of words that describe feelings that people have. Please read each one carefully. Then circle ONE number corresponding to the adjective phrase which best describes **HOW YOU HAVE BEEN FEELING DURING THE LAST SEVEN DAYS INCLUDING TODAY.**

Not at all	***A Little***	***Moderately***	***Quite a Bit***	***Extremely***
0	***1***	***2***	***3***	***4***

1.	Tense	0	1	2	3	4
2.	Angry	0	1	2	3	4
3.	Worn-out	0	1	2	3	4
4.	Unhappy	0	1	2	3	4
5.	Lively	0	1	2	3	4
6.	Confused	0	1	2	3	4
7.	Peeved	0	1	2	3	4
8.	Sad	0	1	2	3	4
9.	Active	0	1	2	3	4
10.	On edge	0	1	2	3	4
11.	Grouchy	0	1	2	3	4
12.	Blue	0	1	2	3	4
13.	Energetic	0	1	2	3	4
14.	Hopeless	0	1	2	3	4
15.	Uneasy	0	1	2	3	4
16.	Restless	0	1	2	3	4
17.	Unable to concentrate	0	1	2	3	4
18.	Fatigued	0	1	2	3	4
19.	Annoyed	0	1	2	3	4
20.	Discouraged	0	1	2	3	4
21.	Resentful	0	1	2	3	4
22.	Nervous	0	1	2	3	4
23.	Miserable	0	1	2	3	4
24.	Cheerful	0	1	2	3	4

ID:_____

Not at all	***A Little***	***Moderately***	***Quite a Bit***	***Extremely***
0	***1***	***2***	***3***	***4***

25.	Bitter	0	1	2	3	4
26.	Exhausted	0	1	2	3	4
27.	Anxious	0	1	2	3	4
28.	Helpless	0	1	2	3	4
29.	Weary	0	1	2	3	4
30.	Bewildered	0	1	2	3	4
31.	Furious	0	1	2	3	4
32.	Full of pep	0	1	2	3	4
33.	Worthless	0	1	2	3	4
34.	Forgetful	0	1	2	3	4
35.	Vigorous	0	1	2	3	4
36.	Uncertain about things	0	1	2	3	4
37.	Bushed	0	1	2	3	4

ID:_____

Center for Epidemiological Studies – Depression (CES-D)

Circle the number of each statement which best describes how often you felt or behaved this way **DURING THE PAST WEEK**.

During the past week:	**Rarely or none of the time (less than 1 day)**	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of the time (3-4 days)**	**Most or all of the time (5-7 days)**
1) I was bothered by things that usually don't bother me	0	1	2	3
2) I did not feel like eating; my appetite was poor	0	1	2	3
3) I felt that I could not shake off the blues even with help from my family and friends	0	1	2	3
4) I felt that I was just as good as other people	0	1	2	3
5) I had trouble keeping my mind on what I was doing	0	1	2	3
6) I felt depressed	0	1	2	3
7) I felt that everything I did was an effort	0	1	2	3
8) I felt hopeful about the future	0	1	2	3
9) I thought my life had been a failure	0	1	2	3
10) I felt fearful	0	1	2	3
11) My sleep was restless	0	1	2	3
12) I was happy	0	1	2	3
13) I talked less than usual	0	1	2	3
14) I felt lonely	0	1	2	3
15) People were unfriendly	0	1	2	3
16) I enjoyed life	0	1	2	3
17) I had crying spells	0	1	2	3
18) I felt sad	0	1	2	3
19) I felt that people disliked me	0	1	2	3
20) I could not get "going"	0	1	2	3

ID:_____

Insomnia Severity Index

1. Please rate the severity of your insomnia problem(s) in the **LAST 2 WEEKS**

	None	Mild	Moderate	Severe	Very Severe
a. Difficulty falling asleep:	0	1	2	3	4
b. Difficulty staying asleep:	0	1	2	3	4
c. Problem waking up to early:	0	1	2	3	4

2. How satisfied/dissatisfied are you with your current sleep pattern?

Very satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

3. To what extent do you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

Not at all interfering	A little	Somewhat	Much	Very much interfering
0	1	2	3	4

4. How noticeable to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all noticeable	A little	Somewhat	Much	Very much noticeable
0	1	2	3	4

5. How worried/distressed are you about your current sleep problem?

Not at all worried	A little	Somewhat	Much	Very much worried
0	1	2	3	4

ID:_____

Pittsburgh Sleep Quality Index (PSQI)

The following questions relate to your usual sleep habits during **THE PAST MONTH ONLY**. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month, what time have you usually gone to bed at night?

BED TIME: _____

During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES: _____

During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME: _____

During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed).

HOURS OF SLEEP PER NIGHT: _____

For each of the remaining questions, check the one best response. Please answer <u>all</u> questions.

During the past month, how often have you had trouble sleeping because you …

Cannot get to sleep within 30 minutes

not during the past month _____	less than once a week _____	once or twice a week _____	three or more times a week _____

Wake up in the middle of the night or early morning

not during the past month _____	less than once a week _____	once or twice a week _____	three or more times a week _____

ID:_____

Have to get up to use the bathroom

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

Cannot breathe comfortably

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

Cough or snore loudly

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

Feel too cold

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

Feel too hot

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

Had bad dreams

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

Have pain

not during the past month	less than once a week	once or twice a week _____	three or more times a week
_____	_____		_____

ID:_____

Other reason(s), please describe

_____

How often during the past month have you had trouble sleeping because of this?

not during the past month _____	less than once a week _____	once or twice a week _____	three or more times a week _____

During the past month, how would you rate your sleep quality overall?

Very good _____ Fairly good _____ Fairly bad _____ Very bad _____

During the past month, how often have you taken medication (prescribed or "over the counter") to help you sleep?

not during the past month _____	less than once a week _____	once or twice a week _____	three or more times a week _____

During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

not during the past month _____	less than once a week _____	once or twice a week _____	three or more times a week _____

During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

no problem at all_____	only a very slight problem _____	somewhat of a problem _____	a very big problem _____

ID:_____

Functional Assessment of Chronic Illness Treatment

By circling **one number per line,** please indicate how true each statement has been for you during the **PAST SEVEN DAYS**.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

ID:_____

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness ..	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

ID:_____

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix D. Light use log

Light Use Tracking Sheet

Participant ID #: _____ Date Started: _____ Date Ended: _____

Week 1	Time Awake	Time Light On	Time Light Off	Minutes Away	What were you doing while using the light?
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					

Comments:

Week 2	Time Awake	Time Light On	Time Light Off	Minutes Away	What were you doing while using the light?
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					

Comments:

Week 3	Time Awake	Time Light On	Time Light Off	Minutes Away	What were you doing while using the light?
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					

Comments:

Week 4	Time Awake	Time Light On	Time Light Off	Minutes Away	What were you doing while using the light?
Day 1					
Day 2					
Day 3					
Day 4					
Day 5					
Day 6					
Day 7					

Comments:

Date Received: _____
Entered By: _____ Date: _____
Checked By: _____ Date:_____

Appendix E. Permissions

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