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A Pilot Trial of Light Therapy on Fatigue, Mood, Sleep Quality, and Quality of Life in Individuals with Post-Treatment Cancer-Related Fatigue

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A Pilot Trial of Light Therapy on Fatigue, Mood, Sleep Quality, and Quality of Life in Individuals with Post-Treatment Cancer-Related Fatigue

by

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Abstract

Cancer-related fatigue (CRF) is a common and distressing symptom reported by individuals with cancer, with 33% of patients continuing to experience fatigue for months or years following treatment. Despite its prevalence, CRF remains relatively undertreated and poorly understood. Light therapy is an effective treatment for a variety of fatigue disorders. This study evaluated the impact of a one-month light therapy treatment on fatigue, mood, sleep quality, and quality of life (QOL) in post-treatment cancer survivors with CRF. Eight participants were randomized to either bright white light (BWL) or dim red light (DRL) and completed baseline and post-treatment measures. Participants in both the BWL and DRL treatments groups showed reductions in fatigue, and improvements in sleep quality and QOL. Given the small sample size and the time of year the study was conducted, the results should be interpreted with caution.

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List of Symbols and Abbreviations

Symbol	Definition
ACTH	Adrenocorticotropic hormone
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATP	Adenosine-triphosphate
BWL	Bright white light
CAM	Complementary and alternative medicine
CBT	Cognitive-behavioral therapy
CES-D	Center for Epidemiological Studies – depression
CEQ	Credibility Expectancy Questionnaire
CRF	Cancer-related fatigue
CRH	Corticotropin-releasing hormone
DRL	Dim red light
DSM-IV	Diagnostic and Statistical Manual for Mental Disorders – Fourth Edition
FACT-F	Functional Assessment of Cancer Therapy - Fatigue
FACT-G	Functional Assessment of Cancer Therapy - General
HPA	Hypothalamic-pituitary-adrenal axis
ICD-10	International Classification of Diseases – Tenth Edition
IL	Interleukin
ISI	Insomnia Severity Index
ISQ	Insomnia Screening Questionnaire

LED	Light emitting diode
MFSI-SF	Multidimensional Fatigue Symptom Inventory – Short Form
NCCN	National Comprehensive Cancer Network
NWAK	Number of awakenings
POMS-SF	Profile of Mood States – Short Form
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized controlled trial
RM-ANOVA	Repeated measures analysis of variance
SCN	Suprachiasmatic nucleus
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TST	Total sleep time
QOL	Quality of life
WASO	Wake after sleep onset

Introduction

Cancer is the leading cause of death in Canada, accounting for nearly one third of all deaths, followed by cardiovascular disease and chronic lower respiratory disease (Statistics Canada, 2012). The Canadian Cancer Society reports that there will be an estimated 187,600 new cancer diagnoses in Canada in 2013, with 16,200 new diagnoses in Alberta alone (Canadian Cancer Society, 2013). With advances in detection and treatment, the five year survival of Canadians diagnosed with cancer is predicted to be 63% (Canadian Cancer Society, 2013), meaning that many will live as long-term survivors requiring supportive care for ongoing symptoms. Symptoms that can persist over time include behavioural complications such as depression, sleep disturbances, and cognitive dysfunction, or physical symptoms such as pain and nausea (Shi et al., 2011), though fatigue is often reported as the most debilitating symptom experienced by cancer survivors (National Comprehensive Cancer Network, 2010).

Cancer-related fatigue (CRF) is described as one of the most frequent and most distressing symptoms reported by patients (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004 Vogelzang et al., 1997). CRF 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" (NCCN, 2010). It is often characterized by feelings of physical tiredness or weakness, reduced energy, reduced motivation, and mental fatigue (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003). This type of fatigue differs from the fatigue experienced by healthy individuals in that it is not relieved by rest or sleep, it is disproportionate to exertion level, and is often more severe and more distressing (Glaus, Crow, & Hammond, 1996).

Approximately 70% to100% of cancer patients will experience fatigue at some point along the cancer continuum (NCCN, 2010). A systematic review of 40 CRF studies reported that the prevalence of CRF ranges from 46% to 96% depending on the patient group assessed, the method of assessment, and the treatment received (Prue, Rankin, Allen, Gracey, & Cramp, 2006). CRF is not linked to a specific type of cancer or treatment, but is reported by up to 80% of individuals who have received chemotherapy and/or radiotherapy (Curt et al., 2000; Henry et al., 2008; Vogelzang et al., 1997). Fatigue, however, is 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 (Curran, Beacham, & Andrykowski, 2004; Schwartz et al., 2000). 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 even years following treatment (Cella et al., 2001; Curran et al., 2004; Hofman, Ryan, Figueroa-Moseley, Jean-Pierre, & Morrow, 2007; Schwartz et al., 2000). Despite its prevalence, CRF remains relatively undertreated and poorly understood.

CRF has been accepted as a diagnosis in the International Classification of Diseases and Related Health Problems, Tenth Revision (Appendix A; Cella, Peterman, Passik, Jacobsen, & Breitbart, 1998), and clinical practice guidelines for its management have been developed by the National Comprehensive Cancer Network (NCCN, 2010). Currently, CRF is most often measured by various self-report instruments, though a structured interview has been developed to establish the presence of a clinical syndrome based on a set of diagnostic criteria (Appendix B; Cella et al., 1998).

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). Studies involving patients with a range of cancer diagnoses have reported negative correlations between CRF and quality of life including physical, role, emotional, and cognitive function (Ahlberg et al., 2003; Alexander, Minto, Andrews, & Stone, 2009; Curt et al., 2000). For example, patients with fatigue have reported significant impairment in their ability to complete a variety of daily tasks, including walking long distances, cleaning the house, climbing the stairs, and lifting objects (Crawford & Gabrilove, 2000). In a study of 379 patients with a history of chemotherapy, 91% of patients with fatigue 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 was also reported to have a considerable emotional impact (e.g., loss of emotional control, feelings of isolation and solitude), to have a negative impact on social functioning (e.g., maintenance of interpersonal relationships, spending time with friends), to be associated with problems carrying out typical cognitive tasks (e.g., remembering things, maintaining temporal order), to have a marked effect on employment and financial status (e.g., lost work days, change in conditions of employment), and to have a negative effect on caregivers (e.g., lost work days; Curt et al., 2000).

When examining only post-treatment patients, the link between increased fatigue and diminished quality of life becomes more apparent. For example, one study of breast cancer survivors showed large differences between patients with clinically significant CRF and those without CRF in 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, along with greater mood disturbance than those who did not report CRF (Alexander et al., 2009). Taken together, these studies indicate that fatigue plays a major role in patient quality of life. Although the residual symptoms of cancer and its treatments, such as fatigue, can have a profound negative impact on quality of life, they are often not monitored as closely during follow-up compared to during active cancer 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 do not have higher rates of major depressive disorder than controls, they report greater impairment from depression in their home, social, and work life (Pirl, Greer, Temel, Yeap, & Gillman, 2009). Research has suggested that fatigue often co-occurs with depression in cancer patients and survivors (Brown & Kroenke, 2009; Jacobsen, Donovan, & Weitzner, 2003). An increase in psychological symptoms, such as depressed mood, may impact a patients' quality of life by impairing their ability to perform daily activities (Curt et al., 2000), but may also have a negative impact on their treatment outcomes by reducing survival times (Satin, Linden, & Phillips, 2009). Longitudinal research in breast cancer patients engaged in active chemotherapy reported that depressed mood present before treatment was associated with increased fatigue more than two years later (Geinitz et al., 2004). Further, a study investigating fatigue in long-term cancer survivors found that women who experienced depressive symptoms in the first year after diagnosis were at an elevated risk for developing long-term fatigue (Bower et al., 2006). With regard to treatment, however, one study of 249 lung cancer patients with anemia suggested

that improvements in fatigue were 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 showed reductions in depressive symptomatology, but had no such effect on levels of fatigue (Roscoe et al., 2005).

The consistent 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 & Weitzner, 2004). Though there is support for each of these theories, research has not been able to disentangle the directionality of the relationship. Regardless of the cause, there is the potential for interventions that specifically target CRF to provide additional benefits for patients who struggle with depression, and vice versa.

Mechanisms of CRF

Although CRF is reported by up to 96% of cancer patients at one time or another, the specific mechanisms involved in its pathophysiology remain poorly understood. Given that fatigue is a non-specific, multidimensional and multifactorial symptom, 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; Ancoli-Israel, Moore, & Jones, 2001; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). 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 (i.e., physical 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). Alternatively, central fatigue (i.e., mental fatigue) originates in the central nervous system and refers to "difficulty in the initiation or maintenance of voluntary activities" (Chaudhuri & Behan, 2004). It then manifests as "a failure to complete physical and mental tasks that require self-motivation and internal cues, in the absence of demonstrable cognitive failure or motor weakness" (Chaudhuri & Behan, 2000; Okada, Tanaka, Kuratsune, & Sadato, 2004). These differences between peripheral and central fatigue help 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, Ekman, Gaston-Johansson, & Mock, 2003).

Peripheral fatigue.

Adenosine-triphosphate (ATP) and muscle metabolism dysregulation. Many patients complain of feelings of "weakness" or "lack of energy" during and after cancer treatment and this supports the theory that dysregulation in muscle metabolism and ATP may be one potential mechanism underlying CRF (Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002). ATP is the main source of energy for most cellular functions in the body, so any alteration in its synthesis or availability can result in loss of function. For example, ATP provides energy required for the contraction of skeletal muscle, so defects in the mechanism that regenerates ATP in the skeletal muscle will subsequently impede the ability to perform physical tasks (Andrews et al., 2004) and can compromise muscle function (Ryan et al., 2007). Though evidence for ATP dysregulation in cancer patients is limited, research in populations with chronic fatigue syndrome has

demonstrated defects in ATP synthesis and metabolism (Barsevick et al., 2010). It is important to note that many cancer patients report changes in appetite during treatment either because of treatment-induced illness or a decrease in desire for food, so it is possible that through reduced caloric intake, ATP production and synthesis may be limited (Morrow et al., 2002; Ryan et al., 2007), resulting in feelings of physical fatigue or weakness.

Vagal afferent nerve hypothesis. Based on animal studies, the vagal afferent nerve hypothesis proposes that "cancer and/or its treatments cause a peripheral release of neuroactive agents that activate vagal afferent nerves, leading to the suppression of somatic muscle activity and induction of *sickness behavior*" (Ryan et al., 2007, p. 27). This suppression of muscle activity then leads to a decrease in muscle tone that may be perceived as weakness (Andrews et al., 2004). Although there is some support for this theory in animal models, it is not widely accepted as a potential mechanism in humans (Morrow et al., 2002).

Central fatigue.

Cytokine dysregulation. The proinflammatory cytokine hypothesis is one potential mechanism of CRF that has recently gained momentum in the literature. The theory was developed when it was observed that patients undergoing treatment for cancer reported similar symptoms to those displayed in animals models of cytokine-induced sickness behavior (Cleeland et al., 2003; Lee et al., 2004). 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 certain proinflammatory cytokines (Dantzer, 2001; Hart, 1988) such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α. Elevated levels of these circulating cytokines have been observed in patients with cancer (Ryan et al., 2007). One study examining the presence of immune markers in breast cancer survivors

reporting significant fatigue following treatment completion found elevated levels of markers associated with increased proinflammatory activity (Bower, Ganz, Aziz, Fahey, & Cole, 2003). If present, there is the potential for the elevated levels of cytokines to contribute to other symptoms, such as depression, fever, and anemia that may then feed-back and exacerbate fatigue symptoms (Kurzrock, 2001). Although the impact and precise mechanisms of cytokine dysregulation in the etiology of CRF have not been fully elucidated, current trends in research have been focused on gaining a better understanding of its impact on various symptoms associated with cancer and its treatments.

Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction. Disturbance of HPA-axis functioning is another potential mechanism that has been implicated in CRF. 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 corticotropin-releasing hormone (CRH) is secreted from the paraventricular nucleus of the hypothalamus and acts with vasopressin to release adrenocorticotropic hormone (ACTH) from the anterior pituitary (Barsevick et al., 2010). ACTH then stimulates the release of cortisol from the adrenal cortex. 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). This process of releasing cortisol also takes place in response to psychological and physical stress (Ryan et al., 2007).

It is proposed that elevated levels of proinflammatory cytokines and chronic inflammation (i.e., biological stress) may reduce the synthesis and release of CRH (Shanks et al., 1998), that then results in lower cortisol output from the adrenals and is experienced as feelings of fatigue. There is some research evidence that HPA-axis function is altered in CRF. In

particular, the presence of CRF has been associated with reduced cortisol output. For example, one study reported that a subgroup of breast cancer survivors showed blunted cortisol responses to stressors, where as non-fatigued survivors showed normal responding (Bower, Ganz, & Aziz, 2005). Furthermore, patients with fatigue also had a slower decline in cortisol levels over the day (Bower et al., 2005). 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). Furthermore, low levels of circulating cortisol have been observed in patients with chronic fatigue syndrome (Cleare, 2003), so it is possible that the same mechanism may also be linked with CRF.

Serotonin (5-HT) dysregulation. One hypothesis that has been proposed to explain CRF is an increase in brain serotonin levels and/or an upregulation of serotonin receptors as a result of cancer and its treatments (Ryan et al., 2007). Given that central serotonin levels have been implicated in both exercise-induced fatigue and chronic fatigue syndrome (Andrews et al., 2004), it is possible that serotonin dysregulation that occurs as a result of alterations in the systems that control serotonin could account for the increased feelings of fatigue after cancer treatment. There is evidence that proinflammatory cytokines, such as TNF, can influence serotonin metabolism, either by the existence of a feedback loop whereby TNF causes an increase in serotonin release into the synaptic space (Morrow et al., 2002), or through increasing transporter function (Mossner et al., 1998; Zhu, Blakely, & Hewlett, 2006). Alterations or dysregulation in this feedback loop that may occur as a result of increased circulating TNF (i.e., increased release of serotonin or increased upregulation of receptors) could then signal the release of CRH,

modifying HPA-axis function, that then results in intense feelings of decreased physical ability or fatigue (Andrews et al., 2004).

Circadian rhythm disruption. Another potential mechanism by which cancer may be associated with fatigue is through circadian rhythm disruption. Circadian rhythms are endogenous physiological and genetic patterns that run on a 24-hour cycle to control several biological functions 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 central clock that is located in the hypothalamic suprachiasmatic nucleus (SCN), in which circadian rhythms are generated internally using complex feedback loops and genes (Eismann, Lush, & Sephton, 2010). This internal clock can be entrained by environmental (e.g., alterations in light and dark) and psychological cues (e.g., stress, anxiety, and illness; Ryan et al., 2007), and may also be affected by signal disruption or input from other areas of the brain (Barsevick et al., 2010). Alterations in any part of this system may result in the disruption of arousal and sleep patterns (Barsevick et al., 2010).

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), 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., altered rest-activity rhythms), period changes, and erratic peaks and troughs (Ryan et al., 2007). These can be categorized as disorders of

timing, magnitude of change, or synchronization (Lanuza & Farr, 2003). These alterations typically worsen with tumor progression (Eismann et al., 2010), with the most dramatic alterations observed in patients with advanced cancers (Mormont & Levi, 1997). 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).

It has also been hypothesized that greater levels of fatigue in patients with cancer may result from reduced exposure to light (Liu et al., 2005). In a prospective study assessing the relationship between fatigue and light exposure in a sample of 63 women recently diagnosed with breast cancer, increased fatigue was found to be significantly correlated with decreased intensity and duration of bright light exposure (Liu et al., 2005). Although this study proposed a link between light exposure and fatigue, it was not possible to determine whether decreased light exposure was the cause or result of fatigue.

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. The models available to date provide a solid foundation for understanding these mechanisms and have helped to guide research in uncovering the precise mechanisms involved in the development of CRF.

The first model is the "Biobehavioural Model of Fatigue" proposed by Morrow and colleagues (2002). This model places emphasis on the hypothesis that serotonin dysregulation is key to the development of CRF. Therefore, of the mechanisms discussed above, more weight is placed on the role of the HPA-axis, cytokines, and serotonin. It is hypothesized that cancer and its treatments (i.e., chemotherapy, surgery, and/or radiotherapy) lead to an increase in proinflammatory cytokines (i.e., TNF, IL-1, IL-6) that can alter the amounts of serotonin available in the central nervous system. More specifically, it is proposed that TNF, in particular, may alter central serotonin by increasing neuronal release of serotonin and up-regulating serotonin transporters. Concurrently, it is proposed that elevated levels of TNF also lead to elevated levels of circulating tryptophan, a precursor for serotonin synthesis (Morrow et al., 2002). The relationship between TNF and serotonin is then characterized as a complex regulatory feedback loop that becomes dysfunctional with increased levels of circulating cytokines that are a result of cancer and its treatments. 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 behavioral expression of fatigue and depression (Morrow et al., 2002). It is suggested that the association between depression and fatigue in patients with cancer can be explained by this common mechanism.

The authors state that this model is not meant to serve as a physiological certainty, but instead as a reasonable summary of current biobehavioural findings of the development of CRF. Overall, this model is simple and provides a framework for future investigations. Despite that, the relationships between variables, shown as simple arrows, represent complex interrelationships that have not been fully explicated. Furthermore, there is evidence from

clinical trials on the use of selective serotonin reuptake inhibitors for the treatment of CRF that suggest that the serotonin dysregulation hypothesis is not the primary mechanism involved in the development and maintenance of CRF (Morrow et al., 2003; Roscoe et al., 2005).

The second model, proposed by Bower (2007), is similar to the model by Morrow and colleagues (2002) in that it places an emphasis on cytokine dysregulation. First, cancer and its treatments activate proinflammatory cytokines that can lead to the development of fatigue through cytokine effects on the central nervous system. Chronic inflammation may then develop when long-term changes in immune homeostasis and neuroendocrine function are altered as a result of cancer and its treatments. Finally, Bower (2007) proposes that individual difference factors (e.g., HPA-axis dysregulation, depression, cytokine gene polymorphisms) may increase the risk of chronic inflammation with a cancer diagnosis, though HPA-axis dysregulation and depressive symptomatology may also have a direct effect on fatigue.

A key strength of this model is that, unlike the previous model, it takes into account individual differences. Given that the physical and mental manifestations of fatigue and that 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 more variability in symptom expression. Although this model provides a compelling foundation for the mechanisms involved in the development of CRF, it does not take into account a many of the other potential mechanisms, such as circadian disruption.

Miller and colleagues (2008) propose a model called “The Neuroendocrine-Immune Model of Behavioral Co-morbidities in Cancer Patients”. This theory, like those previously described, proposes 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 then activates alterations in the sleep-wake cycle that can disrupt neuroendocrine system functioning (e.g., HPA-axis functioning). This neuroendocrine function disruption then 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).

The key strength of this model is that it encompasses many of the proposed mechanisms of CRF described above, for example sleep-wake alterations and neuroendocrine dysfunction, that the other models were lacking. Nevertheless, with additional pathways included, this model has the potential to provide an even more inclusive description of the development and maintenance of CRF.

Taking into account the strengths and weaknesses of the models discussed and incorporating a variety of the mechanisms above, a revised model of the mechanisms and mediators of the behavioural alterations that occur during cancer and its treatments, with a specific focus on fatigue, is presented in Figure 1. In this revised model, as in the model proposed by Bower (2007), there is a direct link between cancer and its associated treatments, an increase in proinflammatory cytokines, and fatigue. Therefore, unlike the models suggested by Morrow and colleagues (2002) and Miller and colleagues (2008) wherein serotonin dysregulation is the final pathway through which cancer and its treatments may lead to fatigue, this revised model proposes that serotonin dysregulation can have a direct and/or indirect effects on the development of fatigue, without being a central component. This model also incorporates the relationship between increased inflammation and circadian rhythm disruption, as described in

Miller and colleagues (2008). As an addition, this one-way relationship has been changed to a represent a reciprocal relationship. That is circadian rhythm and sleep disruption feeds back to increase the production of proinflammatory cytokines in addition to elevated levels of proinflammatory cytokines influencing sleep-wake cycles. As described above, it is proposed that these changes in circadian rhythms can then lead to alterations in neuroendocrine function that then subsequently lead to elevations in cytokine production. In this model, the influence of individual differences in gene expression and HPA-axis functioning has also been included as an influence on symptoms of fatigue. As Bower (2007) suggested, this can occur through an indirect route via inflammatory cytokines, as well as through a direct route on symptom expression. By including this mediator, differences in the experience of fatigue among cancer patients and survivors can be taken into account.

The present study has been designed to assess the proposed pathway between increased proinflammatory cytokines and circadian rhythm disruption. More specifically, this study will examine whether circadian rhythm entrainment, via the use of early morning bright light, may reduce symptoms of fatigue. It is proposed that through circadian rhythm entrainment, subsequent alterations in HPA-axis function and serotonin dysregulation may be dampened, therefore reducing symptoms of fatigue.

Treatments for CRF

Although fatigue is reported as one of the most common side effects of chemotherapy or radiotherapy, 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). 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. Recommended treatments to manage fatigue for cancer patients post-treatment include those that are educational, non-pharmacological, and pharmacological (NCCN, 2010).

Education and counseling. Upon treatment completion, it is important for both the patient and family to gain an understanding of the duration and severity of fatigue that may be experienced by the patient (NCCN, 2010). Given that many patients experience fatigue for months or years following the conclusion of treatment (Curran et al., 2004; Hofman et al., 2007; Schwartz et al., 2000), it is suggested that patients regularly monitor their fatigue levels and discuss ongoing screening of fatigue with their physician (NCCN, 2010).

Non-pharmacological interventions. Similar to treatments recommended for fatigued patients undergoing active treatment, patients with post-treatment CRF are encouraged to increase their activity levels, engage in psychosocial interventions, or seek assistance with nutrition and diet (NCCN, 2010). For many patients, a common consequence of cancer treatment and associated fatigue is an overall reduction in physical activity. Recent meta-analyses indicate large improvements in fatigue were associated with increased physical activity. For example, one analysis of 19 studies assessing the effectiveness of physical activity on fatigue, reported that 35% of the studies demonstrated an improvement in fatigue-related outcomes, although stronger effects were noted when the interventions were administered during cancer treatment as opposed to post-treatment (Kangas, Bovbjerg, & Montgomery, 2008). Further, an analysis of 28 randomized controlled trials investigating the effects of exercise on CRF found that exercise was more successful in relieving fatigue than control conditions, and was effective both during and after treatment (Cramp & Daniel, 2008). Based on this evidence, activity enhancement is an NCCN Category 1 intervention, meaning that the recommendation is based on high-level

evidence (i.e., RCTs) and that there is a uniform consensus on its endorsement (NCCN, 2010), and should therefore be a first line of fatigue treatment recommended by health care practitioners. Though the NCCN Guidelines do not provide specific recommendations for the amount of physical activity required to see benefits specific to fatigue in this population, any exercise is encouraged (NCCN, 2010), although the American Cancer Society recommends that cancer survivors should aim to exercise at least 150 minutes per week (Rock et al., 2012). The NCCN Guidelines recommend that the exercise program should be individualized for each patient, that it should begin at a low level of intensity, and that the duration of activity be modified as the individual's condition changes (NCCN, 2010).

Participation in psychosocial interventions is also a NCCN category 1 recommendation for the management of CRF. Psychosocial interventions, such as cognitive behavioral therapy (CBT), supportive expressive therapy, stress management, coping strategy training, and psychoeducational therapies, may help patients cope with psychological symptoms (e.g., symptoms of anxiety and depression) that are commonly associated with fatigue (Mustian et al., 2007). These interventions may be particularly beneficial for individuals for whom exercise is not recommended. A systematic review of 27 trials reported that interventions with a specific focus on fatigue management are more effective at reducing symptoms of fatigue for patients with CRF than analogous interventions without a focus on fatigue (Goedendorp, Gielissen, Verhagen, & Bleijenberg, 2009).

An estimated 20% to 80% of cancer patients will develop malnutrition at some point during their illness (Kubrak & Jensen, 2007). Therefore, consultation with a dietician is recommended to help restore nutritional deficiencies that may be a result of treatment-induced illness, subsequently producing symptoms of fatigue (Brown, 2002). Patients are also

encouraged to use strategies suggested for the management of general fatigue, such as energy conservation and distraction (NCCN, 2010). Energy conservation involves prioritizing and pacing activities and delegating less essential activities so the patient can either maintain activities for longer or conserve their energy for activities that are more important (Barsevick et al., 2004). Distraction techniques, such as games, reading, and socializing, can be used to take the patient's mind off of how fatigued they feel and help them cope with bouts of low energy (Barsevick et al., 2004). The NCCN Guidelines also recommend that patients keep a daily or weekly diary of fatigue levels to aid in determining peak energy periods, allowing them to plan activities during periods when they can expect to feel most energized (NCCN, 2010).

Although not explicitly recommended by the NCCN Guidelines because of limited empirical support, there are also various complementary and alternative medicine (CAM) interventions available that may benefit cancer survivors with residual fatigue. A systematic review of 20 studies resulted in a total of six studies to date that have evaluated effectiveness of various CAM interventions at reducing fatigue specifically in patients who have completed treatment (Finnegan-John, Molassiotis, Richardson, & Ream, 2013). The results of two studies indicated that acupuncture was highly effective at reducing fatigue when compared to controls (Johnston et al., 2011; Molassiotis, Sylt, & Diggins, 2007). A Reiki intervention, tested by Tsang and colleagues (2007), showed improvements in fatigue and quality of life, while a study investigating the effectiveness of biofield healing showed large effect sizes and greater improvement in mental and physical fatigue than controls (Jain et al., 2012). Improvements in fatigue were also reported in a studies that examined the Bojungikki-tang herbal combination (a Chinese herbal prescription of 10 herbs; Jeong et al., 2010), as well as Swedish massage (Listing et al., 2009). Overall, the evidence generated by trials investigating the usefulness of CAM

interventions for reducing fatigue is lacking and replications of the current literature are required. Nonetheless, these therapies could be delivered alongside well-established treatments while larger, more robust trials are conducted (Finnegan-John et al., 2013).

Pharmacological interventions. Current pharmacological treatments for post-treatment CRF focus on the use of psychostimulants. A trial of 37 breast cancer survivors reported a 54% response rate to methylphenidate (Hanna et al., 2006), a psychostimulant commonly used in the treatment of attention-deficit hyperactivity disorder and narcolepsy, while another randomized trial of 154 patients post-treatment reported improvements in symptoms of fatigue with its use (Lower et al., 2009). Research has also revealed encouraging results for the effectiveness of modafinil, an analeptic drug used in the treatment of narcolepsy and other fatigue disorders. For example, a study of 51 breast cancer survivors prescribed 200 mg per day of modafinil, reported that 86% of participants showed reductions in fatigue after one month (Morrow et al., 2005). Although these drugs show promising results for patients with post-treatment CRF, the NCCN Guidelines recommend that these drugs only be considered after all other causes of fatigue are ruled out (e.g., anemia, insomnia, depression).

Overall, education, counselling, and other non-pharmacological interventions (e.g., activity enhancement and psychosocial interventions) represent the first line of treatment for CRF. It is noteworthy, however, that although many of these treatment modalities offer relief for some patients, not all patients benefit and may be reluctant or incapable of undertaking such rigorous lifestyle changes.

Light Therapy

Light therapy is a safe and inexpensive alternative for the treatment of a variety of fatigue disorders. There are two possible hypotheses to explain how light therapy could potentially benefit cancer survivors with post-treatment CRF.

Circadian rhythm entrainment. To date, light therapy represents the most successful clinical application of the resynchronization of circadian rhythms (Monteleone, Martiadis, & Mario, 2011). Bright light therapy has demonstrated efficacy for a variety of circadian rhythm and fatigue disorders, such as seasonal and nonseasonal depression (Desan et al, 2007; Golden et al., 2005), delayed and advanced sleep phase syndromes (Terman et al., 1995), jet lag syndrome (Boulos et al., 1995), and shift work syndrome (Eastman et al., 1995). 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). As discussed earlier, in individuals with cancer it is hypothesized that there may be a dysregulation at some point in the circadian rhythm system (Roscoe et al., 2002; Ryan et al., 2007) that could potentially produce symptoms of fatigue. It is therefore possible that by providing a corrective phase advance through the use of early morning bright white light, as is recommended for seasonal depression, the circadian rhythm disruption could be corrected (Monteleone et al., 2011), and symptoms of fatigue reduced.

Improvements in mood. Research investigating the efficacy of light therapy for seasonal and nonseasonal depression has shown that bright light therapy has robust antidepressant effects (Terman & Terman, 2005; Terman, Terman, Lo, & Cooper, 2001). 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 by improving mood through the use of light therapy, there could also be simultaneous reductions in fatigue.

A recent 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., 2012). Patients completed baseline assessments of fatigue and quality of life prior to the start of chemotherapy, as well as at four time points throughout treatment (i.e., 3-week cycles of chemotherapy): 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 chemotherapy treatment, patients used 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, 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. Results of this trial 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 undergoing active treatment, the lack of deterioration in total fatigue during a period where symptoms typically worsen is encouraging.

Rationale for Current Study

Given that light is an important regulator of mood, circadian sleep rhythms, and certain biological systems (Eismann et al., 2010), it is hypothesized that through these pathways exposure to light may help improve symptoms of CRF. Although other treatment strategies, discussed earlier, have shown promising results for decreasing the impact of CRF on some aspects of functioning, not all patients benefit and many may be reluctant or incapable of making the required changes. One approach that has been demonstrated as a safe, inexpensive, and-easy to-administer alternative, is bright white light therapy. 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). Therefore, there is the potential for this therapy to provide additional benefits for cancer survivors that are still experiencing symptoms of fatigue. This study evaluates the effect a one-month treatment regime of morning exposure to either bright white light (BWL) or dim red light (DRL) on self-reported fatigue, mood disturbance, sleep quality, and quality of life in a sample of post-treatment cancer survivors.

Aims

Primary aim. The primary aim of this study is to evaluate the impact of BWL and DRL treatments on self-reported fatigue in individuals with post-treatment CRF.

Secondary aim. The secondary aims of this study are to investigate the effects of BWL and DRL treatments on subjective measures of mood disturbance, sleep quality, and quality of life in individuals with post-treatment CRF.

Hypotheses

Primary hypothesis. The primary hypothesis is that relative to DRL treatment, BWL treatment will be associated with greater improvements in self-reported fatigue.

Secondary hypotheses. The secondary hypothesis is that relative to DRL treatment, BWL treatment will be associated with greater improvements in subjective measures of mood disturbance, sleep quality, and quality of life.

Method

Trial Design

This was a 6-week double-blind randomized controlled trial comparing the effects of BWL and DRL on symptoms of fatigue, mood disturbance, sleep quality, and quality of life post-treatment CRF (Figure 2). Participants were assigned to one of the two treatment conditions using a 1:1 allocation ratio created by a random number generating computer program (Research Randomizer: www.randomizer.org) and block randomized in groups of two. This randomization sequence took place prior to the recruitment of participants by a research assistant not associated with the study. The light devices were stored in non-descriptive packaging without indication of the type of light they have been fitted with to ensure that both the investigators and participants were blinded to the treatment condition. All study procedures were reviewed and approved by the Conjoint Health Research Ethics Board at the University of Calgary in Calgary, Alberta and participants were required to provide written informed consent before taking part in the research study.

Participants

Participants included English-speaking men and women over the age of 18 years with non-metastatic cancer and treatment completion at least 3 months prior to participation in the study. Patients were required to meet the criteria for CRF as defined by the ICD-10 criteria (Appendix A; Cella et al., 1998). Exclusion criteria for this study included: anemia, being on active chemotherapy or radiotherapy, 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 Axis I disorder, excluding major depression and anxiety, the presence of a medical condition that may impact levels of fatigue (e.g., cystic fibrosis, HIV/AIDS), presence of eye disease or eye surgery within the last two weeks, conditions contraindicated to the use of light therapy or the use of photosensitizing medications, and pregnancy. Participants were not excluded for the use of hormone treatments or psychotropic medication (e.g., antidepressants, antipsychotics) provided that the dose had remained stable over the past 6 weeks.

Recruitment and Screening

Participants were recruited between February 2013 and June 2013. The primary means of recruitment was through self-referral. Participants were able to self-refer and were made aware of the study through: a) posted announcements and pamphlets available in the main areas of the Tom Baker Cancer Center, the Holy Cross Hospital, and community support groups (e.g., Wellspring, University of Calgary Thrive Center); b) information provided to patients at the "Energy to Fight Fatigue" education seminars held at the Holy Cross Hospital, the "Living With Cancer" seminar series held at the Foothills Hospital, and the "Sleep and Fatigue" workshops held at the University of Calgary's Thrive Center; c) referral by Tom Baker Cancer Center oncologists, psychiatrists, and nurses, as well as psychologists and social workers from the Department of Psychosocial Resources; d) information provided at community fundraising events (e.g., Relay for Life); and e) information posted on social media websites (e.g., Facebook, Kijiji Calgary). Patients were also able to obtain information about the research study on the study website (http://www.thelitestudy.ca) or by contacting the researcher by phone or email.

Individuals interested in study participation were contacted by phone, informed of the protocol and randomization design of the study, and were offered to be screened to determine if they were eligible. If interested, the researcher administered the Diagnostic Interview Guide for Cancer-Related Fatigue (P-ICD10), the Insomnia Screening Questionnaire (ISQ), and specific questions about medical history over the phone. If they were deemed as eligible, participants were invited to participate in the study and an appointment was scheduled to complete informed consent and baseline measures.

Equipment

The light therapy equipment used in this study was the Litebook Elite (The Litebook Company Ltd., Medicine Hat, Alberta, Canada) treatment device. The Litebook is a small (5" x 5" x 1") and lightweight (11 oz.) device that is designed to be placed on a table at an arm's length distance (12-24 inches) 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 contained 25 white light-emitting diode (LED) lights that emitted 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 contained 25 red LEDs that emitted red light at <400 lx (at 20 inches) and had a distribution of energy that was concentrated in the longer wavelengths of visible light (peak between 632-633 nanometers). For safety purposes, neither the BWL nor DRL Litebook devices emitted ultraviolet light. The devices were programmed to turn off after 30 minutes. Each Litebook was modified to include an integrated logger (HOBO State Data Logger, Onset Computer Corporation, Bourne, MA) that monitored adherence by recording the time and duration that the light device was on each day.

Measures

Screening tools. (Appendix B)

Cancer-related fatigue. The Diagnostic Interview Guide for Cancer-Related Fatigue (P-ICD10) was used to screen potential participants for CRF. This diagnostic interview is a 14-item structured interview derived from the ICD-10 diagnostic criteria for CRF (Cella et al., 1998). Participants were asked to answer whether the listed statements were true for them every day or nearly every day during the same 2-week period in the past month and respond to each question with a "yes" or "no". To be eligible for the study, each participant was required to meet at least 6 of the 11 criteria. The internal consistency and reliability of the items is adequate with a Cronbach's alpha coefficient of 0.82, 100% sensitivity, and 86% specificity compared to other validated instruments (i.e., Functional Assessment of Cancer Therapy Fatigue subscale and three visual analog scales; van Belle et al., 2005).

Sleep disorders. The Insomnia Screening Questionnaire (ISQ; Centre for Sleep and Human Performance, 2007) is a 17-item screening tool used as a guide in the clinical evaluation of insomnia and to screen for primary sleep disorders. Overall it is designed to assess the severity of sleep-onset and sleep maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, impairment attributed to the sleep problem, and degree of distress elicited. There are 6 diagnostic domains: insomnia, psychiatric disorders, circadian rhythm disorder, movement disorders, parasomnias, and sleep disordered breathing (i.e., sleep apnea). Participants were asked to report how often over the past month they had experienced the listed symptoms (1 = never, 5 = always) with a total possible score ranging from 17 to 85. Participants that indicated the presence of sleep disorders other than insomnia were excluded from participating in the study.

Medical history and demographics (Appendix D). The medical history and demographics questionnaire was administered at baseline assessment. This questionnaire was used to obtain patient demographic information (e.g., sex, age, ethnic background, education, marital status, current employment status), medical history (e.g., type of cancer, dates of diagnosis and treatment, types of treatment received), psychiatric history, and current medication use.

Depressive symptomatology. The Center for Epidemiological Studies – Depression (CES-D) is a 20-item measure developed to identify current depressive symptomatology related to major or clinical depression in adults and adolescents (Radloff, 1977). Domains include depressed mood, feelings of guilt, worthlessness and helplessness, psychomotor retardation, loss of appetite, and sleep difficulties. Patients are asked to self-report the frequency of occurrence of each symptom during the past week on a 4-point scale (0 = rarely or none of the time, 3 = most or all of the time). The total score ranges from 0 to 60, with higher scores representing greater depressive symptomatology. A score ≥16 is indicative of "significant" or "mild" depressive symptomatology.

Primary outcome measure.

Fatigue. The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF; Stein, Jacobsen, Blanchard, & Thors, 2004) was administered at baseline assessment, after each week of treatment, and at the post-treatment assessment. It is a 30-item comprehensive measure of the physical and psychological aspects of fatigue. This scale has 5 subscales: General, Physical, Emotional, Mental Fatigue, and Vigor. Each subscale includes six items rated on a five-point scale that specify how true the statement was during the last week (0 = not at all, 4 = extremely). The range of possible scores for each subscale is 0 to 24, with higher scores

indicating more severe fatigue, with the exception of the Vigor subscale where a higher score indicates less fatigue. The subscales are summed to obtain a total score that is within the range of -24 to 96, with a higher score indicating more severe fatigue. Normative data suggest a score above 0.85 indicates fatigue (Stein, Martin, Hann, & Jacobsen, 1998). The internal consistency of the scale ranges from .87 to .92 with test-retest reliabilities ranging from .51 to .70.

Secondary outcome measures.

Mood disturbance. Mood disturbance was measured using the Profile of Mood States-Short Form (POMS-SF; Shacham, 1983) at both baseline and post-treatment assessments. The POMS-SF is a 37-item scale that assesses six affective dimensions of mood: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Participants are asked to rate each adjective phrase that best describes their mood during the past week (0 = not at all, 4 = extremely). A total mood disturbance score can range from -24 to 124. The measure has demonstrated good internal consistency, Cronbach's alpha ranging from .80 to .91.

Insomnia symptom severity. Insomnia symptom severity was assessed using the Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001) at both baseline and post-treatment assessments. The ISI is a brief 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, and degree of distress elicited. Participants are asked to rate the current (i.e., last 2 weeks) severity of their insomnia problems on a 5 point scale (0 = none, 4 = very severe). A total score is calculated by summing scores for all seven items with a total score that can range from 0 to 28. This scale has been validated for use with cancer populations. Optimal cut-off scores include: 0-7 (no clinically significant

insomnia), 8-14 (subthreshold insomnia), 15-21 (presence of clinically significant insomnia; moderate severity), 22-28 (presence of clinically significant insomnia; severe) (Savard, Savard, Simard, & Ivers, 2005).

Sleep quality. The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds III, Monk, Berman, & Kupfer, 1989) was used to assess sleep quality at baseline and post-treatment. The PSQI is a 19-item self-report scale designed to assess sleep quality and disturbances over a one-month time period 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. The sum of these component scores yields a global score that can range from 0 to 21, with higher scores indicating worse sleep quality. A global PSQI score >5 yields a diagnostic sensitivity of 89.6% and specificity of 86.5% in good and poor sleepers. The seven component scores demonstrated an overall Cronbach's alpha of .83, indicating a high degree of internal consistency.

Quality of life. The Functional Assessment of Cancer Therapy- General & Fatigue (FACT-G & FACT-F; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997) questionnaires were used to assess quality of life at both baseline and post-treatment. The FACT-G is a 27-item general quality of life measure, while the FACT-F is a 13-item fatigue subscale. The FACT-G contains questions specific to cancer, its treatments, and symptoms. Participants are asked to indicate how true each statement has been for them in the past 7 days (0 = not at all, 4 = very much). It is comprised of four subscales: Physical Well-Being, Social Well-Being, Emotional Well-Being, and Functional Well-Being. Total scores on the FACT-G range from 0 to 108 with higher scores indicating better quality of life. The FACT-F is intended to assess the specific

concerns of individuals with fatigue. Possible scores on the FACT-F range from 0 to 52 with lower scores indicating greater fatigue.

Credibility of treatment and expectancy effects. The Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000) was used to assess participants' attitudes towards the treatment's credibility and expectancy for improvement in fatigue symptoms. The CEQ is a 6-item scale that can be broken up into two distinct factors, credibility and expectancy. The credibility factor focuses on cognitively-based beliefs about the treatment and is assessed with 3 items that measure 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. These three items are scored on a 9-point scale (1= not at all logical/useful/confident; 9 = very logical/useful/confident). Therefore, the total possible score on this subscale can range from 3 to 27. The expectancy factor focuses affectively-based beliefs about the treatment and is assessed with 3 items that measured 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. One of these items is scored on a 9-point scale (1 = not at all; 9 = very much), while the other two items are scored on an 11-point scale in 10% increments (0% to100%). The two items rated on an 11-point scale were standardized by combining the middle scores (i.e., 4,5,6) and forcing the raw scores onto a 9-point scale (Nock, Ferriter, & Holmberg, 2007). The total possible score on each subscale can range from 3 to 27. The CEQ was administered at both baseline and post-treatment to evaluate the impact of changes in expectancies during treatment with the word tense changed in the post-treatment questionnaire.

This scale has been shown to demonstrate high internal consistency and good test-retest reliability in adult clinical samples (Devilly & Borkovec, 2000).

Subjective sleep. A sleep log (Centre for Sleep and Human Performance, 2008) was used to calculate changes in subjective reports of number of awakenings (NWAK), wake after sleep onset (WASO), total sleep time (TST), napping frequency and duration, and subjective sleep quality from baseline to post-treatment. The log provides a night-by-night, self-report of sleep pattern and quality. The sleep log also contains questions that specifically ask the participant to rate their sleep quality each night on a scale of 0 (very poor) to 10 (very good).

Treatment adherence. A weekly Litebook usage log (Appendix E) was designed to track: 1) the number of minutes between waking and turning on the light; 2) the number of minutes the device was used each day; 3) the number of minutes that were spent away from the device while it was on; 4) activities that the participant was engaged in while using the light; 5) other comments about the light or its use. Participants filled out this log every day during the one-month treatment period. As described above, each Litebook was modified to include an integrated logger (HOBO State Data Logger, Onset Computer Corporation, Bourne, MA) that monitored adherence by recording the time and duration that the light device was on each day. The information from the logger was used to determine the exact number of minutes the device was on each day.

Intervention

Eligible participants met with the researcher at the Behavioural Medicine Laboratory at the University of Calgary where the study procedures were explained and written consent was obtained (Appendix C). They completed baseline self-report assessments of fatigue, mood, sleep quality, and quality of life. Once complete, they were instructed on how to track their sleep

pattern for 7 days using a sleep log and were scheduled to return to the lab on the same day the following week.

The participant returned to the Behavioural Medicine Lab after one week of tracking their sleep. After returning the sleep log, the participant was provided with a Litebook (BWL or DRL) according to their randomization assignment along with instructions for its use and a log to track its use. The researcher demonstrated how to use the device without turning it on, and instructed the participant to use the device as soon as possible after awakening for 30 minutes each morning for 4 weeks. The participant then completed the CEQ and an appointment was set to meet 4 weeks later.

Participants were contacted on a weekly basis to verbally complete the MFSI-SF fatigue assessment. After each weekly assessment, the researcher reminded the participant to continue to use the device daily for 30 minutes and answered any questions the participant had.

After 4 weeks of use, the participant returned to the Behavioural Medicine Laboratory to meet with the researcher, return the Litebook and light use diary, and completed post-treatment assessments of fatigue, mood disturbance, sleep quality, and quality of life, as well as the CEQ. The researcher then reviewed instructions on how to track sleep patterns for 7 days using a sleep log, and scheduled an appointment for the participant to return one week later. On their final visit, participants returned their sleep log and discussed the study design with the researcher.

Sample Size Calculation

The primary outcome of this study is self-reported fatigue, as measured by the MFSI-SF total score, administered on 5 different occasions (pre-treatment, weekly for 4 weeks during treatment, and post-treatment), and analyzed using linear mixed-effects models analyses. This analysis requires only 28 participants per group (Hedeker, Gibbons, & Waternaux, 1999).

A repeated-measures analysis of covariance (ANCOVA) was proposed to test secondary hypotheses on the self-report assessment items that are administered pre and post (i.e., sleep quality, quality of life, mood). Although BWL has been shown to prevent a worsening of fatigue during chemotherapy (Ancoli-Israel et al., 2012), no precedent has been set for the effectiveness of BWL on measures of sleep quality, quality of life, and mood in post-treatment cancer patients and has not been demonstrated to be more beneficial than other wavelengths of light, such as DRL. For this reason, 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, 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-assessments. With an estimated attrition rate of 20%, the number of participants required becomes 62 per group (124 total).

Data Analysis

To verify that the BWL and DRL groups were comparable on continuous and categorical demographic variables, depressive symptomatology, and all outcomes measures, a series of one-way (BWL vs. DRL) between subjects analysis of variance (ANOVA) and Pearson chi-squared tests were conducted. If between-group differences existed at baseline, such differences were adjusted for statistically in subsequent analyses. Missing data points from all outcome measures were replaced with pro-rated values determined from the participant's mean score for the subscale containing the missing value if no more than 80% of the subscale was missing (FACIT manual, 1997).

Given the small sample size, the proposed linear mixed-effects models analysis was not conducted to test the primary hypothesis. Alternatively, to evaluate the impact of light therapy on self-reported fatigue, as well as self-reported mood disturbance, sleep quality, quality of life, and

credibility and expectancy, a series of mixed design repeated measures analyses of variance (RM-ANOVAs) were conducted, with Group as the between-subjects factor (BWL vs. DRL), and Time as the within-subjects factor (Baseline vs. Post-treatment). Effect sizes (Cohen's d) were calculated using means and standard deviations. All data analyses were carried out using SPSS for Windows Version 19.0.

Results

Recruitment and Sample Characteristics

Out of 22 potential participants screened for eligibility, a total of 8 participants were randomized to either BWL (n = 4) or DRL (n = 4) (Figure 2). The majority of participants were women (75%) and currently on disability (62.5%). Patients ranged in age from 35 to 74 with a mean age of 56.6 (SD = 11.4) years. The amount of time since last cancer treatment ranged from 3 months to 5.4 years, with an average of 25.5 (SD = 26.08) months. Mean scores on the CES-D were above the cutoff (i.e., total score ≥16) for both the BWL group (M = 19.0, SD = 14.3) and the DRL group (M = 22.5, SD = 11.0). Participant characteristics by group are presented in Table 1 and Table 2. All participants completed baseline and post-treatment measures, with one participant unable to complete the sleep log at the post-treatment assessment.

A series of one-way between-subjects ANOVAs indicated no baseline differences on any of the continuous demographic variables (e.g., age, years of education) between participants in the BWL and DRL groups. Pearson chi-square analyses revealed no baseline differences between the BWL and DRL groups on categorical demographic variables (e.g., marital status, employment status).

Treatment Adherence

Mean values of light use by intervention group are presented in Table 3. One-way ANOVAs revealed no difference in the mean number of minutes the lights were used each day between the BWL group (M = 26.83, SD = 6.61) and the DRL group (M = 30.73, SD = 4.58), $F(1,6) = .94$, $p = .369$. There were also no group differences in the average number of minutes between awakening and turning on the light, $F(1,5) = 1.75$, $p = .244$, the average number of minutes spent away from the light, $F(1,6) = .99$, $p = .359$, or the average number of days the light was on for, $F(1,6) = .554$, $p = .485$. Common activities reported by patients while using the light included: using the computer (e.g., reading, checking email), reading the newspaper, drinking coffee, eating breakfast, listening to the radio, or sitting in silence.

Adverse Effects

No adverse reactions to either the bright white light or dim red light were reported. One participant in the bright white light group reported some discomfort when exposed to natural sunlight soon after using the light for the recommended duration during the first week of use. The researcher reminded the participant that they were able to discontinue use if they felt that this symptom was too much of a burden. After the participant indicated that they wanted to continue to use the light, the researcher recommended waiting a longer period of time after using the light to be exposed to natural sunlight, to continue using eye protection when exposed to natural sunlight, and to discontinue use if any other physical symptoms occur (i.e., headache) or if it becomes painful. After the first week of use, the participant reported that using the light no longer had this negative effect, and they continued to use the light.

Primary Outcome Measure

Fatigue. Results from the mixed design RM-ANOVA revealed that from baseline to post-treatment assessment, there was a main effect of time, $F(1,6) = 8.89$, $p = .025$, $d = 0.90$,

such that both groups showed improvements in fatigue. There was no main effect of group, $F(1,6) = .04$, $p = .844$, and no Time x Group interaction, $F(1,6) = .02$, $p = .906$. The observed reduction in overall fatigue symptoms is presented in Figure 3. Upon analysis if the MFSI-SF subscales, it was determined that there was a main effect of time for general fatigue symptoms, $F(1,6) = 8.28$, $p = .028$, $d = 1.13$, physical fatigue symptoms, $F(1,6) = 6.89$, $p = .039$, $d = 0.73$, and mental fatigue symptoms, $F(1,6) = 23.80$, $p = .003$, $d = 0.65$, from baseline to post-treatment. There were no main effects of time for the emotional subscale, $F(1,6) = 1.75$, $p = .234$, $d = 0.53$, or the vigor subscale, $F(1,6) = 1.82$, $p = .226$, $d = -0.53$, from baseline to post-treatment. There were no group effects and no significant Time x Group interactions detected on any of the subscales. Means and standard deviations for the total score and subscales by treatment group are reported in Table 4.

Secondary Outcome Measures

Mood disturbance. Results from the mixed design RM-ANOVA revealed no main effect of time from baseline to post-treatment, $F(1,6) = 2.99$, $p = .135$, $d = 0.71$, no main effect of group, $F(1,6) = .05$, $p = .829$, and no Time x Group interaction, $F(1,6) = .02$, $p = .900$. There was, however, a main effect of time on the confusion-bewilderment subscale from baseline to post-treatment, $F(1,6) = 9.15$, $p = .023$, $d = 0.62$, such that both groups showed improvements overtime. There were no other time effects, group effects, or Time x Group interactions observed for any of the mood disturbance subscales. Means and standard deviations for the total score and subscales by treatment group are reported in Table 5.

Insomnia symptom severity. The outcome from the mixed design RM-ANOVA showed no main effect of time, $F(1,6) = 1.14$, $p = .327$, $d = 0.35$, no main effect of group, $F(1,6) = 1.14$,

p = .326, and no Time x Group interaction, $F(1,6)$ = .41, p = .546 (Figure 4). Means and standard deviations by treatment group are reported in Table 6.

Sleep quality. A mixed design RM-ANOVA analysis revealed main effect of time for overall self-reported sleep quality from baseline to post-treatment, $F(1,6)$ = 12.27, p = .013, d = 0.62 (Figure 5), such that both groups showed improved sleep quality over time. There was no significant main effect of group, $F(1,6)$ = .003, p = .957, and there was no Time x Group interaction $F(1,6)$ = 1.36, p = .287. Means and standard deviations by treatment group are reported in Table 6.

Quality of life. Results from a mixed design RM-ANOVA revealed a marginal main effect if time for overall general quality of life from baseline to post-treatment, $F(1,6)$ = 5.76, p = .053, d = -0.44, but no main effect of group, $F(1,6)$ = .01, p = .920, and no Time x Group interaction, $F(1,6)$ = .07, p = .796. Analysis of the subscales revealed main effects of time for physical wellbeing, $F(1,6)$ = 9.50, p = .022, d = -0.56, and emotional wellbeing, $F(1,6)$ = 22.22, p = .003, d = -0.57. Main effects of time were not observed in the social/family wellbeing subscale, $F(1,6)$ = .003, p = .957, d = 0.01, or functional wellbeing subscale, $F(1,6)$ = 2.79, p = .146, d = -0.49. There were no main effects of group for any of the general quality of life subscales, nor were there any Time x Group interactions. Analysis of the fatigue specific subscale revealed no main effect of time from baseline to post-assessment, $F(1,6)$ = 4.15, p = .088, d = -0.62, nor was there a main effect of group, $F(1,6)$ = .57, p = .479. There was also no Time x Group interaction, $F(1,6)$ = 5.06, p = .741. Means and standard deviations of the total score and subscale are reported by group in Table 7.

Sleep log. Results of a series of mixed design RM-ANOVAs indicated a main effect of group for number of awakenings, $F(1,5)$ = 12.15, p = .018 , such that the DRL group had more

awakenings than the BWL group. There was no main effect of time nor was there a Time x Group interaction for number of awakenings. There were also no main effects of time, main effects of group, or Time x Group interactions from baseline to post-treatment for wake after sleep onset, total sleep time, frequency or duration of naps, or average sleep quality rating. Means and standard deviations of the total score and subscale are reported by group in Table 6.

Credibility and Expectancy

Mixed design RM-ANOVAs revealed no main effect of time for treatment credibility from baseline to post-treatment, $F(1,6) = 4.08$, $p = .09$, $d = 0.90$, no main effect of group, $F(1,6) = .11$, $p = .753$, and no Time x Group interaction, $F(1,6) = .45$, $p = .526$. Similar analyses revealed no main effect of time for treatment expectancy from baseline to post-treatment, $F(1,6) = 3.84$, $p = .098$, $d = 0.86$, no main effect of group, $F(1,6) = .64$, $p = .642$, and no Time x Group interaction, $F(1,6) = .14$, $p = .724$. Means and standard deviations by group are reported in Table 8.

Discussion

This was the first study to examine the effects of a one-month light therapy treatment regime on self-reported measures of fatigue, mood disturbance, sleep quality, and quality of life in a sample of post-treatment cancer survivors with CRF. The main finding of the study is that self-reported fatigue decreased in both the BWL group and DRL group after the one-month treatment period. Further investigation into the specific subscales of the fatigue measure showed decreases in general fatigue, physical fatigue, and mental fatigue from baseline to post-treatment for both groups. Previous research examining the use of light therapy for fatigue in cancer patients undergoing active chemotherapy, a period when fatigue symptoms typically worsen, showed no change in fatigue levels from baseline for the BWL condition (Ancoli-Israel et al.,

2012). In this study, it was hypothesized that in a sample of post-treatment survivors, participants in the BWL treatment condition would show greater improvements in symptoms of fatigue than those in the DRL condition. Although the outcome of this study did not support the hypothesis, the overall decline in fatigue after only one month of light treatment is encouraging.

Participants in both groups also showed improvements in overall sleep quality, the confusion-bewilderment subscale of the mood disturbance measure, physical and emotional wellbeing subscales of the general quality of life measure, and marginal improvements in overall general quality of life (FACT-G Total Score). There were no improvements in fatigue-specific quality of life, though the effect sizes ranged from medium for the BWL group to large for the DRL group. Analysis of insomnia symptom severity revealed a medium effect for the BWL group along with a clinically meaningful decline in insomnia symptom severity from baseline to post-treatment, while the DRL group remained relatively unchanged (Figure 4). Theoretically this outcome provides evidence for the hypothesis that light therapy may address problems of fatigue through the entrainment of the circadian rhythm system. Insomnia is typically characterized by longer sleep onset latency, early morning awakenings, and terminal wakefulness, so repeated exposure to light early in the biological day may lead to advances in activity onset and phase-shifting (Czeisler & Gooley, 2007), subsequently mitigating symptoms of insomnia (e.g., sleep onset insomnia) and in turn reducing fatigue. Unfortunately, both the BWL and DRL group exhibited decreases in symptoms of fatigue, while only the BWL group showed a clinically meaningful decline in insomnia symptom severity.

There are several potential explanations to describe why both groups showed reductions in both the primary and secondary outcomes, and not just the BWL group. First, given that these analyses are underpowered as a result of the small sample size, it is possible that these changes

over time may be better explained by Time x Group interactions. For example, it is possible that one group is showing greater improvements than the other at any given time point, but because the tests are underpowered, these interactions cannot be detected. Second, given that participants were not provided specific information about the two types of light, only that two different wavelengths were being tested, it is possible that the decreases in the outcome measures observed in the DRL condition were the result of a placebo effect, such that participants believed that the light was improving their symptoms, though it may not have had any actual benefit. There is also the potential that the DRL is indeed having a real effect on the outcomes of interest, as even dim light has been shown to have an effect on the circadian system (Brainard et al., 1988). Although the DRL produces light at a lower lux than the BWL (<400lx) and at a longer wavelength (~650 nm) to which the circadian system is not particularly sensitive (Thapan, Arendt, & Skene, 2001), it is important to note that the DRLs in this study produced light at just under 400 lx, a level that is much higher than that reported in a previous trial (i.e., <50 lx; Ancoli-Israel et al., 2012) which may be accounting for the outcomes observed in the DRL group. Finally, it is also plausible that the observed improvements over time are a result of seasonal changes in available daylight, and not exposure to the lights provided. At the start of this trial, it was apparent that the time of year the study was being conducted would need to be addressed as a potential confounding variable. More specifically, the trial began in February 2013, approximately one month after the winter solstice (December 21, 2012) when daylight levels are at their lowest, and ended in June 2013 at the time of the summer solstice (June 21, 2013) when daylight levels are at their peak. It is possible that with the increasing amount of available daylight, both in terms of intensity and duration that occurred concurrently with the use of the Litebooks, it may be these seasonal changes in daylight that account for the observed

improvements in both groups. Though it has not been determined whether CRF is affected by seasonality, it's consistent association with greater depressive symptomatology and depression may result in varying degrees of seasonal fatigue among those who suffer from CRF.

Overall adherence to the treatment in this study was much greater than anticipated. In a previous trial of light therapy for fatigue (Ancoli-Israel et al., 2012), the light devices were used during only 50% of the recommended days. In the present study, adherence was measured both by self-report, as well as by built-in logger devices. On average, participants used the light on >90% of the recommended days, and for just under the recommended 30-minute duration, with no difference in light use between groups. Participant self-report of light use was generally consistent with objective logger data, except in one case where the participant underreported her light use. That is, the participant self-reported using the light for the recommended 30 minutes, but the logger recorded the light being on for over an hour on several days during the first week of treatment. The high rate of treatment adherence in this study could be a result of the demographic characteristics of the sample. More specifically, given that 7 of the 8 participants were either on disability or retired, it is possible that they had more time to dedicate to using the light each morning. Also, unlike the trial conducted by Ancoli-Israel and colleagues (2012), this sample was not undergoing active chemotherapy and therefore did not have the burden of treatment-related physical symptoms that could have acted as a barrier to light therapy adherence. Finally, the research protocol employed may also have facilitated compliance with the treatment. When participants were provided with the Litebook, the researcher went over in detail how to use the light, how to track its use, and discussed with participants their plan for using the light each morning (e.g., How did they think light use will fit into their morning routine? What activities do they normally engage in each morning?). It was also highlighted that

there was a logging device attached to the Litebook that would track the date and duration the light was turned on. Additionally, participants were contacted weekly to discuss their light use and any issues or barriers to its use.

Although treatment adherence remained very high throughout the duration of the study, treatment credibility and expectancy showed large decrements from baseline to post-treatment for both groups, though they were not statistically significant. Credibility is defined as "how believable, convincing, and logical the treatment is," while expectancy is defined as "improvements that clients believe will be achieved" (Kazdin, 1979, p. 82). The CEQ, used to measure treatment credibility and expectancy for improvement, was completed at two time points, once before the participants took the Litebook home and again when they returned the Litebook one month later. The decline in credibility and expectancy for the BWL group were characterized by large effect sizes (d >1.0), while the DRL group showed medium effect sizes (d >.6). The discrepancy between reported improvements on a number of the outcome measures and decreased credibility and expectancy was unexpected. Perhaps inclusion of follow-up questions about patient perceptions of the treatment would have helped to determine what may be causing this decline in credibility and expectancy.

Recruitment of participants for this study proved more difficult than initially anticipated. Though this study was conducted in close proximity to the Tom Baker Cancer Centre, a major Canadian cancer center, the passive recruitment methods employed were not successful at recruiting a high volume of potential participants. The most effective method of informing potential participants of this trial were through posters and pamphlets displayed at Wellspring Calgary, a community-based charity that provides resources and programs for people living with cancer, and through in-person advertising that took place at education seminars for cancer

survivors. It was apparent that in-person contact was important for this population, as many of the participants had met one or more persons on the research team before they were screened for eligibility. Another barrier to recruitment could be that this is a population that spends more of their time at home than out in the community. Given that the majority of participants in this sample were on disability and potentially spending a large proportion of time at home, it is possible that the passive recruitment methods employed were not targeting the correct demographic.

Strengths

The key strength of this study was its design. The double-blind, randomized design resulted in two groups that were equivalent at baseline on demographic and baseline measures, and equal in sample size. Participants were blinded to the treatment conditions until they returned their Litebook and completed a post-treatment sleep log, and the researcher was blinded to all participant treatment allocations until all data was collected, entered, and checked to prevent any bias in scoring. Another notable strength was the retention rate of participants. None of the participants that had consented and were randomized dropped out of the study. Only one participant was unable to complete the post-treatment sleep diary due to an urgent medical issue. Additionally, there were very little missing data which may be attributable to having each participant come into the laboratory to fill out questionnaires in person, rather than have them fill them out and mail them back. This allowed the researcher to answer any questions about the items and also scan the questionnaire for missed items before the participant left. The questionnaires were also formatted to aid in readability and to help prevent missed pages (e.g., single sided, alternating shaded rows).

Limitations

The key limitation of this study is the small sample size. With a sample size of $N = 8$, the results of the analyses are considerably underpowered and therefore definitive statements about treatment effectiveness are not possible. Even with this small sample, however, there were several notable outcomes that produced medium to large effect sizes when comparing baseline to post-treatment values, though they should be interpreted with caution. Another key limitation, discussed above, is the confounding effect of the time of year the study was conducted. Given that light exposure was the independent variable of interest, and that a simultaneous increase in available daylight occurred with the treatment, it is unclear to what degree the observed changes in the outcome measures can be attributed to light exposure from the Litebooks versus natural daylight.

Future Research

The preliminary nature of this study provides many advantages for the planning of a larger upcoming trial. First, given the issues with recruitment, it is apparent that all avenues to reach the population of interest must be explored, including a detailed and wide-reaching media release and the use of the Alberta Cancer Registry. As discussed above, many participants in this study were on disability, so it is possible that the passive methods of recruitment employed to date (i.e., posters and pamphlets) may not effectively reach the target population. Second, depressive symptomatology was only measured at baseline to characterize the sample. Including a post-treatment measure of depressive symptomatology would provide more information about how depressive symptoms change over the course of treatment and may provide additional information about the potential mediating effects of depression on symptoms of fatigue. Third, the sleep diary used in this study did not provide adequate information about sleep onset latency or time in bed, therefore sleep efficiency could not be calculated. Using a measure that

encompasses other relevant characteristics of sleep would provide a more detailed representation of change in sleep patterns and would complement objective measures of sleep (i.e., actigraphy). Additionally, the post-treatment sleep diary should be administered during the final week of light use rather than during the week following treatment termination as it is unclear how long potential treatment effects last after treatment is ceased. Finally, the randomization sequence used in this study (i.e., blocks of two) is not recommended as the potential to break the code of randomization is greater than with larger blocks (e.g., blocks of 8; Schulz, 1995). This method was employed in an attempt to achieve equal sample sizes in each group as it was unknown how many participants could be recruited in the amount of time available. The full trial should use random blocks of 2, 4, and 6, to prevent potential bias due to breaks in randomization code (Moher et al., 2010).

Conclusion

At the end of this 6-week randomized, double-blind controlled trial, participants in both the BWL and DRL treatments groups exhibited reductions in fatigue and confusion, as well as improvements in sleep quality and quality of life. Given the small sample size and the time of year the study was conducted, the analyses were underpowered and potentially confounded, so results should be interpreted with caution.

Table 1

Demographic Characteristics by Intervention Group

	Intervention Group			
	BWL (*n* = 4)	**DRL (*n* = 4)**		**Total (*N* = 8)**
	M(SD) or n(%)	M(SD) or n(%)	*p-value*	M(SD) or n(%)
Age (years)	56.8 (4.2)	56.5 (16.9)		56.6 (11.4)
Range	51-61	35-74	.978	35-74
Education (years)	16.5 (4.7)	15.5 (2.7)		16.0 (3.6)
Range	12-23	13-19	.722	12-23
Sex				
Female	3 (75)	3 (75)		6 (75)
Male	1 (25)	1 (25)	1.00	2 (25)
Marital Status				
Single	2 (50)	1 (25)		3 (37.5)
Married	1 (25)	2 (50)		3 (37.5)
Divorced	1 (25)	1 (25)	.717	2 (25)
Employment Status				
Disability	3 (75)	2 (50)		5 (62.5)
Retired	0 (0)	2 (50)		2 (25)
Full-time	1 (25)	0 (0)	.202	1 (12.5)

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

Table 2

Disease, Treatment, and Depressive Symptomatology Characteristics by Intervention Group

	Intervention Group			
	BWL (*n* = 4)	**DRL (*n* = 4)**		**Total (*N* = 8)**
	M(SD) or n(%)	M(SD) or n(%)	*p-value*	M(SD) or n(%)
Months since diagnosis	26.8 (18.3)	39.8 (31.2)		33.3 (24.7)
Range	15-54	13-72	.499	13-72
Months since last treatment	17.5 (20.6)	33.5 (31.5)		25.5 (26.1)
Range	3-48	3-65	.428	3-65
Cancer Location				
Colorectal	2 (50)	1 (25)		3 (37.5)
Head and Neck	1 (25)	1 (25)		2 (25)
Breast	1 (25)	1 (25)		2 (25)
Cervical	0 (0)	1 (25)	.712	1 (12.5)
Previous Treatments				
Surgery	3 (75)	4 (100)	.285	7 (87.5)
Chemotherapy	3 (75)	3 (75)	1.00	6 (75)
Radiotherapy	3 (75)	3 (75)	1.00	6 (75)
Hormonal	1 (25)	0 (0)	.285	1 (12.5)
Current Treatments				
Antidepressants	2 (50)	2 (50)	1.00	4 (50)
Stimulants	0 (0)	1 (25)	.285	1 (12.5)
TSH	0 (0)	3 (75)	.028	3 (37.5)
Depressive Symptomatology				
CES-D Total Score	19.0 (14.3)	22.5 (11.0)	.711	20.8 (12.0)

Note. BWL = bright white light; CES-D = Center for Epidemiological Studies – depression; DRL = dim red light; TSH = thyroid stimulating hormone.

Table 3

Litebook Use During Treatment Period by Intervention Group

Measure	Intervention Group		Total
	BWL	DRL	
	M(SD)	M(SD)	M(SD)
Average Time On (mins)			
Week 1	30.1 (0.3)	33.4 (13.0)	31.8 (8.7)
Week 2	22.6 (15.0)	30.8 (1.1)	26.7 (10.8)
Week 3	26.0 (8.9)	28.4 (5.4)	27.2 (6.9)
Week 4	28.2 (3.5)	30.3 (0.2)	29.3 (2.6)
Total	26.8 (6.6)	30.7 (4.6)	28.8 (5.7)
Average Until Start (mins)			
Week 1	18.4 (7.9)	30.6 (26.2)	23.6 (17.4)
Week 2	22.1 (22.6)	31.9 (19.9)	27.0 (19.8)
Week 3	11.3 (8.6)	26.4 (11.2)	17.8 (12.0)
Week 4	14.2 (9.2)	34.0 (20.4)	22.7 (17.1)
Total	15.8 (11.0)	30.8 (19.3)	22.2 (15.8)
Average Time Away (mins)			
Week 1	0.4 (0.7)	0.1 (0.2)	0.2 (0.5)
Week 2	0.0 (0.0)	0.4 (0.7)	0.2 (0.5)
Week 3	0.3 (0.7)	0.0 (0.1)	0.2 (0.5)
Week 4	0.4 (0.6)	0.2 (0.4)	0.3 (0.5)
Total	1.0 (2.0)	0.0 (0.0)	0.5 (1.4)
Average Days Used			
Week 1	7.0 (0.0)	6.5 (1.0)	6.8 (0.7)
Week 2	5.3 (3.5)	7.0 (0.0)	6.1 (2.5)
Week 3	6.0 (2.0)	6.8 (0.5)	6.4 (1.4)
Week 4	7.3 (0.5)	7.5 (1.0)	7.4 (0.7)
Total	25.5 (5.7)	27.8 (2.1)	26.6 (4.1)

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

Table 4

Statistical Details of the Mixed Design Repeated Measures Analysis of Variance Assessing the Effect of Time and Group on Fatigue Outcomes

Outcome	Group	Assessment Time Mean (SD)		Effect Size Cohen's d	RM-ANOVA F (df) [p]		
		Baseline	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
MFSI							
Total Score*	BWL	45.75 (34.29)	23.75 (32.62)	0.66	8.89 (1,6)	.04 (1,6)	.02 (1,6)
	DRL	41.50 (11.33)	21.25 (13.65)	1.61	[.025]*	[.844]	[.906]
General*	BWL	17.25 (7.89)	10.25 (8.26)	0.87	8.28 (1,6)	.85 (1,6)	.000 (1,6)
	DRL	20.75 (2.22)	13.75 (5.25)	1.74	[.028]*	[.393]	[1.00]
Physical*	BWL	10.25 (7.93)	5.50 (6.46)	0.66	6.89 (1,6)	.15 (1,6)	.24 (1,6)
	DRL	8.00 (4.97)	4.75 (2.50)	0.83	[.039]*	[.708]	[.640]
Emotional	BWL	9.00 (7.12)	5.50 (4.80)	0.58	1.75 (1,6)	.09 (1,6)	.13 (1,6)
	DRL	7.25 (5.12)	5.25 (4.65)	0.41	[.234]	[.772]	[.730]
Mental*	BWL	16.25 (8.06)	12.00 (10.10)	0.47	23.80 (1,6)	.42 (1,6)	.26 (1,6)
	DRL	13.50 (4.44)	8.25 (4.79)	1.14	[.003]*	[.542]	[.626]
Vigor	BWL	7.00 (4.97)	9.50 (7.59)	-0.39	1.82 (1,6)	.12 (1,6)	.004 (1,6)
	DRL	8.00 (4.69)	10.75 (2.87)	-0.71	[.226]	[.738]	[.951]

Note. N=8 (BWL n=4; DRL n=4). BWL = bright white light; DRL = dim red light; MFSI = multidimensional fatigue symptom inventory; RM-ANOVA = repeated measures analysis of variance.

*p <.05.

Table 5

Statistical Details of the Mixed Design Repeated Measures Analysis of Variance Assessing the Effect of Time and Group on Mood Disturbance Outcomes

Outcome	Group	Assessment Time Mean (SD)		Effect Size Cohen's d	RM-ANOVA F (df) [p]		
		Baseline	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
POMS-SF							
Total Score	BWL	45.75 (42.82)	22.75 (40.57)	0.55	2.99 (1,6)	.05 (1,6)	.02 (1,6)
	DRL	48.50 (22.13)	28.75 (16.11)	1.02	[.135]	[.829]	[.900]
Depression-Dejection	BWL	10.75 (11.35)	6.25 (8.02)	0.46	3.38 (1,6)	.02 (1,6)	.02 (1,6)
	DRL	10.50 (6.25)	5.25 (2.99)	1.07	[.116]	[.901]	[.892]
Vigor-Activity	BWL	7.25 (6.85)	10.50 (8.35)	-0.43	1.48 (1,6)	.27 (1,6)	.41 (1,6)
	DRL	4.00 (2.71)	5.00 (1.83)	-0.43	[.270]	[.268]	[.544]
Anger-Hostility	BWL	10.75 (9.22)	7.50 (5.32)	0.43	1.64 (1,6)	1.46 (1,6)	.07 (1,6)
	DRL	8.25 (5.38)	3.25 (1.71)	1.25	[.247]	[.272]	[.795]
Tension-Anxiety	BWL	7.50 (6.25)	4.25 (4.99)	0.57	1.46 (1,6)	.16 (1,6)	.41 (1,6)
	DRL	8.00 (7.35)	7.00 (6.38)	0.15	[.273]	[.705]	[.546]
Confus.-Bewilder.*	BWL	10.25 (5.85)	7.00 (7.07)	0.50	9.15 (1,6)	.01 (1,6)	.01 (1,6)
	DRL	10.00 (6.06)	6.50 (4.20)	0.67	[.023]*	[.929]	[.914]

Outcome	Group	Assessment Time Mean (SD)		Effect Size Cohen's d	RM-ANOVA F (df) [p]		
		Baseline	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
Fatigue-Inertia	BWL	13.75 (7.50)	8.25 (8.26)	0.70	2.77 (1,6)	.572 (1,6)	.07 (1,6)
	DRL	15.75 (5.06)	11.75 (4.57)	0.83	[.147]	[.478]	[.802]

Note. N=8 (BWL n=4; DRL n=4). BWL = bright white light; DRL = dim red light; POMS-SF = profile of mood states – short form; RM-ANOVA = repeated measures analysis of variance.

*p <.05.

Table 6

Statistical Details of the Mixed Design Repeated Measures Analysis of Variance Assessing the Effect of Time and Group on Sleep Quality Outcomes

Outcome	Group	Assessment Time Mean (SD)		Effect Size Cohen's d	RM-ANOVA F (df) [p]		
		Baseline	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
ISI Total Score[a]	BWL	12.00 (10.10)	8.00 (4.83)	0.51	1.14 (1,6)	1.14 (1,6)	.41 (1,6)
	DRL	15.25 (6.24)	14.25 (6.13)	0.16	[.409]	[.326]	[.546]
PSQI Total Score[a]*	BWL	10.25 (4.43)	7.75 (3.86)	0.60	12.27 (1,6)	.003 (1,6)	1.36 (1,6)
	DRL	9.75 (2.06)	8.50 (1.92)	0.63	[.013]*	[.957]	[.287]
Sleep Log[b]							
NWAK*	BWL	0.22 (0.36)	0.47 (0.67)	-0.47	.00 (1,5)	12.15 (1,5)	.54 (1,5)
	DRL	1.90 (1.23)	1.66 (0.08)	0.28	[.998]	[.018]*	[.497]
WASO (mins)	BWL	6.83 (8.91)	22.86 (27.99)	-0.77	1.13 (1,5)	6.34 (1,5)	.49 (1,5)
	DRL	44.49 (26.43)	47.62 (5.01)	-0.17	[.336]	[.053]	[.517]
TST (mins)	BWL	7.64 (0.98)	7.22 (0.48)	0.54	1.50 (1,5)	.04 (1,5)	.54 (1,5)
	DRL	7.74 (2.75)	7.63 (2.12)	0.05	[.275]	[.844]	[.496]
Number of naps	BWL	0.57 (0.42)	0.57 (0.45)	0.00	.00 (1,5)	3.27 (1,5)	.00 (1,5)
	DRL	0.14 (0.15)	0.14 (0.15)	0.00	[1.00]	[.130]	[1.00]

Outcome	Group	Assessment Time Mean (SD)		Effect Size Cohen's d	RM-ANOVA F (df) [p]		
		Baseline	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
Duration of naps (mins)	BWL	75.80 (63.82)	84.64 (65.38)	-0.14	.02 (1,5)	4.19 (1,5)	.11 (1,5)
	DRL	12.62 (11.87)	9.28 (8.11)	0.33	[.887]	[.096]	[.755]
Sleep quality	BWL	6.83 (2.50)	6.87 (2.64)	-0.02	.04 (1,5)	.96 (1,5)	.08 (1,5)
	DRL	5.46 (1.11)	5.24 (0.93)	0.22	[.845]	[.384]	[.790]

Note. [a]N=8 (BWL n=4; DRL n=4); [b]N=7 (BWL n=4; DRL n=3). BWL = bright white light; DRL = dim red light; ISI = insomnia severity index; NWAK = number of awakenings; PSQI = pittsburgh sleep quality index; RM-ANOVA = repeated measures analysis of variance; TST = total sleep time; WASO = wake after sleep onset.

*p <.05.

Table 7

Statistical Details of the Mixed Design Repeated Measures Analysis of Variance Assessing the Effect of Time and Group on Quality of Life Outcomes

Outcome	Group	Assessment Time Mean (SD)		Effect Size Cohen's d	RM-ANOVA F (df) [p]		
		Baseline	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
FACT-G							
Total Score	BWL	60.92 (21.46)	69.75 (26.01)	-0.37	5.76 (1,6)	.01 (1,6)	.07 (1,6)
	DRL	60.42 (13.75)	69.75 (13.48)	-0.69	[.053]	[.920]	[.796]
Physical*	BWL	17.00 (7.53)	19.25 (6.90)	-0.31	9.50 (1,6)	.63 (1,6)	.45 (1,6)
	DRL	13.50 (2.38)	17.00 (1.41)	-1.79	[.022]*	[.458]	[.528]
Social	BWL	17.92 (7.36)	17.00 (8.41)	0.12	.003 (1,6)	.33 (1,6)	.60 (1,6)
	DRL	20.42 (9.41)	21.21 (8.38)	-0.09	[.957]	[.587]	[.469]
Emotional*	BWL	15.00 (4.32)	18.25 (5.12)	-0.69	22.22 (1,6)	.01 (1,6)	2.00 (1,6)
	DRL	16.00 (5.16)	17.75 (4.11)	-0.38	[.003]*	[.942]	[.207]
Functional	BWL	11.00 (3.92)	15.25 (7.50)	-0.71	2.79 (1,6)	.40 (1,6)	1.07 (1,6)
	DRL	10.50 (4.66)	11.50 (4.12)	-0.23	[.146]	[.551]	[.341]
FACT-F							
Total Score	BWL	20.50 (15.46)	28.25 (14.08)	-0.52	4.15 (1,6)	.57 (1,6)	.12 (1,6)
	DRL	16.25 (4.35)	21.75 (5.91)	-1.06	[.088]	[.479]	[.741]

Note. N=8 (BWL n=4; DRL n=4). BWL = bright white light; DRL = dim red light; FACT-G = functional assessment of cancer therapy – general; FACT-F = functional assessment of cancer therapy - fatigue; RM-ANOVA = repeated measures analysis of variance.

*p <.05.

Table 8

Statistical Details of the Mixed Design Repeated Measures Analysis of Variance Assessing the Effect of Time and Group on Credibility and Expectancy Outcomes

		Assessment Time		**Effect Size**	**RM-ANOVA**		
		Mean (SD)		Cohen's d	F (df) [p]		
Outcome	**Group**	**Baseline**	**Post-Treatment**	**Baseline to Post-Treatment**	**Time Effect**	**Group Effect**	**Time*Group Interaction**
CEQ							
Credibility	BWL	24.00 (1.41)	18.00 (8.04)	1.04	4.08 (1,6)	.11 (1,6)	.45 (1,6)
	DRL	21.50 (1.92)	18.50 (6.56)	0.62	[.090]	[.753]	[.526]
Expectancy	BWL	16.50 (2.38)	10.75 (7.50)	1.03	4.66 (1,6)	.22 (1,6)	.11 (1,6)
	DRL	14.00 (4.83)	9.75 (8.30)	0.63	[.074]	[.655]	[.757]

Note. N=8 (BWL n=4; DRL n=4). BWL = bright white light; CEQ = credibility expectancy questionnaire; DRL = dim red light; RM-ANOVA = repeated measures analysis of variance.

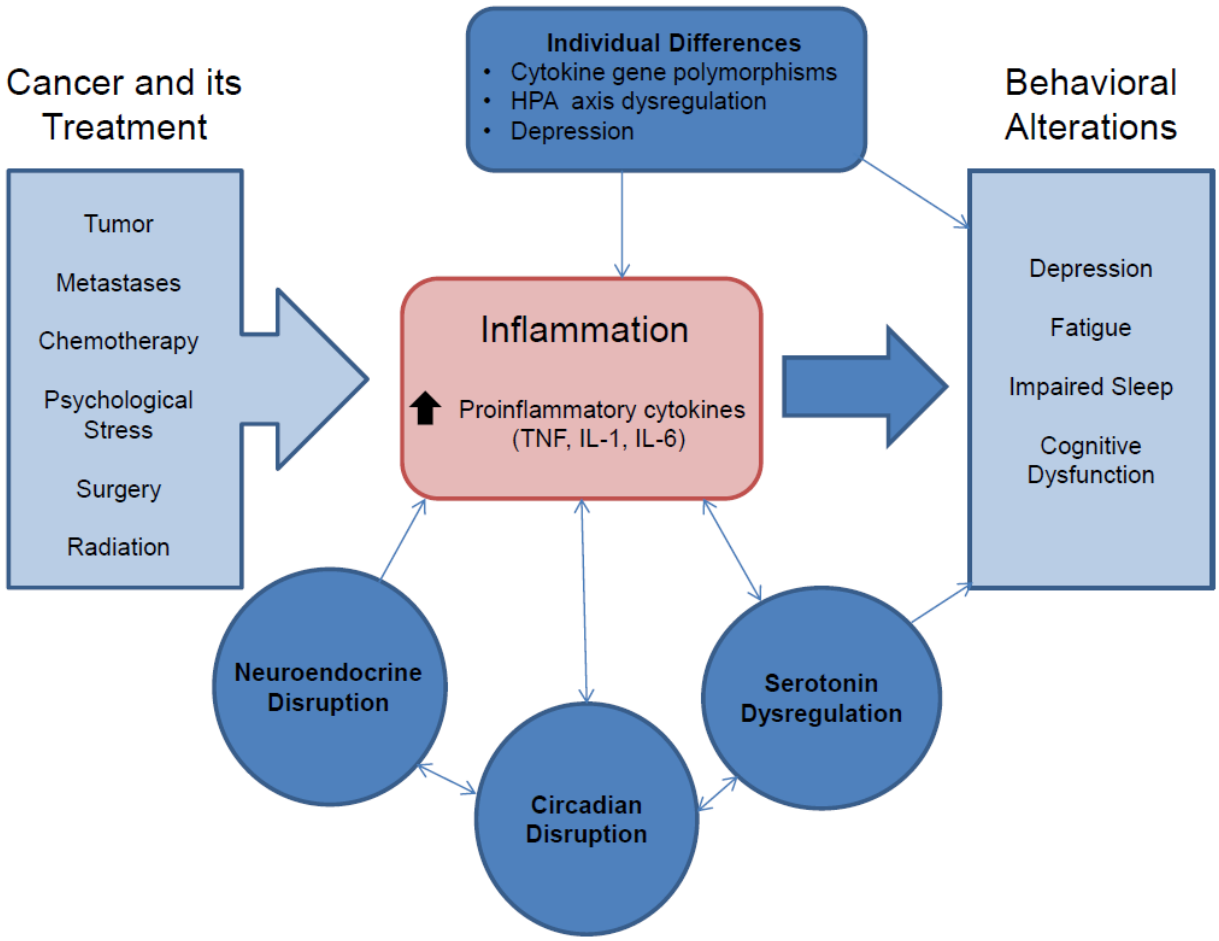

Figure 1. A revised model of cancer-related fatigue.

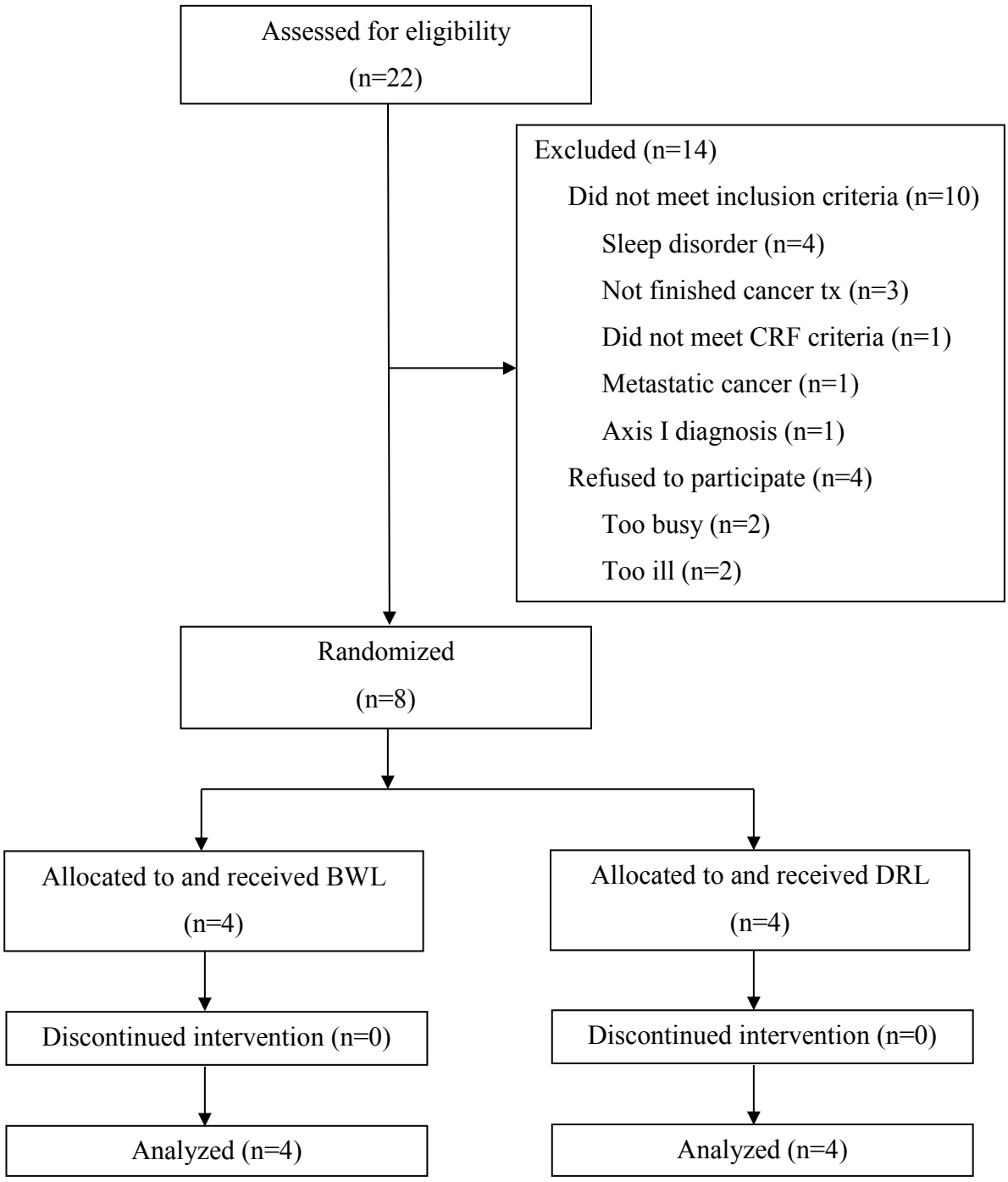

Figure 2. Participant flow chart following CONSORT guidelines. BWL = bright white light; CRF = cancer-related fatigue; DRL = dim red light

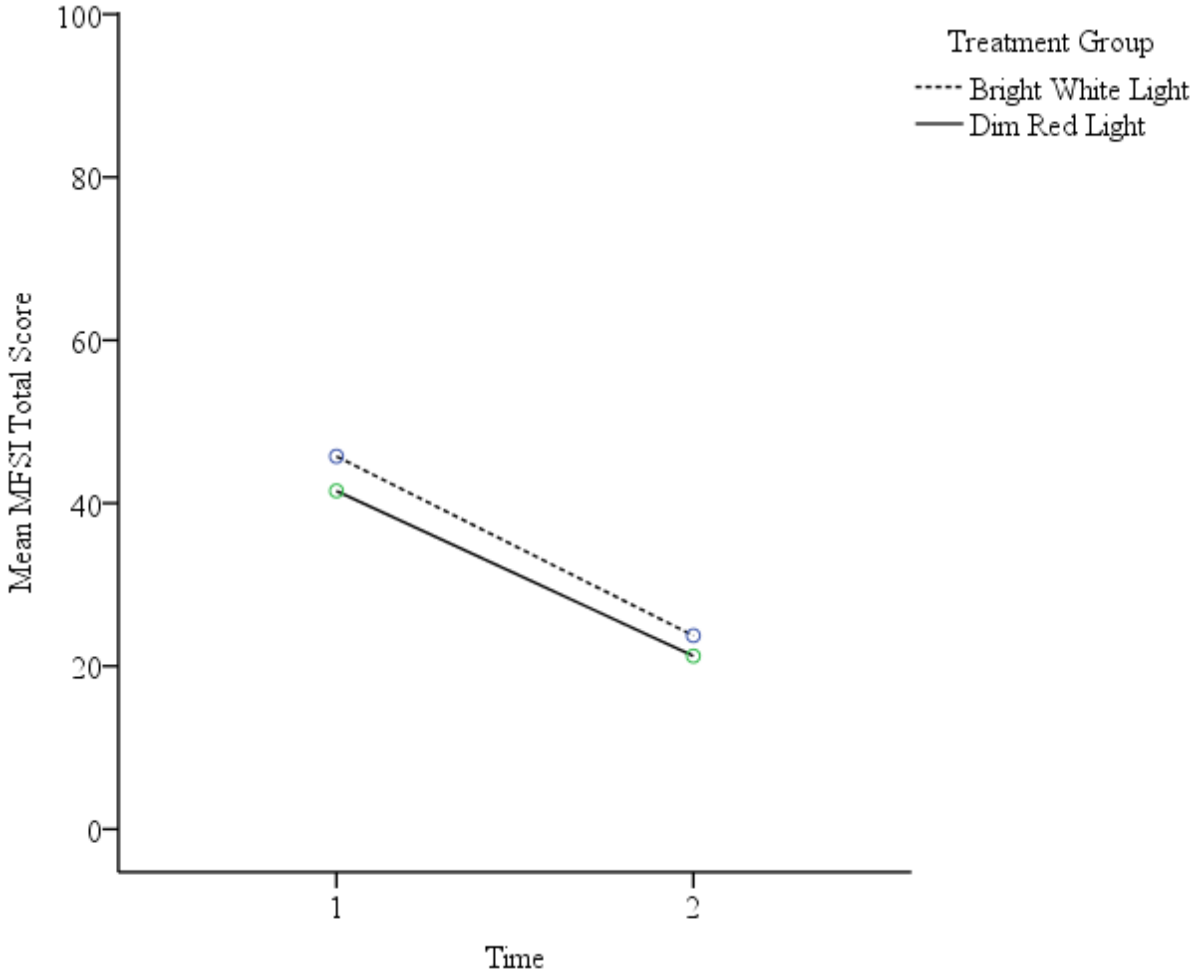

Figure 3. Main effect of time from baseline to post-treatment for MFSI Total Score.

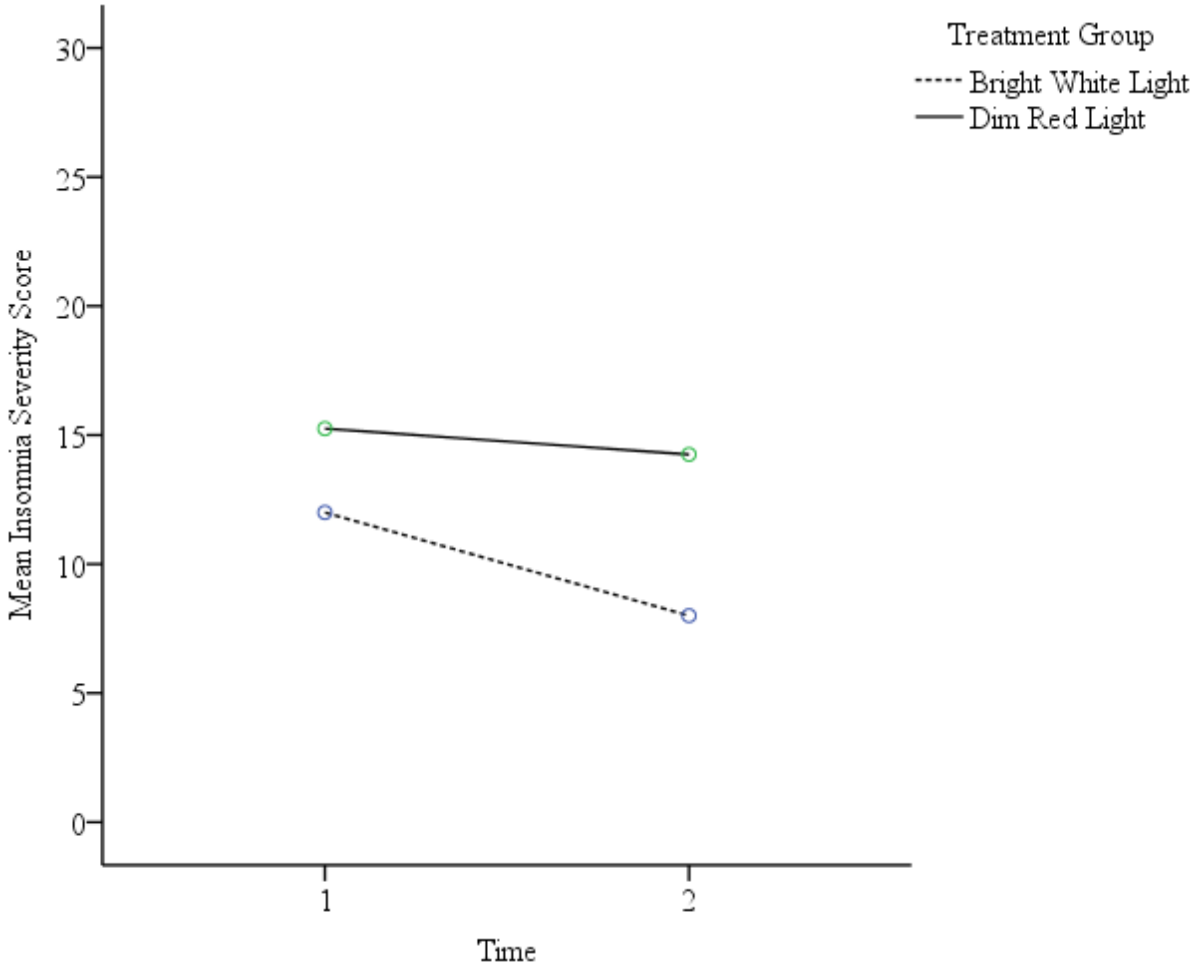

Figure 4. Main effect of time from baseline to post-treatment for ISI Total Score.

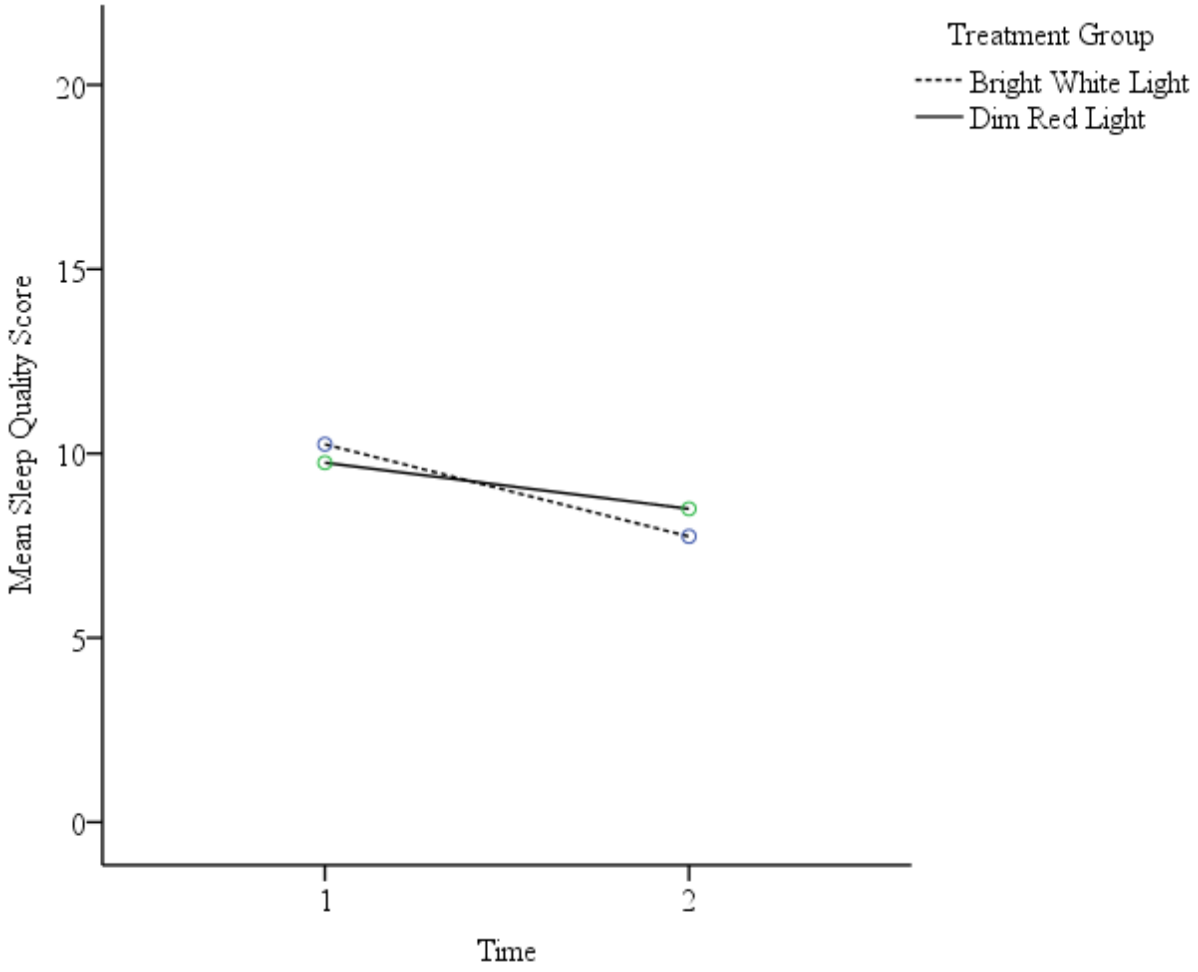

Figure 5. Main effect of time from baseline to post-treatment for PSQI Total Score.

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Appendix A

ICD-10 Criteria for Cancer-Related Fatigue

ICD-10 Criteria for Cancer Related Fatigue
A. Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, with at least 1 symptom (A1) being significant fatigue A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity A2. Complaints of generalized weakness or limb heaviness A3. Diminished concentration or attention A4. Decreased motivation or interest to engage in usual activities A5. Insomnia or hypersomnia A6. Experience of sleep as unrefreshing or nonrestorative A7. Perceived need to struggle to overcome inactivity A8. Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued A9. Difficulty completing daily tasks attributed to feeling fatigued A10. Perceived problems with short-term memory A11. Postexertional malaise lasting several hours
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. Evidence from the history, physical examination, or laboratory findings shows that the symptoms are a consequence of cancer or cancer therapy
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delerium

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Appendix B

Screening questionnaires

Date: _____ Assessed by: _____

Name: _____

Phone Number: _____ Alternate: _____

Email Address: _____

How did you hear about study? _____

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? _____

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? (every day or nearly	Yes	No

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

Appendix C

Consent form

BEHAVIOURAL MEDICINE LABORATORY

DEPARTMENT OF PSYCHOLOGY
Administration Building 225 – 2500 University Drive NW
Calgary, Alberta T2N 1N4
Phone: (403) 210-8606 Fax: (403) 282-8249

THE LITE STUDY: A RANDOMIZED CONTROLLED TRIAL OF LIGHT THERAPY ON BIOMARKERS, SLEEP/WAKE ACTIVITY, AND QUALITY OF LIFE IN INDIVIDUALS WITH POST-TREATMENT CANCER-RELATED FATIGUE

SPONSOR: The Canadian Cancer Society

INVESTIGATORS: Dr. Tavis Campbell, Mrs. Jillian Johnson, Dr. Steve Simpson & Dr. Linda Carlson

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more detail about something mentioned here, or information not included here, please ask. Take the time to read this carefully and to understand any accompanying information. You will receive a copy of this form.

BACKGROUND

Cancer-related fatigue is one of the most common and distressing symptoms associated with a cancer diagnosis. It is unlike the fatigue that most people experience, both in the degree of extreme exhaustion which can strike unexpectedly at any time, and because sleep is often not restorative. Fatigue related to cancer often appears before a diagnosis, worsens during treatment, and lasts for years after treatment in up to 35% of patients. Despite the long-term effects of cancer-related fatigue, the treatment options available are not always appropriate or helpful for all patients.
Light therapy is an effective treatment for other disorders related to fatigue. This study will

investigate if light therapy helps to reduce the impact of cancer-related fatigue in individuals post-treatment.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of the study is to investigate the role of light therapy on quality of life, sleep patterns, and physical measures of immune function and stress hormones in individuals with post-treatment cancer-related fatigue.

WHAT WOULD I HAVE TO DO?

If you choose to participate in this 6-week study, you will be asked to do the following:

Week 1:
During your initial visit to the Behavioural Medicine Laboratory, you will be asked to read and complete this consent form along with four sets of questionnaires asking about your fatigue, quality of life, sleep quality, and mood. You will then be instructed on how to provide saliva samples 4 times per day over the next 3 days so we can measure your levels of cortisol, a stress hormone. We will also show you how to track your sleep patterns over the next 7 days using a sleep diary and a sleep watch (a wrist watch that estimates your activity and sleep time through your body movements). You will be required to provide a blood sample during this first week at a time that is convenient for you. We will provide you with the requisition form and the necessary materials to have this blood sample collected at the Tom Baker Cancer Center. On day 8, you will return to the Behavioural Medicine Lab to return the sleep diary, sleep watch, and saliva samples. At this time, you will be provided with one of two types of light boxes along with instructions on how to use it.

Week 2-Week 5:
You will use the light box every day after you wake in the morning for 30 minutes (i.e., while you drink your coffee, eat your breakfast, etc.). During these 4 weeks, you will be contacted once a week by a member of the research team to complete a questionnaire about your fatigue during that week. They will also be able to answer any questions you may have.

Week 6:
On day 36, you will meet with a member of the research team to return the light box and complete the same four sets of questionnaires that ask about your fatigue, quality of life, sleep quality, and mood. The researcher will review instructions on how to complete 3 days of saliva collection (4 times/day) and how to track your sleep pattern over 7 days using the sleep diary and sleep watch. You will be required to provide a second blood sample during this final week at a time that is convenient for you. We will provide you with the requisition form and the necessary materials to have this blood sample collected at the Tom Baker Cancer Center. At the end of Week 36, you will return to the Behavioural Medicine Lab to return your sleep diary, sleep watch, and saliva samples. At this time we will discuss the study with you and answer any questions you may have regarding the study.

Your participation in this study is voluntary. If you agree to participate in this study, you may withdraw at any time. You may also withdraw your permission for us to use the information we have collected from you at any time during the study.

WHAT ARE THE RISKS?

There are no identifiable risks associated with participation in this study. The type or quality of treatment you will receive will not be in any way related to this study.

The light box you will be provided with is safe and has been used for other types of fatigue previously. This product separates specific wavelengths of visible light in an easy to use, safe, and non-invasive way. This device does not produce ultraviolet (UV) light.

WILL I BENEFIT IF I TAKE PART?

If you agree to participate in this study, there may or may not be a direct benefit to you. Light therapy has been shown to be an effective treatment for other disorders related to fatigue. However, there is no research on the impact of light therapy in individuals with post-treatment cancer-related fatigue; therefore there is no guarantee that this research will help you. The information we receive from this study may provide better treatment options in the future for individuals with post-treatment cancer-related fatigue.

DO I HAVE TO PARTICIPATE?

Your participation in this research is completely voluntary. You are free to withdraw from the study at any time.

If at any time you are required to begin further treatment or you are instructed by your physician to begin taking certain medications that may affect your sleep you may become ineligible for the study. You are asked to inform the researchers of any changes in your health status or regimen. If you are required to withdraw from the study, you will be informed of the reason and provided with additional resources to help you.

WILL I BE PAID FOR PARTICIPATING, OR DO I HAVE TO PAY FOR ANYTHING?

You are not required to incur any costs as a result of participating in this research, nor will you be paid for your participation. If required, fees for parking will be covered.

WILL MY RECORDS BE KEPT PRIVATE?

If you agree to participate, your records will be kept completely private. Only the investigators will have access to the information you provide. There are no names on the questionnaires, so you will not be identified as an individual in any report coming from this study. This consent form will be stored in a separate locked cabinet so it cannot be linked to your questionnaire answers. The questionnaires will be kept in a locked cabinet in the Department of Psychology.

This information will be stored for 7 years in a locked filing cabinet and/or on a computer disk, at which time it will be permanently erased.

Only group information will be summarized for any presentation or publication of results. All material and data obtained from this study will be stored and may be used for future analysis without obtaining further consent from you. However, each study arising as a result of information obtained in this study will be submitted for ethics approval.

We may also want to look into your medical records to obtain or verify information about your cancer illness and treatment. Your signature on this form also gives us this permission.

IF I SUFFER A RESEARCH-RELATED INJURY, WILL I BE COMPENSATED?

In the event that you suffer injury as a result of participating in this research, no compensation will be provided to you by the University of Calgary, Alberta Health Services, or the Researchers. You still have all your legal rights. Nothing said in this consent form alters your right to seek damages.

SIGNATURES

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a subject. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You are free to withdraw from the study at any time without jeopardizing your health care. If you have further questions concerning matters related to this research, please contact:

Dr. Tavis Campbell (403) 210-8606

Or

Mrs. Jillian Johnson (403) 201-8606

If you have any questions concerning your rights as a possible participant in this research, please contact The Chair of the Conjoint Health Research Ethics Board, University of Calgary, at 403-220-7990.

Participant's Name	Signature and Date
Investigator/Delegate's Name	Signature and Date
Witness' Name	Signature and Date

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

A signed copy of this consent form has been given to you to keep for your records and reference.

Appendix D

Demographics and Medical History Questionnaire

Demographics and Medical History Questionnaire

Name: _____ **Date** (mm/dd/yy): ____/____/____

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

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

Employment: ☐ Homemaker ☐ Full-time ☐ Part-time ☐ Retired ☐ Disabled

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

Date of Diagnosis (mm/dd/yy): ____/____/____ **C-Number** (e.g. C123456): _____

Type of Cancer and Stage: _____

Treatments previously received: ☐ Surgery ☐ Chemotherapy ☐ Radiation ☐ Hormonal (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	2
3	4
5	6
7	8
9	10
11	12

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:	

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 _____

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		

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 E

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: