ADDRESSING FATIGUE IN CANCER SURVIVORS USING COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA: A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

By

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Abstract

Cancer-related fatigue is frequently experienced by cancer survivors and is often comorbid with insomnia, perceived cognitive impairment (PCI), depression, and anxiety. This project consisted of 132 cancer survivors randomized into a treatment or waitlist control group. This thesis examined whether cognitive behavioural therapy for insomnia (CBT-I) can also improve fatigue among cancer survivors with insomnia disorder and PCI.

The first study examined the efficacy of CBT-I for fatigue. Fatigue was measured using the Multidimensional Fatigue Symptom Inventory- Short Form. The treatment group experienced a 20.6-point reduction in fatigue compared a 3.7-point reduction in the waitlist control group, after statistically adjusting for improvements in comorbidities. Within-group mediation analyses demonstrated that improvements in fatigue were fully mediated by improvements in insomnia, PCI, depression, and anxiety.

The second study (within-group) examined which factors were associated with a significant improvement in fatigue after CBT-I, defined as a decrease of 10.79 points on the fatigue measure. Three out of four participants (75%) experienced a significant reduction in fatigue. Younger participants (under 55 years) were more likely to experience improvement in fatigue after CBT-I.

Considering the efficacy of CBT-I for fatigue in the current study, future research should focus on using CBT-I for fatigue and other negative symptoms experienced among cancer survivors.

General Summary

This thesis examined the efficacy of cognitive behavioural therapy for insomnia (CBT-I) for the treatment of fatigue among cancer survivors. Cancer survivors with insomnia disorder and cognitive impairment symptoms were recruited from across Atlantic Canada to participate in a randomized controlled trial of CBT-I. The first study examined whether treatment with CBT-I resulted in reduced fatigue symptoms after adjusting for the influence of insomnia, perceived cognitive impairment, and mood disturbances. The treatment group experienced a statistically and clinically significant 20.6-point reduction in fatigue after the intervention, compared to a 3.7-point reduction in the waitlist control group. The second study examined the demographic and clinical factors associated with a significant reduction in fatigue following CBT-I. Being younger (less than 55 years) was significantly associated with a reduction in fatigue after CBT-I. These findings support the use of CBT-I for fatigue in cancer populations.

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Chapter 1: Cancer-Related Fatigue: An Overview

Overview

This thesis examines the use of cognitive behavioural therapy for insomnia (CBT-I) for cancer-related fatigue (CRF). The first chapter will review the literature on the prevalence, impact, and mechanisms of cancer-related fatigue and concludes with the research objectives. Chapter two is the first manuscript examining the effect of CBT-I on CRF, while accounting for the comorbidities of CRF. Chapter three is the second manuscript assessing the symptom, clinical, and demographic factors that may be associated with an improvement in fatigue after CBT-I. Lastly, chapter four will discuss the implications of these results and put them in context with the current literature.

Cancer-Related Fatigue

While cancer is the leading cause of death in Canada, the overall mortality from cancer is decreasing (Brenner et al., 2022). This is largely due to prevention and screening efforts, as well as advancements in cancer treatment. In 2023, the predicted 5-year survival rate for all cancer types was 64% (Canadian Cancer Statistics Advisory Committee, 2023). Despite these advances, cancer treatment is still associated with considerable negative side effects and the consequences of having a cancer diagnosis do not immediately stop when cancer treatment is finished. With such a high number of people surviving cancer, it is imperative that research focuses on how to improve the negative consequences that can present or persist into survivorship.

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" (Berger et al., 2015). CRF is also unrelated to activity and not relieved by rest and/or sleep (Barsevick et al., 2013). The fatigue that is experienced by people with cancer has been reported to be more severe than

fatigue in the general population as patients with CRF report it to be more persistent, intense, and distressing than fatigue caused by over working or lack of sleep (Jacobsen et al., 2007; Poulson, 2001). In a study of 221 breast cancer survivors and their aged matched, non-cancer controls, fatigue severity was significantly higher among cancer survivors (Jacobsen et al., 2007).

CRF is one of the most commonly-reported adverse effects of cancer (Glaus et al., 1996). Estimates suggest that approximately 60% of cancer survivors experience mild to moderate levels of CRF post-treatment (Lawrence et al., 2004; Servaes et al., 2002). A study that systematically assessed fatigue prevalence among 2244 cancer survivors showed that physical, emotional, cognitive, and total fatigue was present in all 15 cancer types studied and was present up to 2 years post-treatment (Schmidt et al., 2020). Moreover, differences in prevalence could not be explained by age, sex, BMI, or type of cancer therapy. Levels of physical fatigue were higher for stomach, lung, kidney, pancreatic and endometrium cancers compared to breast cancer. A meta-analysis examining 12,327 breast cancer survivors across 27 studies showed a prevalence of severe post-treatment fatigue ranging from 7% to 52%. (Abrahams et al., 2016). The pooled prevalence was 26.9% of all participants experienced severe fatigue post-treatment. Further, the symptoms of CRF often do not remit after the cancer has been treated and can last several years after finishing cancer treatment. Among 379 cancer survivors (mixed types) who underwent chemotherapy, those who had had chemotherapy more than five years ago reported still having CRF symptoms (Cella et al., 2001). In conclusion, CRF is a highly prevalent consequence of cancer, that is not specific to a cancer type.

Mechanisms of Cancer-Related Fatigue

The mechanisms of CRF are complex, and CRF can develop via several demographic, biological, and cancer-related factors. The mechanisms of CRF can be conceptualized using the

3P model comprised of predisposing, precipitating, and perpetuating factors (Spielman et al., 1987). This model was initially developed for the factors that maintain and perpetuate insomnia disorder but has been applied to CRF due to their similar etiology and relationship that will be discussed in the next section.

Predisposing Factors

Predisposing factors are the underlying factors that may make someone more susceptible to developing CRF. There is some evidence that biological sex may be a predisposing factor for CRF. Specifically, females have a greater likelihood of developing CRF compared to males (Huang et al., 2022; Ma et al., 2020). This may be due to females generally having lower levels of hemoglobin which causes a lower capacity to carry oxygen, and may result in fatigue (Cella, 1998). Anemia, defined as a low amount of hemoglobin in the body, has also been identified as a predisposing factor for developing CRF in cancer populations (Berger et al., 2015). The National Comprehensive Cancer Network (NCCN) has advised that anemia contributes to the development of CRF, and a decrease in anemia contributes to relieved CRF symptoms (Berger et al., 2015). Moreover, a preliminary study of 12 metastatic melanoma patients undergoing chemotherapy proposed that female endocrine levels tend to affect their emotions more than male endocrine levels, which may contribute to females appearing more sensitive and vulnerable, which may also account for sex differences in CRF (Fu et al., 2002).

In addition, there are genetic factors that may predispose individuals to developing CRF. Inflammation has a close relation with CRF; therefore, research has focused on examining which genetic factors influence pro-inflammatory cytokine activity as potential risk factors. Most of the research involves the examination of single nucleotide polymorphisms (SNPs) in inflammation-related genes including interleukin-1 beta (IL1B), interleukin 6 (IL6), and tumor necrosis factor

(TNF). There is evidence that variations in these genes are associated with CRF during and after treatment (Bower, 2014). In two longitudinal studies with patients undergoing radiation therapy (185 cancer survivors; mixed types), polymorphisms in TNF and IL6 were associated with greater CRF before, during, and four months after treatment (Aouizerat et al., 2009; Miaskowski et al., 2010).

Precipitating Factors

Precipitating factors are specific occurrences that contribute to the onset of CRF. In addition to the literature suggesting that cancer may lead to a dysregulation of pro-inflammatory cytokines in the central nervous system which contributes to the development of CRF, the hypothalamic-pituitary-adrenal (HPA) axis may also be involved in the development and maintenance of CRF (Bower, 2014). Dysregulation of the HPA axis leads to changes in glucocorticoid production and dysregulated circadian rhythms, which in turn, may contribute to the onset of CRF. Research that evaluated this idea in 100 ovarian cancer patients found higher levels of nocturnal cortisol and less cortisol variability compared to benign tumor controls and healthy controls, which were significantly associated with greater levels of CRF among cancer patients (Weinrib et al., 2010).

Cancer treatment is also associated with CRF. The treatment of cancer may involve a combination of surgery, chemotherapy, radiation therapy, hormonal therapy, or immunotherapy. These treatments are associated with negative physiological effects, emotional impacts, and unwanted side effects, which can contribute to the development of CRF (Ma et al., 2020). Two meta-analyses (12,327 breast cancer survivors, 8733 colorectal cancer survivors) assessing the impact of certain cancer treatments reported that chemotherapy has often been the treatment most associated with CRF (Abrahams et al., 2016; Huang et al., 2022). Cancer treatment has also

been associated with the release of neuroactive agents that activate vagal afferent nerves which leads to suppression of somatic muscle activity, and ultimately leads to "sickness behaviour" that contributes to CRF (Ryan et al., 2007). Andrews (2004) studied various biological mechanisms of CRF and found that a cancer diagnosis or treatment may lead to a defect in the mechanism for regenerating adenosine triphosphate (ATP) in skeletal muscle, which is a major energy source for muscle movement. Those with CRF have been shown to have depleted muscle metabolism and low ATP. Additionally, Andrews (2004) showed that cancer and/or cancer treatment is associated with an increase in serotonin or 5-hydroxytryptemine (5-HT) dysregulation in the brain. This leads to reduced somatic motor drive, altered HPA axis function, and a feeling of reduced capacity to perform physical work. Lastly, a cancer diagnosis comes with considerable stress, lifestyle changes, and interruption of daily activities which have been shown to contribute to CRF (Ho et al., 2015; Lu et al., 2021).

A cancer diagnosis may cause an interruption in a person's occupation. Financial burden and worry may also be present, which can be very stressful. A scoping review by Ngan et al. (2023) found that cancer survivors frequently reported facing financial problems after their cancer diagnosis including debt, issues paying bills, spending savings, needing financial help, and altering their usual activities to cope. This was related to a considerable impact on the individuals benefit/welfare system, mental health, and financial well-being. In a study with 2458 prostate cancer survivors, financial stress was found to be a predictor of experiencing CRF (Lu et al., 2021).

Perpetuating Factors

Lastly, there are perpetuating factors that contribute to the maintenance and exacerbation of CRF. For instance, poor diet may play a role in the maintenance of CRF symptoms. A pilot

randomized controlled trial of 23 men with prostate cancer suggested that eating pro-inflammatory foods like processed meats and high-sugar foods has been associated with TNF and IL6 which has been linked to CRF (Baguley et al., 2021). In contrast, evidence suggests that anti-inflammatory foods (e.g., fruits, green vegetables, and whole grains) are associated with less CRF symptoms by reducing inflammation (Baguley et al., 2021; Zick et al., 2013). Another perpetuating factor of CRF is poor sleep habits. Poor sleep habits include frequent napping and sporadic sleep/wake time, where long naps during the day, or having very different sleep and waking times can disrupt circadian rhythm, which is related to trouble sleeping at night (Ancoli-Israel et al., 2014; Huang et al., 2022). Lastly, fear of cancer recurrence has been identified as a perpetuating factor of CRF (Kuswanto et al., 2023). Fear of cancer recurrence is when a fear of relapse of cancer causes significant distress in those who have finished their cancer treatment (Vickberg, 2003). CRF and fear of cancer recurrence have been shown to exacerbate each other where CRF symptoms are sometimes perceived as cancer recurrence symptoms, and fear of cancer recurrence contributes to CRF symptoms through constant worry and distress about the possibility of recurrence (Lebel et al., 2018).

Impact of Cancer-Related Fatigue

CRF has negative impacts on the quality of life of cancer survivors. Quality of life may be defined in several ways, but among cancer survivors, the term ‘health-related quality of life’ is used to define their quality of life post-treatment based on physical, mental, social aspects, as well as abilities, relationships, satisfaction, well-being, and perceptions (Wood-Dauphinee, 1999). In a survey study with a sample of 379 cancer survivors, 91% reported that their CRF symptoms prevented them from living a ‘normal’ life (Curt et al., 2000). Moreover, 79% of the sample felt “sluggish” and tired, and when fatigue was experienced, respondents reported

sleeping an average of 2.8 additional hours (Curt et al., 2000). A review about the occurrence, assessment, and treatment of CRF (13 studies, mixed cancer types) has identified CRF to be distressing and has the ability to negatively impact mood, daily activities, and relationships, which all greatly influence quality of life (Lawrence et al., 2004). In summary, CRF is a highly prevalent, distressing problem that can negatively influence the quality of life and daily functioning of cancer survivors.

Comorbidities of Cancer-Related Fatigue

CRF is frequently comorbid with other conditions in cancer survivors, including insomnia, anxiety, depression, and cognitive impairment (Brown & Kroenke, 2009; Jacobsen et al., 2003; Lange et al., 2019; Minton & Stone, 2012; Morrow et al., 2002). CRF, insomnia, cognitive impairment, anxiety and depression exacerbate and influence each other, and have been proposed to work in a self-reinforcing feedback loop (Palagini et al., 2021). Cognitive impairment, including deficits in memory, concentration and attention are also associated with CRF, insomnia, anxiety and depression.

A symptom cluster is defined as three or more symptoms related to one another that may share the same aetiology (Dodd et al., 2001). Symptom clusters can be important in providing causal relationships of symptoms and helping create interventions targeted for clusters of symptoms. Some literature have identified several different symptom clusters in cancer survivors such as fatigue-pain, fatigue-insomnia, depression-fatigue, and fatigue-insomnia-pain (Kirkova et al., 2011). A systematic review that examined 32 studies with respect to symptom clusters in breast cancer survivors found evidence for a “psychological cluster” that included anxiety and depression as the main symptom, and then sleep disturbance, CRF, and cognitive impairment as

other comorbid symptoms (So et al., 2021). These symptom clusters provide evidence for the close relationships between CRF, insomnia, anxiety, depression, and cognitive impairment.

Sleep issues are an independent risk factor for depression among cancer populations (Irwin et al., 2013). Similarly, fatigue has been associated with issues such as pain, depression, and sleep problems (Kirkova et al., 2011). Subjective cognitive impairment in cancer populations has been associated with fatigue, depression, and anxiety (Pullens et al., 2010).

Cancer-Related Fatigue and Insomnia

Poor sleep is one of the most common negative side effects reported by cancer survivors (Savard & Morin, 2001). Estimates suggest that approximately 60% of cancer survivors experience insomnia symptoms (Savard et al., 2011). Insomnia is characterized as difficulties falling asleep, maintaining sleep, or waking up too early and occurs at least three nights per week for at least three months (American Psychiatric Association, 2013). Similar to CRF, sleep problems often persist for a long time after cancer treatments have finished. A longitudinal study observed that 47% of cancer patients (mixed types) experienced their insomnia symptoms one-year post-treatment (Schieber et al., 2019). Insomnia also has the ability to negatively impact quality of life and interrupt daily functioning, which can be distressing (Ross et al., 2020).

CRF and insomnia are closely related. In a sample of 114 breast cancer survivors with CRF, 44% also met diagnostic criteria for insomnia. In comparison, 16% of cancer survivors without CRF met the criteria for insomnia (Minton & Stone, 2012). Poor sleep predicts higher levels of fatigue among cancer survivors after adjusting for activity levels and mood disturbances (Goedendorp et al., 2013; Pertl et al., 2014). In a study that examined predictors of fatigue pre- and post-chemotherapy in a sample of 100 cancer patients (mixed types), Pertl and colleagues (2014) observed that sleep was associated with CRF at the beginning of chemotherapy treatment.

Moreover, a study that assessed CRF in 68 cancer patients (mixed types) observed that 22% experienced persistent CRF 6 months after they finished their cancer treatment (Goedendorp et al., 2013). They also found that more negative interpersonal interactions, fatigue catastrophizing, and impaired sleep were factors significantly predicting higher levels of persistent CRF. The high rate of comorbidity between insomnia and CRF may be due to poor sleep contributing to symptoms daytime fatigue (Ancoli-Israel et al., 2001). In contrast, CRF symptoms may warrant individuals feeling like they need more sleep, which in turn, can contribute to having an increased time in bed or greater napping time during the day, which can contribute to insomnia (Palagini et al., 2021). This demonstrates a bidirectional relationship between CRF and insomnia. In conclusion, CRF and insomnia are frequently comorbid after a cancer diagnosis.

Cancer-Related Fatigue and Cognitive Impairment

In addition to a strong relationship with insomnia, CRF also influences cognitive functioning. Cognitive impairment among cancer survivors affects the following domains: attention, executive function, processing speed, language, motor function, and various memory impairments including working memory, long- and short-term, as well as visual and verbal memory (Horowitz et al., 2019). A multifactorial model proposed that cancer-related cognitive impairment is influenced by multiple factors, including social determinants of health, patient specific-factors, co-occurring symptoms, treatment factors, and biologic mechanisms (Oppegaard et al., 2023). A meta-analysis of the prevalence of cognitive impairment that examined 52 studies that reported on breast cancer survivors who completed chemotherapy observed that about one third of patients experienced cognitive impairment after receiving chemotherapy (Whittaker et al., 2022). Other cancer treatments such as surgeries, hormone therapy, and adjuvant therapy, as well as the stress of having cancer have also been associated

with cognitive impairment (Chen et al., 2012; Shilling et al., 2003). The prevalence of cognitive impairment among cancer survivors varies but estimates suggest that it is present in approximately 45% of cancer survivors, depending on the measure used (Schilder et al., 2010). Cancer survivors often attribute certain cognitive symptoms they experience to CRF. For instance, some may experience issues with attention, which may be attributed to fatigue. Compared to non-cancer controls, women with breast cancer receiving chemotherapy demonstrate poorer processing speed, which was associated with fatigue levels (Menning et al., 2015). Therefore, these findings suggest that fatigue and cognitive impairment share commonalities, and that certain symptoms of cognitive impairment may be attributed to CRF.

Cancer-Related Fatigue, Anxiety, and Depression

Anxiety and depression are also frequently comorbid with CRF (Grusdat et al., 2022; Jacobsen et al., 2003). When someone receives a cancer diagnosis, many feelings such as anger, depression, anxiety, confusion, and fear of death are common (Fortin et al., 2021; Sarfraz et al., 2022; Thomas et al., 2000). Many of these emotions persist after cancer treatment is finished. A longitudinal study that followed the trajectory of 653 women with breast cancer found that depression persisted at least two years post-treatment (Avis et al., 2015). Moreover, approximately 20% of participants in the study had levels of depressive symptoms indicative of clinical depression. Factors related to this trajectory were illness intrusiveness, social support, fatigue, pain, and vasomotor symptoms. Further, a secondary analysis of a randomized controlled trial found that decreasing depression symptoms over the first year were associated with longer survival for women with breast cancer (Giese-Davis et al., 2011).

In a systematic review and meta-analysis (59 studies, 12,103 cancer survivors, mixed types), depression was associated with CRF in 51 of the 59 included studies (Brown & Kroenke,

2009). They estimated that CRF shared about 31% of its variance with depression and approximately 23% of its variance with anxiety, which provides evidence that depression and anxiety may share similarities. Moreover, in a longitudinal study of 68 women undergoing chemotherapy for breast cancer, participants had higher levels of fatigue and depression compared to non-cancer controls after one-year post-treatment, (Ancoli-Israel et al., 2014). Similarly, depression and fatigue were positively correlated in a cross-sectional study of 77 patients with liver cancer, where depression mediated the relationship between sleep disturbances and fatigue (Huang & Lin, 2009). Lastly, a meta-analysis that included 84 studies with 114,813 participants (mixed cancer types) identified that participants with depression also had greater levels of CRF (Ma et al., 2020). Overall, these findings further suggest that CRF is heavily influenced and co-morbid with other negative symptoms in cancer survivors.

In summary, literature provides evidence for CRF having several comorbidities that are often presented in symptom clusters.

Treatments of Cancer-Related Fatigue

There is currently no consensus on the recommended treatment for CRF (Bower, 2014). However, exercise interventions, mindfulness-based strategies, cognitive behavioural therapy, and some pharmaceutical interventions have been investigated with varying efficacy.

Exercise

Exercise interventions currently have the most efficacy for reducing CRF in cancer survivors. A meta-analysis of 72 studies compared the effectiveness of exercise as a treatment to usual care or a non-exercise control. Exercise, regardless of type, significantly improved CRF symptoms, with a moderate effect size (Tomlinson et al., 2014). Depression and sleep disturbance symptoms were also improved with exercise. Another meta-analysis of 127

randomized controlled trials compared exercise, pharmaceutical, and psychological interventions for the treatment of CRF in cancer survivors (Mustian et al., 2017). All of the interventions improved fatigue symptoms, but exercise interventions had the largest overall improvement.

Despite the evidence showing that exercise can be helpful for CRF symptoms, there is a large amount of variation when considering exercise interventions, such as the amount of exercise required, the type of exercise, and the timing of when the exercise is completed. In addition, there is also evidence that exercise is not always effective for CRF symptoms. Moreover, the efficacy of exercise interventions may vary if participants have any physical limitations.

Mindfulness-Based Interventions

Mindfulness-based stress reduction (MBSR) interventions have been successful in reducing fatigue symptoms. A study that looked at the effectiveness of MBSR on 63 cancer outpatients found that the intervention significantly improved CRF symptoms as well as sleep disturbance, stress, mood disturbance, and sleep quality (Carlson & Garland, 2005). A meta-analysis that examined 14 randomized control trials found that MBSR significantly reduced CRF symptoms with a large effect size (Xie et al., 2020). Similarly, Johns et al. (2015) found that MBSR significantly reduced CRF symptoms after treatment compared to a waitlist control. They also found that improvements were maintained at the 6-month follow-up.

Although MBSR may be a treatment for CRF that is effective for many cancer survivors, like exercise interventions, MBSR often contains some form of body movement such as yoga and/or mindful walking. As mentioned, interventions with an exercise component may not work for those who have physical limitations that prevent them from participating. Currently, there is

no literature surrounding the impact of MBSR on CRF in a sample who has limited physical abilities. Therefore, it is difficult to know if MBSR will be effective in these populations.

Pharmacological Interventions

There is also literature surrounding pharmacological interventions for the treatment of CRF symptoms. Mainly, central nervous system stimulants such as armodafinil and methylphenidate can be used to block presynaptic dopamine and norepinephrine reuptake (Berridge et al., 2006). These drugs can have positive effects on mood. Antidepressants or SSRI's have also been used to treat fatigue. CRF and depression share some biological mechanisms relating to the hypothalamic pituitary axis dysfunction and dysregulation of inflammatory pathways (Nemeroff & Owens, 2004).

Pharmacological interventions may also pose different challenges for cancer survivors. As part of cancer treatment, patients have used several different medications that all led to different side effects. It is possible that cancer survivors may be reluctant to try pharmacological interventions for their CRF symptoms as it would be adding another medication. In addition, these medications for CRF may produce their own side effects, which patients may not want to endure. Lastly, some medications may produce tolerance or dependence effects, where the dosage may need to be incrementally increased to obtain the same effect or the patient may become dependent on the medication. Overall, pharmacological treatments may be effective for some patients however, patients may be reluctant to using this treatment as there can be negative side effects and risk of tolerance and dependence.

Cognitive Behavioural Therapy for Insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is the recommended treatment for insomnia by the American Academy of Sleep Medicine, the American College of Physicians,

and European Sleep Research Society (Edinger et al., 2021; Qaseem et al., 2016; Riemann et al., 2017). CBT-I has also demonstrated efficacy in cancer survivors (Johnson et al., 2016). CBT-I addresses the cognitive factors and behaviours that contribute to poor sleep while providing patients with tools to prevent recurrence of insomnia symptoms (Spielman et al., 1987).

Considering the close relation between CRF and insomnia, research has begun to explore the potential benefits of CBT-I on comorbid CRF. A randomized controlled trial compared CBT-I to a wakefulness-promoting agent, Armodafinil, to see if there would be any improvements in CRF symptoms in 96 post-treatment cancer survivors (mixed types; Heckler et al., 2016). CRF significantly improved only among the participants who received CBT-I, with no additional improvement when the medication was used. This finding exemplified that CRF is greatly influenced by sleep, and that a sleep intervention may be effective in treating CRF. Another randomized controlled trial that used CBT-I to improve insomnia, CRF, mood, and quality of life in a sample of 72 breast cancer survivors found that the treatment group had significant improvements in CRF symptoms compared to a control group, who only received the sleep education and sleep hygiene components of CBT-I (Dirksen & Epstein, 2008). Moreover, a randomized controlled trial that examined the efficacy of internet-delivered CBT-I in 255 women with breast cancer found that CRF was significantly improved at post-treatment and results were maintained at the 15-week follow-up (Zachariae et al., 2018). In this trial, 73% of participants reported clinically severe fatigue at baseline, but only 34% of the treatment group reported fatigue after treatment, compared to 65% in the waitlist control group. Overall, several studies have assessed the potential to treat CRF with a sleep treatment, but the literature does not account for any of the comorbidities (insomnia, perceived cognitive impairment, depression, and

anxiety) in their analyses. Considering that CRF is frequently comorbid with these other symptoms, it is likely that treatment for one symptom may improve the other symptoms as well.

Feasibility of Treatments for Cancer-Related Fatigue

Despite the high prevalence of fatigue among cancer survivors and the harmful impact on quality of life, CRF does not have a gold standard treatment. CBT-I, exercise interventions, and MBSR interventions have provided efficacy for CRF, however, the preference of the patient is what matters (Tomlinson et al., 2014; Xie et al., 2020; Zachariae et al., 2018). Patients devote an abundance of time, money, and effort to treat their cancer, and it may not be realistic for them to undergo additional intervention to improve CRF. Another point to consider is that cancer survivors are often disconnected from many of the cancer-related resources after they complete active treatment of cancer, such as support groups, counsellors, and specialists. Additionally, cancer survivors may no longer be associated with an oncologist, and transitioned to their general practitioner for care. This often leaves cancer survivors with limited access to resources that can offer treatments for post-cancer conditions, such as CRF. Depending on the healthcare system, it may be difficult to receive a treatment targeted solely for CRF, as interventions have great impacts financially and they take a lot of time, so it may not be feasible to enter an intervention for one problem. One final point to consider is that several studies have shown that CBT-I is effective for the treatment of CRF, however, the full effects on symptoms other than insomnia are not well understood (Dirksen & Epstein, 2008; Zachariae et al., 2018).

Primary Research Objectives

Considering there is no literature assessing CBT-I as a treatment for CRF while accounting for the comorbidities of insomnia, PCI, depression, and anxiety, this research will

focus on assessing the efficacy of CBT-I for CRF while also accounting for the comorbidities. The primary research objectives are as follows:

Chapter 2 objectives:

Primary: To examine if there is a statistically and clinically significant improvement in CRF after CBT-I, when controlling for the comorbid symptoms of insomnia, PCI, and mood disturbances.

Secondary: To determine whether any improvements in CRF were accounted for by improvements in insomnia, PCI, or mood disturbances.

Chapter 3 objectives:

1) To assess if any demographic, symptom, or clinical factors may be associated with a clinically relevant improvement in CRF after CBT-I.

Chapter 4 objectives:

1) To contextualize findings with current literature and provide clinical implications for future use of CBT-I for CRF.

Chapter 2: Impact and Mechanisms of Cognitive Behavioural Therapy for Insomnia on Fatigue among Cancer Survivors: A Secondary Analysis of a Randomized Controlled Trial

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Abstract

OBJECTIVES: Cancer-related fatigue is one of the most common symptoms in cancer survivors. There is evidence that cognitive behavioural therapy for insomnia (CBT-I) can improve fatigue among cancer survivors, but mechanisms are unclear. The current study evaluated whether CBT-I led to a significant improvement in fatigue, accounting for change in comorbid symptoms of insomnia, perceived cognitive impairment (PCI), anxiety, and depression.

METHODS: Cancer survivors with insomnia and PCI were randomized to CBT-I or a waitlist control. Fatigue was measured using the Multidimensional Fatigue Symptom Inventory – Short Form at pre-, mid-, and post-treatment. Significant improvement in fatigue was defined as a reduction >10.79 points. Insomnia, PCI, anxiety, and depression were also assessed. A linear mixed model evaluated whether CBT-I improved fatigue after adjusting for insomnia, PCI, anxiety, and depression. Mediation analysis examined whether change in comorbidities accounted for the effect of CBT-I on fatigue.

RESULTS: The sample consisted of 132 cancer survivors (77% female, M_{age}=60.12 years). The most common cancer type was breast (41%). There was a significant group-by-time interaction on fatigue, $p<.001$, with the CBT-I group experiencing a 20.6-point reduction in fatigue compared to 3.7-points in the control. Improvements in fatigue were fully accounted for by improvements in insomnia, depression, PCI, and anxiety, with change in insomnia accounting for approximately half of the effect observed in fatigue.

CONCLUSION: CBT-I resulted in significant reduction in fatigue relative to waitlist control, and these effects were largely accounted for by change in insomnia. CBT-I is a robust intervention with efficacy for improving CRF among cancer survivors.

Keywords: cancer; cancer-related fatigue; insomnia; cognitive impairment; anxiety; depression

Introduction

Improvements in cancer care are continuing to reduce mortality (Brenner et al., 2022), with the estimated 5- year survival rate for all cancer types reaching 64% in Canada (Canadian Cancer Statistics Advisory Committee, 2023). However, increased survival has resulted in a large number of survivors with considerable negative symptoms associated with treatment. One salient negative symptom is cancer-related fatigue (CRF), defined as a "distressing, persistent, sense of physical, emotional, and cognitive tiredness that may be related to cancer itself or cancer treatment that interferes with daily functioning" (Berger et al., 2015). CRF can persist for years following a cancer diagnosis, and does not always remit following cancer treatment (Cella et al., 2001). CRF is one of the most prevalent negative consequences of cancer with estimates suggesting that approximately three in five cancer survivors experience CRF following cancer treatment (Lawrence et al., 2004; Servaes et al., 2002). Therefore, it is important that interventions focus on treating the negative symptoms that persist into cancer survivorship.

Comorbidities of Cancer-Related Fatigue

CRF is frequently comorbid with insomnia, depression, anxiety, and cognitive impairment among cancer survivors (Brown & Kroenke, 2009; Jacobsen et al., 2003; Lange et al., 2019; Minton & Stone, 2012; Morrow et al., 2002). These symptoms often present together and are referred to as a "symptom cluster" in the literature (Donovan & Jacobsen, 2007; So et al., 2021). These comorbidities share a relationship where all symptoms influence each other and have been proposed to work in a self-reinforcing feedback loop (Palagini et al., 2021). Symptom clusters can be associated with significant emotional and physical problems among cancer survivors when occurring long-term (Ebbestad et al., 2023).

Cancer-Related Fatigue and Insomnia

Approximately 30-60% of people experience insomnia symptoms following a diagnosis of cancer (Savard et al., 2011). Poor sleep is one of the most common comorbidities of CRF among cancer survivors (Savard & Morin, 2001). Almost half of a sample of 114 breast cancer survivors with CRF met diagnostic criteria for insomnia disorder (Minton & Stone, 2012). Poor sleep has also been shown to predict higher levels of CRF after adjusting for activity levels and mood disturbances (Goedendorp et al., 2013; Pertl et al., 2014). Current literature suggests that cancer and/or cancer treatment may lead to a dysregulation of proinflammatory cytokines (primarily interleukin-6 and tumor necrosis factor-α) that disrupts the sleep-wake cycle which in turn, may lead to disruption of the neuroendocrine system, and the hypothalamic-pituitary-adrenal (HPA) axis (Miller et al., 2008). Then, these changes may impact central nervous system pathways that regulate behavior, which can contribute to the development and maintenance of CRF and insomnia (Bower, 2014; Miller et al., 2008).

Cancer-Related Fatigue and Cognitive Impairment

Cancer survivors often experience cognitive impairment which affects the following domains: attention, executive function, processing speed, language, motor function, and various memory impairments including working memory, long- and short-term, as well as visual and verbal memory (Horowitz et al., 2019). Approximately 45% of cancer survivors experience symptoms of cognitive impairment following their diagnosis (Schilder et al., 2010). Cancer treatments have also been associated with symptoms that are indicative of cognitive impairment (Chen et al., 2012; Shilling et al., 2003). Cognitive impairment among cancer populations has been suggested to develop due to reasons such as neuroinflammation, damage to the blood-brain barrier due to chemotherapy, cancer medications, and oxidative stress (Fleming et al., 2023).

Cancer-Related Fatigue and Depression and Anxiety

Depression and anxiety are prevalent experiences during and after cancer treatment (Fortin et al., 2021; Sarfraz et al., 2022; Thomas et al., 2000). A systematic review and meta-analysis of 59 studies with a combined sample of 12,103 cancer survivors examined the relationships between CRF, depression, and anxiety (Brown & Kroenke, 2009). CRF shared about 31% of its variance with depression and 23% with anxiety. Depression and anxiety in cancer populations can develop from biopsychosocial factors, such as a person's reaction to the initial cancer diagnosis, effects from treatment, stress, and change of social and work roles (Pitman et al., 2018). Overall, these findings further suggest that CRF is heavily influenced and comorbid with depression and anxiety among cancer survivors.

Cognitive Behavioural Therapy for Insomnia

Cognitive behavioural therapy for insomnia (CBT-I) is an effective treatment for insomnia and recommended by the American Academy of Sleep Medicine, the American College of Physicians, and European Sleep Research Society (Edinger et al., 2021; Qaseem et al., 2016; Riemann et al., 2017). CBT-I has also demonstrated efficacy among cancer survivors (Johnson et al., 2016). CBT-I addresses the cognitive factors and behaviours that contribute to poor sleep while providing patients with tools to prevent recurrence of insomnia symptoms (Spielman et al., 1987).

Currently, there is no universally recommended treatment for CRF (Bower, 2014), and its associated symptoms. However, research has begun to explore the potential benefits of CBT-I among cancer survivors with comorbid CRF. First, Dirksen and Epstein (2008) explored using CBT-I to improve insomnia, CRF, anxiety, and depression among 72 women with breast cancer. Those who received the intervention experienced a significant improvement in CRF compared to

the control group who received sleep education and sleep hygiene (Dirksen & Epstein, 2008). Moreover, a randomized placebo-controlled trial that compared CBT-I and a wakefulness-promoting agent, Armodafinil, observed that CRF only improved among participants who received CBT-I (Heckler et al., 2016). This finding was the first comparative study design to suggest that a sleep intervention may be effective in treating CRF. Another randomized controlled trial among breast cancer survivors observed that CRF was significantly improved after CBT-I and results were maintained at a 15-week follow-up (Zachariae et al., 2018). In this trial, 73% of participants reported clinically severe CRF at baseline, but only 34% of the treatment group reported CRF after treatment, compared to 65% in the control group.

Understanding Mechanisms of Change

Several studies have assessed the potential to treat CRF with a sleep treatment, but the mechanisms are unclear. To better understand the mechanisms, it is important to take into account the comorbid symptom change after an intervention. Considering that CRF is frequently comorbid with other symptoms, the improvement seen in CRF after CBT-I could be attributed to reduced insomnia severity, mood improvement, or change in perceived cognition. Therefore, research needs to account for the comorbidities to see which factors are contributing to any improvements observed.

Present study

The current study examined whether CBT-I can effectively improve CRF, after adjusting for insomnia, PCI, depression, and anxiety. It was hypothesized that CRF levels will improve over the course of treatment. A secondary aim of this study was to understand the mechanisms of improvement observed by testing insomnia, depression, anxiety, and PCI as mediators of change.

Methods

Study Design

The current study is a secondary analysis of a randomized waitlist-controlled trial of CBT-I to improve perceived cognitive impairment among cancer survivors (clinicaltrials.gov identifier: NCT04026048). The study protocol and results of the primary analysis have been previously published (Garland et al., 2021; Garland et al., 2024).

Participants

The Addressing Cancer Treatment-Related Insomnia Online in Atlantic Canada (ACTION) study recruited cancer survivors from the four easternmost Canadian provinces, collectively known as Atlantic Canada. Participants were self-referred and recruited from Atlantic Canada through clinic referrals, radio advertisements, posters, referrals from oncologists, and from mail-outs to individuals who participated in the Atlantic Partnership for Tomorrow's Health (PATH) study which investigates how genetics, the environment, lifestyle, and behavior contribute to the development of chronic diseases. Participants had to meet the diagnostic criteria for insomnia disorder based on the Diagnostic Statistical Manual of Mental Disorders - fifth edition (American Psychiatric Association, 2013) and have a score of 8 or greater on the Insomnia Severity Index (Morin, 1993). They also had to meet a threshold of perceived cognitive impairment symptoms indicated by a score of "quite a lot" or "always" on the questions pertaining to concentration and memory on the European Organization for Research and Treatment of Cancer Quality of Life Instrument (Aaronson et al., 1993).

Participants were screened for eligibility virtually, with a member of the research team. Participants were not eligible if they were still undergoing active cancer treatment (systemic therapy, chemotherapy, radiation therapy, and targeted therapy), if their treatment finished less

than six months before the trial began, or if they had received cranial radiation. Participants with metastatic cancer were eligible if their cancer treatment regimen was stable. Participants were ineligible if they had an additional sleep disorder (e.g., sleep apnea), psychological disorder that was not well managed, sensory deficits, previous experience with the CBT-I intervention, of if they had poor performance status (Oken et al., 1982).

Participants provided consent to participate. Ethical approval and oversight were obtained from the Health Research Ethics Board (#20200427).

Procedure

Participants were screened virtually to determine whether they met the inclusion criteria. Eligible participants were consented, completed baseline assessment, and were randomly assigned to the treatment or waitlist control group at a 1:1 allocation ratio using blocks of four generated using uniform probability distribution. The immediate treatment group met with their CBT-I therapist after their baseline assessment. The waitlist control group waited 8 weeks after the baseline assessment before they began the same treatment.

The immediate group completed assessments at baseline (0-weeks), mid-treatment (4-weeks), and post-treatment (8 weeks). The waitlist control group completed assessments at baseline (0-weeks), monitoring phase (4-weeks), pre-treatment (8-weeks), mid-treatment (12-weeks), and post-treatment (16 weeks).

Intervention

Cognitive Behavioural Therapy for Insomnia (CBT-I)

CBT-I is a multicomponent psychotherapy consisting of (1) sleep restriction, (2) stimulus control, (3) cognitive restructuring, (4) relaxation training, and (5) sleep hygiene (Edinger et al., 2021; Morin et al., 2023). The intervention was delivered via video teleconferencing over seven,

weekly, one-hour sessions with a trained doctoral student therapist supervised by an experienced doctoral-level clinical psychologist with over ten years of experience delivering CBT-I. All therapists followed a CBT-I treatment manual that was developed for use in cancer populations (Garland, 2021). To ensure treatment fidelity, all therapists received training in the CBT-I protocol and weekly case supervision meetings including video review throughout the duration of the trial. A checklist of the main teaching points to be covered in each treatment session were reviewed. Adherence to the protocol was examined by calculating a total score on the teaching checklist. Therapists with adherence ratings below 90% were provided with additional supervision.

Measures

Fatigue

The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI) is a 30-item self-report measure that quantifies the respondent's experience with fatigue over the past week (Stein et al., 1998). It consists of five domains of fatigue: mental, emotional, vigour, general, and physical. All items were responded to using a 5-point Likert scale ranging from 0 ('not at all') to 4 ('extremely'). The total MFSI score ranges from -24 to 96, where a higher score indicates higher levels of fatigue. The MFSI has been validated for use with cancer populations and has an internal consistency of 0.87 (Donovan et al., 2015; Stein et al., 2004). A decrease of 10.79 points or greater has been established as a minimally clinically important change in this scale (Chan et al., 2018). See Appendix B for the full questionnaire.

Insomnia

The Insomnia Severity Index *(*ISI) is a 7-item self-report measure used for assessing the severity of insomnia symptoms, impact on daytime functioning, and the amount of associated

distress over the last two weeks (Morin, 1993). Each item has a Likert-scale ranging from 0-4 for a total score ranging from 0-28. Total scores ranging from 0-7 indicate no clinically significant insomnia, scores from 8-14 indicate sub-threshold insomnia, scores 15-21 indicate moderate clinical insomnia, and scores 22-28 indicate severe clinical insomnia. This measure has been demonstrated to be reliable and valid for use with cancer populations and has an internal consistency of 0.91 (M. H. Savard et al., 2005). See Appendix C for the full measure.

Perceived Cognitive Impairment

The Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog) is a 37-item self-report measure to examine adult cancer patients with cancer-induced cognitive problems (Wagner, 2009). This study only used the perceived cognitive impairment subscale (18 items), with responses ranging from 0 ("never") to 4 ("several times a day") (Von Ah & Tallman, 2015). The PCI section specifically addresses participants' concerns with their cognitive impairment and the scores range from 0-72, where a higher score indicates greater PCI. This scale has been validated for use in cancer populations and has demonstrated an internal consistency of 0.89 using Cronbach's alpha (Bell et al., 2018; Koch, 2023). See Appendix D for the full measure.

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report measure for depression and anxiety symptoms in medical outpatients and is widely used in cancer populations (Vodermaier et al., 2009; Zigmond & Snaith, 1983). The anxiety and depression subscales both have seven items. Participants are to rate statements describing their symptoms in the past week, based on a 4-point Likert scale ranging from 0-3, where 0 indicates no symptoms, and 3 indicates severe anxiety or depression symptoms. The maximum score for each subscale is

21. A total score ranging from 0-7 indicates normal symptoms, a score from 8-10 indicates a borderline case, and a score from 11-21 indicates a case of anxiety or depression. The HADS has a Cronbach's alpha of .83 and .82 for the anxiety and depression subscales, respectively (Bjelland et al., 2002). See Appendix E for the full scale.

Analytical Methods

Descriptive statistics were conducted to describe the clinical and demographic characteristics of the sample. Linear mixed models were used to identify whether there were differences between the treatment group and the waitlist control group over time. A mixed-effects model was chosen for the ability to specify fixed and random effects as well as to estimate missing data using maximum likelihood estimation. A first-order autoregressive covariance structure was used. Insomnia, depression, anxiety, and PCI were entered into the model as random effects. Lastly, bias-corrected pretest-posttest-control group (dppc2) and standard Cohen's d effect size was calculated for the change in CRF from baseline to post-treatment (Morris, 2008). Small, medium, and large effect sizes are defined as d = 0.2, 0.5, and 0.8, respectively (Cohen, 2013).

For the secondary aim, mediation analyses were performed using the MEMORE package in SPSS version 29 to examine the relationship between CRF and its common comorbidities (insomnia, PCI, depression, and anxiety). This analysis was a within-subjects analysis that used pooled data from participants who completed CBT-I immediately and following a waiting period in order to maximize statistical power. First, a simple mediation model was conducted to see whether change in insomnia symptoms from baseline to post-treatment mediated change in CRF symptoms. Then, a multiple mediation model was used to assess the proportion of change in

CRF that was accounted for by change in insomnia, depression, anxiety, and PCI from baseline to post-treatment.

Results

Demographic Information

The sample (N = 132) was randomly assigned to the immediate (N = 63) or waitlist control group (N = 69). The CONSORT diagram is depicted in Figure 1 and shows additional information about the specific inclusion and exclusion of participants. Participants were mainly women (77%), and the average age of the sample was 60.12 years (SD = 11.37). The most common cancer type was breast (41%). Additional demographic information of the sample is available in Table 1.

Figure 1.

CONSORT Diagram of participant screening

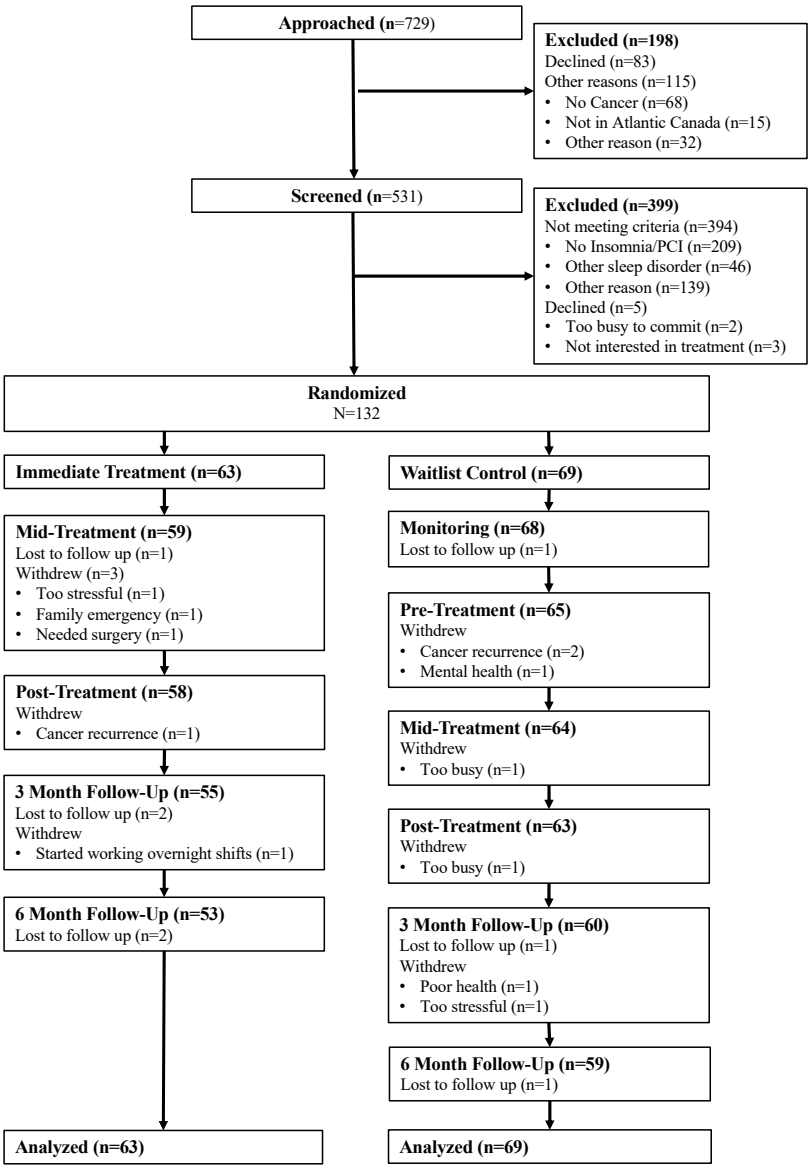


Table 1

Demographic and Clinical Variable Information

Variables		**Treatment group** (*N* = 63)	**Waitlist controls** (*N* = 69)
Demographic variables			
Age (years), mean±SD		59.21±11.93	61.25±10.60
Sex, *N*(%)	Male	13(20.6%)	17(24.6%)
	Female	50(79.4%)	52(75.4%)
Education, *N*(%)	High school (≤11 years)	4(6.3%)	2(2.9%)
	College (12-14 years)	18(28.6%)	24(34.8%)
	Post-secondary (≥15 years)	41(65.1%)	43(62.3%)
Race, *N*(%)	White	57(90.5%)	65(94.2%)
	BIPOC*	6(9.5%)	4(5.8%)
Employment, *N*(%)	Not working/retired	36(57.1%)	48(69.6%)
	Working (part or full-time)	27(42.9%)	21(30.4%)
Clinical variables			
Cancer type, *N*(%)	Breast	25(39.7%)	29(42.0%)
	Prostate and male genitourinary	2(3.2%)	5(7.2%)
	Female genitourinary	6(9.5%)	5(7.2%)
	GI tract	2(3.2%)	5(7.2%)
	Hematological	11(17.5%)	5(7.2%)
	Skin	2(3.2%)	6(8.7%)
	Other	4(6.3%)	2(2.9%)
	Multiple types	11(17.5%)	12(17.4%)
Cancer stage, *N*(%)	Stage 0/In-situ	1(1.6%)	3(4.3%)
	Stage 1	12(19.0%)	15(21.7%)
	Stage 2	13(20.6%)	10(14.5%)
	Stage 3	15(23.8%)	13(18.8%)
	Stage 4	2(3.2%)	5(7.2%)
	Unknown/not applicable	20(31.7%)	23(33.3%)
Time since cancer Diagnosis, *N*(%)	< 2 years	7(11.1%)	7(10.3%)
	2-4 years	11(17.5%)	21(30.9%)
	5-9 years	17(27.0%)	14(20.6%)
	≥10 years	28(44.4%)	26(38.2%)
Cancer treatment**,	Surgery	52(82.5%)	65(94.2%)

Variables		Treatment group (N = 63)	Waitlist controls (N = 69)
N(%)	Chemotherapy	46(73.0%)	35(50.7%)
	Radiation	38(60.3%)	38(55.1%)
	Hormone therapy	13(20.6%)	29(42.0%)
	Other[†]	4(6.3%)	4(5.8%)

[*]Abbreviations: BIPOC=Black, indigenous, or a person of colour; Participants may have received multiple types of treatment. Total number of cancer stages, conditions, or treatments may equal more than 100% of the sample; [†]Other includes immunotherapy and any transplants (e.g., bone marrow).

Effect of Insomnia Treatment of Cancer-Related Fatigue

At baseline, an independent samples t-test showed that CRF in the treatment group (M = 29.57) and waitlist control group (M = 30.21) were not significantly different, $t(129) = -.21$, p = .833. The linear mixed-effects model showed a significant group-by-time interaction on CRF, where the treatment group reported a 20.6-point reduction in fatigue compared to a 3.7-point reduction in the waitlist control with a large effect size ($p < .001$, *Cohen's* $d_{ppc2} = 0.937$). The overall reduction in the treatment group is almost twice the clinically significant change threshold of >10.79 points for the MFSI (Chan et al., 2018). When examined individually, 77% of participants (N = 44) in the treatment group reported significant improvement in CRF as indicated by a decrease of 10.79 points or more on the MFSI relative to 27% (N = 18) of participants in the control group (Chan et al., 2018). Table 2 shows effects and estimated marginal means for the linear mixed model. See figure 2 for the estimated marginal means graph.

Table 2

Between-group comparison of CBT-I on MFSI score.

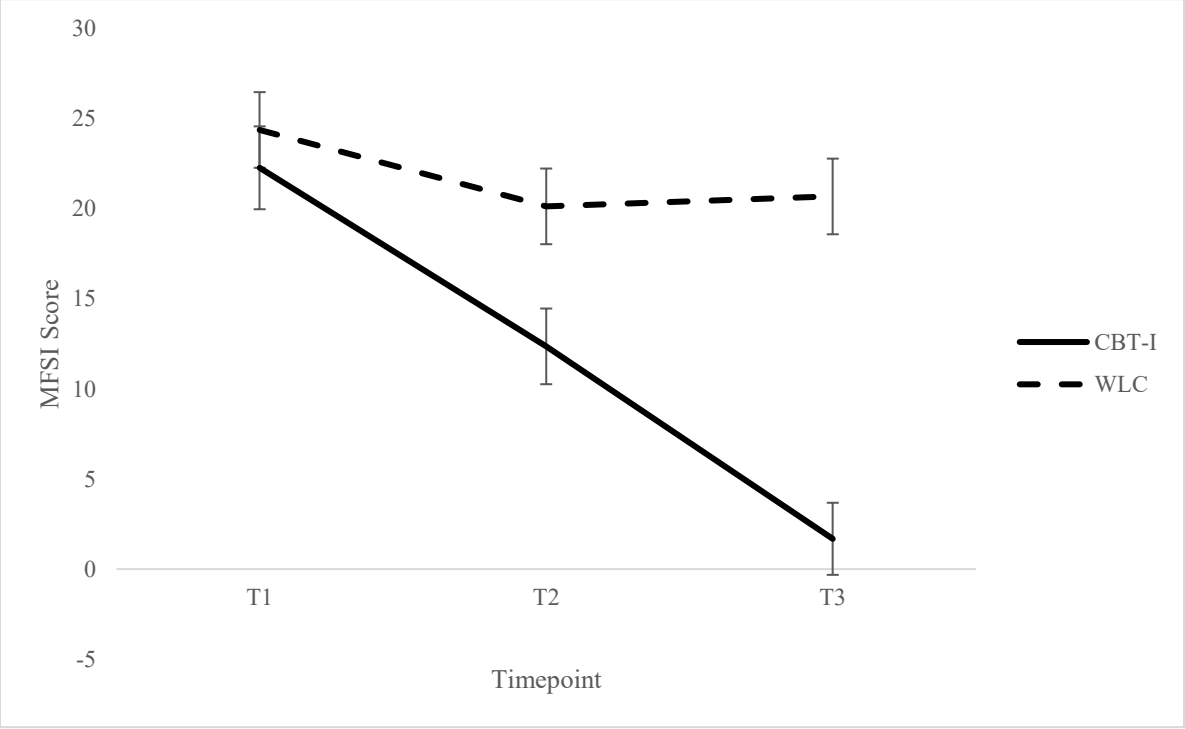
	Linear Mixed-Model					
	Time effect		**Group effect**		**Time-group interaction**	
	F(df)	*P*	F(df)	*P*	F(df)	*P*
Fatigue	40.17(2, 177.88)	<.001	13.12(1, 115.76)	<.001	20.85 (2, 177.87)	<.001

	Estimated Marginal Means		
	Baseline	**Mid-treatment**	**Post-treatment**
	EMM (SE)	EMM (SE)	EMM (SE)
Treatment group	22.27 (2.3)	12.36 (2.06)	1.67 (2.03)
Waitlist group	24.37 (2.09)	20.13 (2.11)	20.67 (2.12)

Note. Insomnia, perceived cognitive impairment, anxiety and depression were included as covariates for all analyses.

Figure 2

Estimated Marginal Means of MFSI Score for each treatment group.



Abbreviations: CBT-I: Treatment group, WLC: Waitlist control group; T1, T2, and T3 refer to baseline, mid-treatment (4 weeks), and baseline (8 weeks), respectively.

Mediating Effect of Insomnia, PCI, Depression, and Anxiety on CRF (pooled analyses)

CBT-I was a significant predictor of change in CRF (*c* = 14.01, 95% CI [10.51, 17.51]). In the simple mediation model, CBT-I was associated with a change in CRF through its effect on change in insomnia severity, (*ab* = 13.26, 95% CI [10.51, 17.51]). Figure 3 shows the results of the full model. In the multiple mediation model, CRF was fully mediated by change in insomnia, symptoms of depression, PCI, and symptoms of anxiety. Change in insomnia accounted for almost 50% of the overall effect, (*ab* = 6.33, 95% CI [2.85, 10.22]). Change in depressive symptoms was the next significant mediator (*ab* = 4.39, 95% CI [2.20, 6.84]). Change in PCI and

anxiety accounted for the remaining variance (*ab* = 2.33, 95% CI [.19, 4.66]) and (*ab* = 1.52, 95% CI [.11, 3.05]) respectively. Figure 4 shows the results of the multiple mediation model.

Figure 3

Single Mediation Model

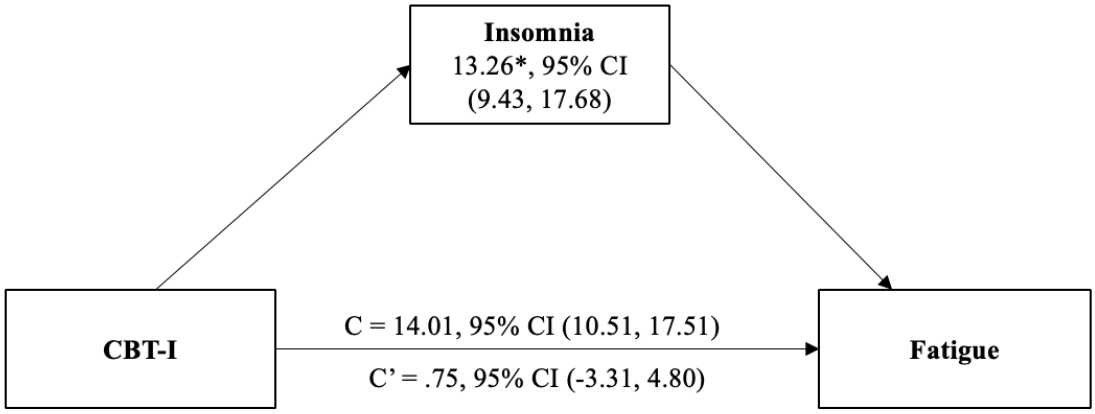
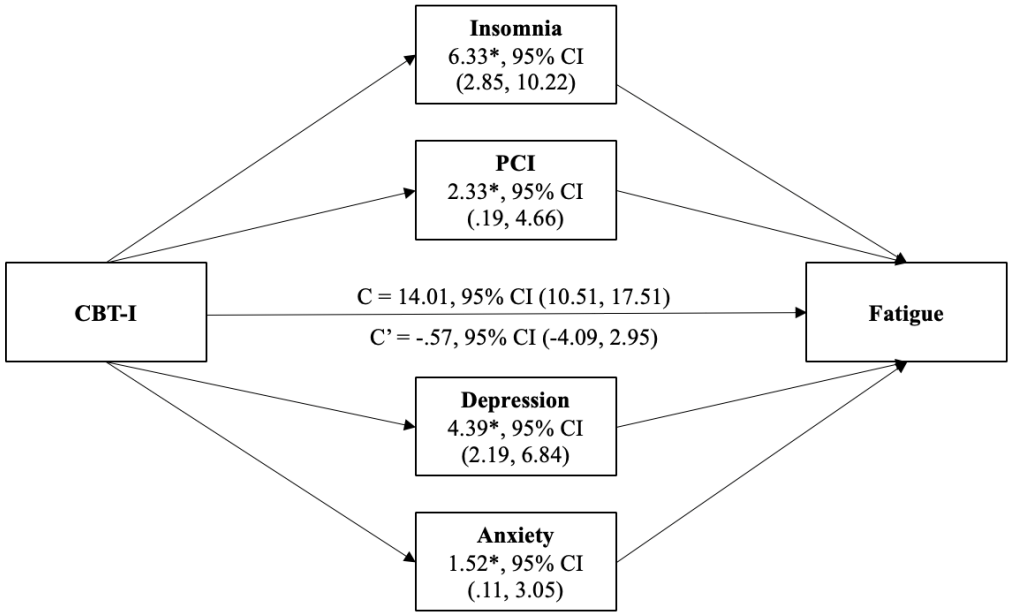


Figure 4

Multiple Mediation Model



Discussion

The results of this study provide additional evidence for the ability of CBT-I to improve CRF in a heterogeneous sample of cancer survivors with insomnia and PCI. After statistically adjusting for insomnia, PCI, depression, and anxiety, the overall reduction in fatigue was almost twice the established clinically significant change threshold. Overall, 75% of participants reported significant improvement in CRF after completing 7 weeks of CBT-I. This methodological approach expands on the existing literature (Dirksen & Epstein, 2008; Heckler et al., 2016; Zachariae et al., 2018) and allows for the isolation of specific mechanisms of change. In a single mediation model, change in insomnia symptoms fully mediated the change in CRF symptoms. When all comorbidities were examined in one model, insomnia accounted for nearly half of the change in CRF, followed by symptoms of depression, PCI and symptoms of anxiety. Considering that CRF is frequently comorbid with insomnia, cognitive impairment, depression, and anxiety among cancer survivors, these results suggest that CBT-I is effective in addressing the complex myriad of comorbid symptoms associated with CRF, which could reduce burden on the patient and optimize the use of treatment resources.

The previously published primary outcome of this trial found that CBT-I significantly improved cancer-related cognitive impairments (Garland et al., 2024). Moreover, depression and anxiety have also been reported to improve after CBT-I (Arico et al., 2016; Peoples et al., 2019; Squires et al., 2022). Therefore, the present study along with the existing literature suggest that improving insomnia through CBT-I can also improve other comorbid symptoms in cancer survivors. The reason for this may be due to the close relation of insomnia to CRF, depression, anxiety, and cognitive impairment, where improving sleep may improve these symptoms as well. These comorbidities may share similar underlying mechanisms, such as an increase of

proinflammatory cytokines, and dysregulation of the HPA axis and autonomic nervous system, as well as behavioural mechanisms (Bortolato et al., 2017; Bower, 2014; Zielinski & Gibbons, 2022). Therefore, it is possible that the improvement of sleep through CBT-I allows for improvement of symptoms with a related etiology.

This study expanded the current literature on using singular interventions for the treatment of multiple symptoms among cancer survivors. A recent systematic review (8 studies, 625 breast cancer survivors) that assessed the efficacy of nonpharmacological interventions (e.g., exercise, Tai-Chi, yoga, relaxation therapies, and acupressure) for symptom clusters (e.g., fatigue-sleep-depression, fatigue-sleep-anxiety-depression-pain) among breast cancer survivors reported that the interventions assessed reduced the severity of diverse symptoms that cut across fatigue, sleep, and mood (Li et al., 2024). However, the review did not find consistent results for the efficacy of the interventions due to the limited number of studies (Li et al., 2024). Another systematic review (16 studies, 2040 breast cancer survivors) assessed the efficacy of pharmacological and non-pharmacological interventions for the fatigue-depression-sleep disturbance symptom cluster among breast cancer survivors (Wong et al., 2023). Overall, this review found that bright-light therapy, acupressure, and psychological nursing interventions significantly reduced symptoms. Moreover, the recommended guideline for management of symptoms among cancer populations has supported the idea of treating multiple symptoms with one single intervention (Kwekkeboom et al., 2020).

Limitations and Directions for Future Research

The sample mainly consisted of well-educated, white women with a diagnosis of breast cancer which limits the generalizability of results, as this population is not representative of all cancer survivors. Future research should seek more diverse samples. Additionally, this study

used a randomized controlled waitlist design, therefore it is possible that effects between groups may have been inflated. However, this design was necessary as we could not ethically withhold an established and effective treatment. Future research should consider using comparative designs with other treatments for CRF, such as exercise that has demonstrated efficacy in CRF (Hilfiker et al., 2018). Moreover, it is possible that improvements in CRF that were measured directly following the intervention may have changed, therefore future research should assess the long-term durability of effects of CBT-I on CRF. In addition, the waitlist control group had a higher number of participants who were completing endocrine therapy, compared to the treatment group, and therefore, may have impacted the results. Future research should attempt to balance the participants who are currently using endocrine therapy. Lastly, although 75% of the sample experienced a significant improvement in CRF following the intervention, future research should focus on understanding why some participants' CRF did not improve.

This study also had several strengths. First, CRF was measured using a multidimensional measure that assessed five domains of CRF. Therefore, this measure allowed us to gain a better understanding of the CRF experienced in the sample. Additionally, the other instruments used were also validated for use in cancer populations. Lastly, the use of the mediation models allowed gave us insight to the relationship between CRF and its frequent comorbidities.

Conclusion

CBT-I was effective in treating CRF among cancer survivors while controlling for the common comorbidities of insomnia, PCI, depression, and anxiety. Improvements in these symptoms fully mediated improvements in CRF. Overall, CBT-I is a robust intervention with efficacy for improving CRF among cancer survivors with insomnia and PCI.

Chapter 3: Factors Associated with Significant Improvement in Cancer-Related Fatigue after Completing Cognitive Behavioural Therapy for Insomnia among Cancer Survivors

Authorship statement: Conceptualization, S.G.; methodology, S.G., K. G., J.R., and E. F.; formal analysis, K.G., investigation, K.G.; resources, K.G, S.G., J.R., and E. F.; data curation, K. G.; writing—original draft preparation, K.G.; writing—review and editing, S.G., J.R., and E.F.; visualization, K.G.; supervision, S.G.; project administration, K.G. and S.G.; funding acquisition, K.G. and S.G. Manuscript is being prepared for submission.

Abstract

PURPOSE: Cancer-related fatigue (CRF) can be a persistent and severe negative consequence following a cancer diagnosis. Cognitive behavioural therapy for insomnia (CBT-I) can improve CRF in those with insomnia comorbid with cancer. This secondary analysis of a randomized controlled trial investigated what proportion of participants benefit and the factors associated with an improvement in CRF following CBT-I.

METHODS: Atlantic Canadian cancer survivors (N=132) with insomnia disorder and perceived cognitive impairment symptoms were recruited to participate in a randomized controlled trial of CBT-I. Fatigue was measured using the Multidimensional Fatigue Symptom Inventory – Short Form. Univariable and multivariable binary logistic regressions were used to assess clinical, symptom, and demographic factors associated with a significant improvement in CRF after CBT-I.

RESULTS: The majority (75%) of the sample (M_{age}=60.12 years, 77% women, 45% breast cancer) experienced a significant reduction in CRF symptoms following the intervention. Being younger (under 55), being female, having anxiety, and undergoing chemotherapy were associated with a greater likelihood of improvement in CRF at the univariable level. At the multivariable level, only being younger was significantly associated with an improvement in CRF after CBT-I.

CONCLUSION: CBT-I demonstrates evidence of efficacy in cancer survivors who experience CRF. Differences in sleep patterns between younger and older people may explain why CBT-I improved CRF more in younger participants. In addition, treatment adherence may explain why some participants experienced significant improvements in CRF after CBT-I. Future research is

needed to better understand the demographic, symptom, and clinical variables that may influence treatment response.

Keywords: cancer; cognitive behavioural therapy for insomnia; cancer-related fatigue; insomnia

Introduction

Cancer-related fatigue (CRF) can be a severe and distressing side effect of cancer treatment with physical, emotional, and cognitive components of exhaustion and tiredness (Berger et al., 2015). CRF is one of the most prevalent negative consequences of cancer with approximately 60% of cancer survivors experiencing CRF following cancer treatment (Lawrence et al., 2004; Servaes et al., 2002). CRF has been linked to the pathophysiological process of cancer, or its treatment, and interferes with daily functioning (Berger et al., 2015). Moreover, CRF rarely remits following cancer treatment and can be experienced for many years following a cancer diagnosis (Cella et al., 2001). CRF also has negative impacts on the quality of life of cancer survivors and is reported to be more severe than fatigue experienced in the general population (Jacobsen et al., 2007).

There is no universally recommended treatment for CRF (Bower, 2014). Exercise interventions have the most evidence of reducing CRF (Kessels et al., 2018), but physical limitations and access to exercise programs can pose challenges. Pharmacotherapy interventions have also been shown to reduce CRF with small effect sizes (Minton et al., 2008). However, Mustian et al. (2017) conducted a metanalysis of 113 studies and showed that exercise and psychological interventions are more effective in treating CRF compared to pharmacological interventions. There is evidence that cognitive behavioural therapy for insomnia (CBT-I) can reduce CRF in patients with comorbid insomnia. CBT-I is an evidence-based treatment for insomnia and is recommended by the American Academy of Sleep Medicine, the American College of Physicians, and the European Sleep Research Society (Edinger et al., 2021; Qaseem et al., 2016; Riemann et al., 2017). CBT-I works by targeting the unhelpful beliefs and behaviours that perpetuate and maintain insomnia (Spielman et al., 1987). This intervention also

uses psychoeducation about sleep and sleep hygiene information to provide patients with tools to prevent recurrence of insomnia symptoms. Randomized controlled trials have demonstrated efficacy for CBT-I to treat CRF among cancer survivors. In a trial comparing CBT-I and a wakefulness-promoting medication armodafinil among a heterogeneous sample of 96 cancer survivors, CRF significantly improved only among the participants who received CBT-I (Heckler et al., 2016). Another study delivered CBT-I for CRF among 72 women with breast cancer, and observed significant improvements following the intervention (Dirksen & Epstein, 2008). Further, both stepped-care and standard delivery methods for CBT-I significantly improved CRF among 177 cancer survivors (Savard et al., 2021). Our team also demonstrated that CBT-I significantly improved CRF among 132 cancer survivors while controlling for insomnia, perceived cognitive impairment, depression, and anxiety (Greeley, 2024). Overall, the literature suggests that CBT-I may be an effective treatment for CRF.

Although literature supports the use of CBT-I for CRF, it is not known which factors may influence who may experience the greatest likelihood of fatigue symptom change. There may be certain demographic or clinical factors that could impact an individual's outcomes following the intervention. For instance, some literature suggests that certain genetic factors influence response to insomnia interventions in cancer populations (Genovese et al., 2021). Moreover, other literature has examined the factors associated with CBT-I outcomes for individuals with comorbid major depressive disorder, where seasonal fluctuations in depressive symptoms and sleep patterns, and daytime dysfunction enhanced CBT-I efficacy (Maruani et al., 2023). However, it is not known what factors may be associated with a significant improvement in CRF after CBT-I. Identifying who may benefit from an intervention supports more personalized and

efficient treatment recommendations and highlights barriers that need to be addressed to enhance treatment engagement and effectiveness.

Present Study

The primary aim of this exploratory study is to identify the proportion of cancer survivors who reported clinically significant improvement in CRF following participation in a waitlist-controlled trial evaluating CBT-I among those experiencing insomnia and perceived cognitive impairment. Then, we sought to identify whether specific demographic and clinical variables were associated with an increased likelihood of clinically meaningful improvements in CRF symptoms.

Methods

Study Design

This study used data from a recently completed randomized waitlist-controlled trial called ACTION: Addressing Cancer Treatment-Related Insomnia Online in Atlantic Canada (clinicaltrials.gov identifier: NCT04026048) (Garland et al., 2021; Garland et al., 2024). The purpose of the ACTION study was to determine if CBT-I would improve perceived cognitive impairment symptoms among cancer survivors. Fatigue, sleep, and symptom measures were completed at the following timepoints: baseline, mid-treatment (4-weeks), post-treatment (8-weeks). Ethical approval was obtained by the Health Research Ethics Board (#20200427). Informed consent was obtained before participation.

Sample

The sample was recruited from treatment clinics, radio advertisements, posters, referrals from oncologists, and from mailouts to individuals who participated in the Atlantic Partnership for Tomorrow's Health study (Sweeney et al., 2017). Eligibility criteria included: English-

speaking cancer survivors of any type or stage residing in Atlantic Canada (Newfoundland and Labrador, Nova Scotia, New Brunswick, and Prince Edward Island), who had completed their cancer treatment at least 6 months prior to study entry. Those with hematological malignancies were eligible to participate if their condition and treatment regimen was stable. Participants had to meet the diagnostic criteria for insomnia disorder based on the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) and report perceived cognitive impairment (PCI) symptoms by indicating a response of "quite a lot" or "always" on questions pertaining to concentration and memory on the European Organization for Research and Treatment of Cancer core quality of life questionnaire (Aaronson et al., 1993; American Psychiatric Association, 2013). Participants also needed access to the internet and a webcam. Exclusion criteria included: having poor performance status (i.e., score greater than 2 on the Eastern Cooperative Oncology Group Performance Status Scale; Oken et al., 1982), an untreated psychological or sleep disorder other than insomnia (e.g., sleep apnea), having received cranial radiation, having a major sensory deficit or other condition that could affect participation or cognitive functioning, or had previous experience with CBT-I.

Intervention

Cognitive Behavioural Therapy for Insomnia (CBT-I)

CBT-I was delivered virtually using a videoconferencing platform. The intervention involved seven weekly one-hour sessions. The therapists were trained psychology doctoral students who were supervised by a PhD-level registered psychologist with over a decade's experience delivering CBT-I. All therapists followed a CBT-I treatment manual that was developed for use in cancer populations (Garland, 2021). To ensure treatment fidelity, all therapists received training in the manualized CBT-I protocol and weekly case supervision

meetings including video review throughout the duration of the trial. A checklist of the main teaching points to be covered in each treatment session were reviewed. Adherence to the CBT-I protocol was examined by calculating a total score on the teaching checklist. Therapists with adherence ratings below 90% were provided with additional supervision. The intervention involved five main components: (1) sleep restriction, (2) stimulus control, (3) cognitive restructuring, (4) relaxation training, and (5) sleep hygiene (Edinger et al., 2021; Morin et al., 2023). More information on the intervention can be found in the primary outcomes paper (Garland et al., 2024).

Measures

Demographic Questionnaire

Participants were administered a demographic questionnaire that measured the following variables: age, gender, race, years of education, employment status, cancer type/stage, and treatment type. See Appendix A for the full questionnaire.

Fatigue

The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI) is a 30-item self-report measure that examines the incidence of fatigue. Five domains of fatigue are measured: mental, emotional, vigour, general, and physical. All items were responded by using a 5-point Likert scale ranging from 0 (‘not at all’) to 4 (‘extremely’). Each subscale had a maximum score of 24. The total score ranges from -24 to 96, where a higher score indicates higher levels of CRF. This measure has been validated for use with cancer populations and has an internal consistency of 0.87 when used in a cancer sample (Donovan et al., 2015; Stein et al., 2004). A significant improvement on the MFSI has been identified as a change of 10.79 points or greater (Chan et al., 2018). The MFSI has been validated for use with cancer populations and has

an internal consistency of 0.87 based on Cronbach's alpha in cancer (Donovan et al., 2015; Stein et al., 2004).

See Appendix B for the full measure.

Insomnia

The Insomnia Severity Index (ISI) is a 7-item self-report measure used for assessing the severity of insomnia symptoms over a two-week period (Morin, 1993). Each item has a 5-point Likert-scale. The highest possible total score is 28. Total scores ranging from 0-7 indicate no clinically significant insomnia, scores from 8-14 indicate sub-threshold insomnia, scores 15-21 indicate moderate clinical insomnia, and scores 22-28 indicate severe clinical insomnia. This measure has an internal consistency of 0.91 and has been validated for use in cancer populations (Morin et al., 2011; M. H. Savard et al., 2005). See Appendix C for the full measure.

Perceived Cognitive Impairment

The Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog) is a 37-item self-report measure to examine adult cancer patients with cognitive problems (Wagner, 2009). Four subscales are assessed: perceived cognitive impairments, impact of perceived cognitive impairments on quality of life, comments from others, and perceived cognitive abilities. Participants are to rate statements about these four domains on a 5-point Likert scale. The FACT-Cog has demonstrated an internal consistency of 0.89 using Cronbach's alpha (Bell et al., 2018). This study will only be assessing the first subscale, perceived cognitive impairment (Von Ah & Tallman, 2015). See Appendix D for the full questionnaire.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report measure to measure depression and anxiety symptoms in medical outpatients (Zigmond & Snaith, 1983).

This measure is widely used among cancer populations (Vodermaier et al., 2009). The HADS uses a combined score of two subscales: anxiety and depression. Participants rate statements describing their symptoms in the past seven days, based on a 4-point Likert scale ranging from 0 (no symptoms) to 3 (severe anxiety or depression symptoms). A total score ranging from 0-7 indicates normal symptoms, a score from 8-10 indicates a borderline case, and a score from 11-21 indicates a case of anxiety or depression. The Cronbach's alpha for the anxiety and depression subscale is 0.83 and 0.82, respectively (Bjelland et al., 2002). See Appendix E for the full scale.

Analytical Methods

These analyses pooled data from participants who completed CBT-I immediately and following a waitlist period to allow for maximal statistical power. Pre- and post-intervention MFSI scores were calculated, and those with a decrease of greater than 10.79 points were defined as significantly improving in CRF. Descriptive statistics (i.e., means and standard deviations) were produced to examine if certain measured variables were associated with a significant improvement in CRF after the intervention. Frequencies were produced for ordinal and categorical variables.

Linear regressions were conducted to assess multicollinearity within the variables. Separate univariable logistic regressions were used to assess which clinical and demographic variables predicted with a significant improvement in CRF (i.e., responder status). Pre-treatment scores for insomnia severity, PCI, anxiety, and depression were adjusted for in the models. Univariate predictors with p-values $< .10$ were then entered simultaneously into a multivariable logistic regression model. Analyses were conducted in SPSS Version 29.

Results

Participants

A total of 132 participants (77% female, 92% white) completed the study. Demographic information is displayed in Table 1. The majority of the sample (N = 85, 64%) had moderate or severe insomnia before CBT-I. In addition, 84 participants (63%) had borderline anxiety or anxiety at baseline, and 55 participants (42%) had borderline depression or depression before the intervention.

Three out of every four participants (N = 91; 75%) met or exceeded the clinical 10.79-point clinical cutoff on the MFSI which is indicative of clinically relevant improvement in CRF and were classified as responders.

Table 1

Demographic and Clinical Variable Information

Variables		**Responders** *(N* = 91)	**Non-Responders** *(N* = 30)
Demographic variables			
Age (years), mean (SD)		58.87 (11.53)	64.43 (9.82)
N (%)	Under 55	31 (25.6%)	4 (3.3%)
	55-65	31 (25.6%)	10 (8.3%)
	Over 65	29 (23.9%)	16 (13.2%)
Sex, *N* (%)	Male	16 (13.2%)	11 (9.1%)
	Female	75 (61.9%)	19 (15.7%)
Education, *N* (%)	High school (≤12 years)	13 (10.7%)	2 (1.6%)
	College (13-14 years)	18 (14.8%)	11 (9.1%)
	Post-secondary (≥15 years)	60 (49.5%)	17 (14%)
Race, *N* (%)	White	85 (70.2%)	27 (22.3%)
	BIPOC*	6 (4.9%)	3 (2.5%)
Employment, *N* (%)	Not working/retired	53 (43.8%)	22 (18.2%)

Variables		Responders (*N* = 91)	Non-Responders (*N* = 30)
	Working (part or full-time)	38 (31.4%)	8 (6.6%)
Clinical variables			
Cancer type, *N* (%)	Breast	39 (32.2%)	10 (8.3%)
	Female and male genitourinary	10 (8.3%)	5 (4.1%)
	Hematological	13 (10.7%)	3 (2.5%)
	Other	14 (11.6%)	6 (4.9%)
	Multiple types	15 (12.4%)	6 (4.9%)
Cancer stage, *N* (%)	Stage 0/In-situ & Stage 1	22 (18.2%)	8 (6.6%)
	Stage 2	14 (11.6%)	6 (4.9%)
	Stage 3	22 (18.2%)	4 (3.3%)
	Stage 4	5 (4.1%)	1 (.8%)
	Unknown/not applicable	24 (19.8%)	8 (6.6%)
Years since cancer Diagnosis, mean (SD)		9.27 (8.03)	11.59 (8.41)
N (%)	< 3 years	24 (19.8%)	6 (4.9%)
	3-6 years	18 (14.8%)	4 (3.3%)
	6-12 years	24 (19.8%)	8 (6.6%)
	≥12 years	24 (19.8%)	12 (9.9%)
Cancer treatment**,	Surgery	79 (65.2%)	27 (22.3%)
N (%)	Chemotherapy	59 (48.7%)	14 (11.6%)
	Radiation	55 (45.4%)	14 (11.6%)
	Hormone therapy	33 (27.3%)	7 (5.7%)
	Other†	6 (4.9%)	2 (1.6%)
Anxiety, *N* (%)	None	26 (21.4%)	16 (13.2%)
	Borderline	24 (19.8%)	7 (5.7%)
	Anxiety	41 (33.8%)	7 (5.7%)
Depression, N (%)	None	50 (41.3%)	19 (15.7%)
	Borderline	20 (16.5%)	8 (6.6%)
	Depression	21 (17.3%)	3 (2.5%)
Insomnia, N (%)	None	0 (0%)	0 (0%)
	Mild	27 (22.3%)	11 (9.1%)
	Moderate	53 (43.8%)	12 (9.9%)

Variables		Responders (*N* = 91)	Non-Responders (*N* = 30)
	Severe	9 (7.4%)	5 (4.1%)
PCI Score, N (%)	≤35	38 (31.4%)	9 (7.4%)
	36-50	30 (24.8%)	13 (10.7%)
	>50	23 (19%)	8 (6.6%)

*Abbreviations: BIPOC=Black, Indigenous, or a person of colour; **Participants may have received multiple types of treatment. Total number of cancer stages, conditions, or treatments may equal more than 100% of the sample; †Other includes immunotherapy and any transplants (e.g., bone marrow).

Univariable Regression

The results of the full analysis are shown in Table 2. At the univariable level, those who were under 55 were significantly more likely to experience improved CRF (OR = 4.27, 95% CI [1.28, 14.29], $p = .018$), compared to those who were over age 65. Women were more likely to improve (OR = 2.71, 95% CI [1.08, 6.79], $p = .033$) compared to men, those with clinically significant anxiety (OR = 3.6, 95% CI [1.31, 9.95], $p = .013$) were more likely to improve than those with subthreshold anxiety, and those who were treated with chemotherapy (OR = 2.11, 95% CI [.91, 4.86], $p = .081$) had a greater likelihood of improvement in CRF compared to those who were not. No other demographic, symptom, or clinical factor reached statistical significance in the univariable model.

Multivariable Regression

Variables that were significant at a threshold of $p < .10$ were entered into a multivariable regression model. The overall model was significant, $\chi^2(6) = 16.58$, $p = .011$, with the included predictor variables accounting for 19% of variance in fatigue improvement (Nagelkerke $R^2 = .19$). The Hosmer and Lemeshow test was not significant, $\chi^2(8) = 4.52$, $p = .81$, indicating a good model fit. The model had an accuracy rate of 76.9%, sensitivity was 78.4%, and specificity was 60%. When all other variables were held constant, only being younger (under 55 years) remained

associated with a significant improvement in CRF after CBT-I, [AOR = 3.83 (95% CI 1.07, 13.67), p = .039].

Figure 1.

CONSORT Diagram of participant screening

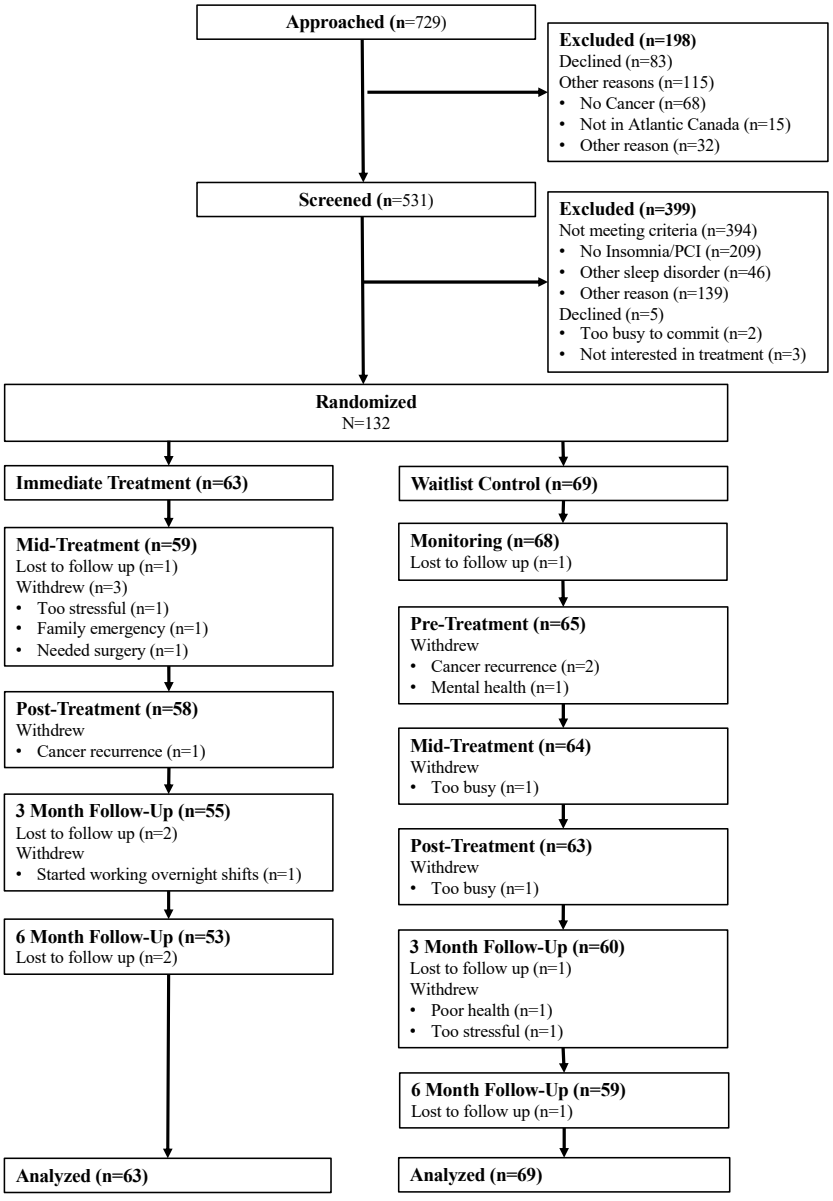


Table 2

Binomial Logistic Regression of Factors Associated with a Significant Change in Fatigue

		Univariable		Multivariable	
		Odds Ratio [95% CI]	***p***	**Adjusted Odds Ratio [95% CI]**	***p***
Age	Over 65 (ref)	1	-	1	-
	55-65	1.71 [.67, 4.37]	.26	1.48 [.55, 4.00]	.44
	Under 55	4.27 [1.28, 14.29]	**.018****	3.83 [1.07, 13.67]	**.039****
Gender	Men (ref)	1	-	1	-
	Women	2.71 [1.08, 6.79]	**.033****	2.73 [.99, 7.5]	.051
Years of Education	High school (≤12 years; ref)	1	-		
	College (13-14 years)	.25 [.05, 1.33]	.11		
	Post-secondary (≥15 years)	.54 [.11, 2.64]	.45		
Race	BIPOC (ref)	1	-		
	White	1.57 [.37, 6.72]	.54		
Employment Status	Working (ref)	1	-		
	Not working/retired	1.97 [.79, 4.89]	.14		
Years since cancer diagnosis	< 3 years (ref)	1	-		
	3-6 years	1.13 [.28, 4.58]	.87		
	6-12 years	.75 [.23, 2.49]	.64		
	≥12 years	.5 [.16, 1.55]	.23		
Cancer type	Breast (ref)	1	-		
	Male and Female Genitourinary	.51 [.14,1.84]	.31		
	Hematological	1.11 [.26, 4.66]	.89		

	Other	.64 [.19, 2.07]	.46		
	Multiple types	.6 [.18, 1.95]	.39		
Cancer stage	Stage 0 & 1 (ref)	1	-		
	Stage 2	.84 [.24, 2.97]	.79		
	Stage 3	2.00 [.53, 7.62]	.31		
	Stage 4	1.82 [.18, 18.04]	.61		
	Unknown	1.09 [.35, 3.4]	.88		
Surgery	No (ref)	1	-		
	Yes	1.37 [.36, 5.21]			
Chemotherapy	No (ref)	1	-	1	-
	Yes	2.11 [.91, 4.86]	**.081***	1.84 [.73, 4.62]	.19
Radiation	No (ref)	1	-		
	Yes	.573 [.249, 1.315]	.189		
Hormonal therapy	No (ref)	1	-		
	Yes	.535 [.207, 1.38]	.196		
Anxiety	No anxiety (ref)	1	-	1	-
	Borderline	2.11 [.74, 6.01]	.16	2.11 [.68, 6.49]	.19
	Anxiety	3.6 [1.31, 9.95]	**.013****	2.29 [.78, 6.78]	.13
Depression	No depression (ref)	1	-		
	Borderline	.95 [.36, 2.52]	.92		
	Depression	2.66 [.71, 9.96]	.15		
Insomnia	Mild (ref)	1	-		
	Moderate	1.8 [.71, 4.61]	.22		
	Severe	.73 [.2, 2.68]	.64		
PCI	≤35 (ref)	1	-		
	36-50	.55 [.21, 1.45]	.23		

	>50	.68 [.23, 2.01]	.48

*Significant at .1 level (univariable regressions only)
**Significant at .05 level

Discussion

The purpose of the present study was to identify clinical or demographic factors that were associated with a clinically relevant improvement in CRF after completing seven virtual sessions of CBT-I. The majority of the sample (75%; $N = 91$) evidenced change in CRF that met or exceeded the reliable change index indicative of clinically relevant improvement after completing CBT-I. This finding is consistent with previous literature that demonstrated secondary improvements in CRF after completing CBT-I. For instance, Zachariae et al. (2018) observed that CRF significantly improved following virtually delivered CBT-I. Similarly, Dirksen & Epstein (2007) demonstrated that CBT-I was effective for CRF among a sample of 72 breast cancer survivors (Dirksen & Epstein, 2008). Therefore, the present study suggests that improving insomnia through CBT-I can also improve other comorbid symptoms in cancer survivors, such as CRF. The reason for this may be due to the close relation and etiology of insomnia and CRF, where improving sleep may improve CRF symptoms as well. These conditions may share similar underlying biological and behavioural mechanisms (Bower, 2014; Zielinski & Gibbons, 2022). Overall, this study showed that CBT-I is effective in reducing CRF symptoms in 3 out of 4 cancer survivors with insomnia, a result which should prompt immediate efforts to increase availability of this treatment as part of comprehensive survivorship care.

Independently, females, those who were younger than 55, those who were treated with chemotherapy, and those with significant anxiety, had a greater likelihood of experiencing a significant reduction in CRF after the intervention. Previous research has demonstrated that being female is a predisposing factor of developing CRF (Huang et al., 2022; Ma et al., 2020). It

may be due to the fact that females generally have lower levels of hemoglobin compared to males, which is associated with fatigue (Cella, 1998). Further, being younger, specifically being under 55 years old, was associated with a greater likelihood of improvement in CRF following CBT-I. Sleep patterns change as a person ages, such as more frequent naps, decreased slow wave sleep, and more frequent awakenings, which contribute to poor sleep (Li et al., 2018). Older adults also experience earlier circadian rhythms which may reduce CBT-I efficacy (Fiorentino & Martin, 2010). Therefore, these differences in sleep patterns between younger and older people may explain why CBT-I seemed to be more effective in younger participants for CRF. Although not statistically significant (p=.081), chemotherapy did meet the threshold of p<.10 to be entered into the multivariable model. Therefore, participants treated with chemotherapy were also more likely to report improved CRF after the intervention. In general, those who have undergone chemotherapy have a greater chance of developing more severe CRF (Huang et al., 2022), therefore, it is possible that those who have had chemotherapy have more room to improve. Lastly, it was also found that those with anxiety were more likely to improve in CRF after CBT-I compared to those without anxiety, or with borderline anxiety symptoms. Anxiety, insomnia, and CRF are frequently comorbid; therefore, those who experience all symptoms may be more likely to benefit as improving sleep may also improve their anxiety (Brown & Kroenke, 2009).

When all four of these factors were entered into a model simultaneously, only being younger (less than 55 years old) remained significant. Participants under 55 years of age were four times more likely to experience clinically meaningful improvement in CRF compared to those who were older than 65 years. It is important to note that this finding does not imply that older adults do not benefit from CBT-I, it is rather that the effects from CBT-I on CRF may not be as pronounced in older adults compared to younger adults. This may be due to the differences

in sleep between younger and older adults, as mentioned above, as sleep problems and CRF have been shown to exacerbate each other (Bower, 2014). Alternatively, it could be due to older adults experiencing more severe CRF than younger adults, making some components of CBT-I, such as sleep restriction, more difficult to adhere to, and thus impacting CRF outcomes (Ma et al., 2020). Lastly, considering that no other assessed demographic or symptom-related factors could impact the CRF outcomes, the robustness of CBT-I for improving CRF is supported.

Limitations

The most significant limitation of the methods used in this study is the inability to demonstrate a causal relationship, as a confounding variable may be responsible for the significant associations. In addition, the multivariable model accounted for 19% of the total variance, which leaves a lot of variance unaccounted for by the model. Therefore, future research should explore other possible factors that may be associated with a significant improvement in CRF. One such factor may be treatment adherence, which was not systematically measured in this study. CBT-I involves several components that include setting specific sleep-wake times and limiting daytime napping. Adherence to these components ranges from 40-70% in the general population (Matthews et al., 2013). Lack of adherence to CBT-I has been associated with poorer outcomes in cancer populations (Matthews et al., 2013; J. Savard et al., 2005). It is possible that certain groups (e.g. older participants, males, etc.) struggled with adherence, which may have influenced their response to treatment. Adherence can be challenging to assess in behavioral interventions. Other trials have assessed adherence subjectively by patient and/or therapist reported measures, assessment of sleep diaries, and weekly homework adherence checks (Berger et al., 2003; Hebert et al., 2010; Tremblay et al., 2009). Future studies should attempt to measure adherence using both self-report and objective methods. Other clinical factors such as comorbid

health conditions may impact the change in CRF after CBT-I. Further, the sample consisted of mainly white women and breast cancer survivors, which is not generalizable to all cancer survivors. Future research should focus on collecting data from diverse samples. Moreover, future research should attempt to use other methods for measuring CRF. Although the MFSI-SF is a valid measure for CRF, other types of measurement, such as biomarkers or ecological momentary assessment, will allow for an objective measurement of CRF.

Conclusions

This study demonstrated that three out of four participants are likely to report clinically meaningful improvement in CRF after completing CBT-I. When entered into a model that included sex, anxiety symptoms, and receiving chemotherapy, only younger age remained significantly associated with improvement in CRF. These results add to the evidence that CBT-I is a robust intervention for insomnia and comorbid symptoms. Efforts need to focus on implementation and increasing access to this potent intervention.

Chapter 4: Contextualizing the Results and Recommendations for Future Research

Summary of Main Findings

This thesis examined the use of CBT-I as a treatment for CRF in Atlantic Canadian cancer survivors with insomnia and PCI. The first study examined the efficacy of CBT-I for CRF in participants, while statistically adjusting for insomnia, PCI, depression, and anxiety. Participants in the treatment group experienced a significant reduction in CRF symptoms compared to the control group, after comorbidities were adjusted for. Next, data from both groups were pooled for analysis with a larger sample size. In the single mediation model, the change in insomnia symptoms fully mediated the change in CRF symptoms after CBT-I. When all comorbidities were examined in a multiple mediation model, insomnia accounted for almost half of the change in CRF, followed by symptoms of depression, PCI and anxiety. Considering that CRF is often comorbid with insomnia, PCI, depression, and anxiety among cancer survivors, these results suggest that CBT-I is effective in addressing the comorbid symptoms associated with CRF. Further, these results help us to better understand the specific mechanisms of CRF.

The second study assessed the pooled data after both groups completed CBT-I and found that 75% ($N = 91$) experienced a significant improvement in CRF. Out of the assessed demographic, clinical, and symptom-related variables, only younger age (under 55 years) was significantly associated with improving in CRF following the intervention. This provides support for the idea that as a person ages, they experience different sleep patterns, and some poor sleep habits (i.e., more frequent napping; (Li et al., 2018). Moreover, this finding could also be due to older people having more comorbid health conditions compared to younger people, which may interfere with CBT-I outcomes. This finding demonstrated the robustness of CBT-I as no other outside factors examined were able to significantly influence the outcomes. The trial did not measure participants adherence to the intervention; therefore, it may be possible that treatment

adherence was responsible for the significant outcomes in CRF. Additionally, there may be other variables that were not measured in the trial that could be acting as a confounding variable for the impact of CBT-I on CRF.

Clinical Implications

Based on this research, CRF is demonstrated to be a mechanism that is exacerbated with the presence of other conditions. It was found that insomnia, PCI, anxiety, and depression were frequently co-occurring with CRF, and influenced each other where benefits in CRF also led to benefits in these comorbidities after the intervention. This finding is consistent with literature that provides evidence for the presence of symptom clusters in cancer populations (So et al., 2021). Therefore, this research provides support for treating CRF with CBT-I.

The finding that 75% of our sample experienced a clinically relevant improvement in CRF after the intervention has significant implications for future use of this intervention as a treatment for CRF. After cancer treatment is finished, many patients are referred back to their general practitioners for care and are no longer in frequent contact with their oncologist or cancer care programs. This causes a lack of survivorship resources for cancer populations, which makes interventions difficult to receive. The results of the current study provide support for treating CRF and its comorbidities with CBT-I. This would provide efficiency for patients and practitioners if cancer survivors who present with CRF and/or the comorbidities can use one single intervention to improve all of their symptoms. Moreover, as forementioned, there is no gold standard treatment for CRF, but there have been many types of interventions that have focused on treating fatigue in people with cancer. Exercise interventions, mindfulness-based strategies, and some pharmaceutical interventions have been found to reduce CRF (Mustian et

al., 2017; Xie et al., 2020). Therefore, having an array of treatment options may allow patients to choose the type of intervention that they prefer.

The results of the second study indicated that those who were younger (i.e., under 55 years) had a greater likelihood of improving in CRF following CBT-I. This finding could help patients make an informed decision on the type of intervention that they would like to use. Moreover, this finding may provide clinicians with better guidelines of who may benefit most from certain interventions. Out of the demographic, clinical, and symptom-related factors assessed, no other factors had a significant association with a clinically meaningful improvement in CRF after CBT-I. This finding may demonstrate that CBT-I is a robust intervention, where demographic or clinical differences among the sample cannot impact the outcomes of CBT-I. Therefore, when considering using CBT-I for CRF, clinicians and patients may be more inclined to use an intervention that is not impacted by demographic or clinical-related differences. The results of this analysis also provide support for interventions that are tailored to specific needs of patients. Considering that older participants experienced less CRF improvement compared to younger participants, perhaps tailoring CBT-I for older populations (e.g., targeting the poor sleep habits experienced in older patients) may improve these outcomes. More broadly, perhaps more tailored interventions are needed for CRF for older adults to achieve the same gains as younger adults.

Directions for Future Research

This thesis contributed to the existing literature evaluating CBT-I as a treatment for CRF. Considering that the results of this study demonstrated efficacy of CBT-I for treating CRF, future research should focus on using CBT-I to treat several types of negative symptoms experienced by cancer survivors, such as anxiety and depression. The current study accounted for anxiety and

depression as they are comorbid with CRF, but future research should assess anxiety and depression as the primary outcome to see how CBT-I may influence these symptoms.

Future research should focus on evaluating the impact of treatment adherence on CRF outcomes as a possible reason for not responding to CBT-I, particularly given that younger age was the only significant predictor of improvement in CRF after CBT-I. Adherence to the intervention may greatly impact CRF outcomes. Additionally, future research should seek out more diverse samples, as this study consisted of mainly white, female, breast cancer survivors. Moreover, future research should use comparative research designs, where different types of interventions for CRF are compared, so the most effective intervention for CRF can be identified. This study used a validated, self-report measure for CRF; however, future studies should attempt to measure CRF using different methods. For instance, ecological momentary assessment, a data collection method where participants report their thoughts, feelings, and symptoms in their daily environment, may provide a more in-depth measure of the CRF symptoms experienced by patients (Moskowitz & Young, 2006). Additionally, considering the biological etiology of CRF, perhaps the use of biomarkers may be a more objective measurement of CRF. Lastly, future research should examine the durability of effects of CRF after the intervention, while still controlling for the comorbidities. It is possible that the effects observed directly after the intervention may change. Assessing the long-term effects of CBT-I on CRF will provide more information for clinicians on the benefits of using CBT-I for CRF.

Strengths

This study had several strengths. There are various comorbidities (e.g., insomnia, perceived cognitive impairment, anxiety and depression) of CRF that may interfere with the outcomes of CRF following CBT-I. Much of the literature does not account for these

comorbidities in their analyses, and this makes it difficult to decipher if improvements in CRF following the intervention were actually due to the intervention itself, or if the comorbidities acted as confounding variables. Therefore, a strength of this study was that we controlled for the comorbidities by adding them as covariates in the mixed effects model. Moreover, this study examined the comorbidities using a mediation analysis, to further examine their relationship to CRF. This is also a strength as much of the literature discusses how they co-occur, but not how much variance each comorbidity accounts for.

Another strength of this study was due to the virtual design. Since this study was conducted completely virtually, we were able to recruit from across Atlantic Canada, which increased accessibility of psychological services for Atlantic Canadian cancer survivors. This also helped our sample represent more areas, as well as allowed us to get a larger sample size. We were also able to gain a sample that consisted of different ages, education levels, household incomes, as well as different cancer types, stages, and treatments. In addition, delivering CBT-I completely virtually allowed for greater flexibility for the participants which may have contributed to our sample size.

Another strength of this study was using the Multidimensional Fatigue Symptom Inventory- Short Form (MFSI). In addition to be validated for use within cancer populations, this measure provided information on five domains of CRF: mental, emotional, physical, vigour, and general. There is inconsistency in the literature where many different measures for CRF are used, which can focus on different aspects of CRF, therefore using a multidimensional measure allowed us to have a broader scope of CRF. Moreover, the use of the Insomnia Severity Index, the Hospital Anxiety and Depression Scale, as well as the Functional Assessment of Cancer

Therapy – Cognition scale were all validated for use in oncology populations. Therefore, the use of these scales as the primary focus of the study is a strength.

Challenges and Limitations

Although this study demonstrated findings that are consistent with the hypothesis and past literature, there were some limitations. First, the design of this study was a randomized waitlist control. Literature suggests that the use of a waitlist control group may inflate estimates of the intervention effect (Cunningham et al., 2013). However, this design was necessary as the intervention is a well-supported treatment for insomnia, and therefore could not ethically be withheld. Next, is the presence of selection bias among the sample. This may have occurred if individuals who chose to participate in the trial differed systematically from those who chose not to participate. Next, the sample composed of mostly white, well educated, female cancer survivors who had a breast cancer diagnosis. Therefore, this sample is not representative of the entire cancer survivor population. It is possible that having a sample that consisted of mostly men could impact the CRF outcomes, as the regression analysis showed that women in this study were more likely to experience a reduction in fatigue compared to men. Our sample consisted of almost exclusively white participants, therefore any effects from other races could not be examined due to the small sample size. Therefore, it is possible that our results would have been different if our sample was more racially diverse. Next, we did not measure treatment adherence. It is possible that adherence to the CBT-I regimen may influence a participant's outcomes. Lastly, the measures used in this trial (i.e., measures for CRF, insomnia, PCI, anxiety, and depression) were self-report. Therefore, response bias may have occurred if participants responded inaccurately to questions due to the order of the questions, extreme responding, or acquiescence.

Conclusion

This study provides important findings for the improvement of CRF with CBT-I among Atlantic Canadian cancer survivors with comorbid insomnia and PCI. Moreover, this study provides further examination into the relatedness of symptom clusters experienced after a cancer diagnosis. Lastly, this study demonstrated the robustness of CBT-I through identifying the demographic and clinical variables associated with improving in CRF following the intervention. Overall, we found that 75% ($N = 91$) of the sample experienced a significant reduction in CRF symptoms after completing the virtual CBT-I intervention. This included improvements in general, emotional, physical, and mental fatigue. The increasing number of cancer survivors demonstrates a need for addressing symptom clusters in this population.

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Appendices

Appendix A:

Demographic Questionnaire

1. What is your birthdate (M/D/Y)? _____
2. What is your postal code? _____
3. What is your height in feet and inches?
    a. Feet: _____
    b. Inches: _____
4. What is your current weight in pounds? _____
5. How would you describe your relationship status?
    a. Single
    b. In a committed relationship/married
    c. Divorced
    d. Widowed
    e. Other – Please Specify _____
6. How many children do you have?
    a. None
    b. 1
    c. 2
    d. 3+
7. How would you describe your race/ethnicity?
    a. White
    b. Asian
    c. Aboriginal
    d. Black
    e. Other
8. How many years of education have you completed? _____
9. Are you currently employed? _____
    a. If yes, during a typical week, how many hours have you spent working at your place of employment? _____
10. When was your cancer diagnosis? (M/D/Y)? _____
11. What type of cancer were you diagnosed with? _____
    a. Breast
    b. Prostate
    c. Lung
    d. Colon/Rectal
    e. Head/Neck
    f. Melanoma

g. Lymphoma
h. Leukemia
i. Other, specify _____

12. What stage of cancer were you diagnosed with? _____
a. Stage 0
b. Stage I
c. Stage II
d. Stage III
e. Stage IV
f. Unknown

13a. Have you been treated with surgeries for your cancer? _____
When? _____
What type of surgery? _____
13b. Have you been treated with chemotherapy? _____
When? _____
What type of chemotherapy? _____
13c. Have you been treated with radiation? _____
When? _____
13d. Have you been treated with hormonal therapies? _____
When? _____
What type of hormonal therapies? _____
13e. Any additional treatments for your cancer (e.g. transplant)?_____
When? _____
What type of treatments? _____
13f. When was your last cancer treatment (month/year)? _____

14. Have you ever been told by a doctor or other health care professional that you had the following conditions? (Check all that apply)

- ☐ Hypertension (high blood pressure)
- ☐ High cholesterol
- ☐ Heart disease
- ☐ Diabetes (high blood sugar)
- ☐ Osteoporosis
- ☐ Osteopenia
- ☐ Inflammatory conditions, such as Rheumatoid arthritis. Please specify: _____
- ☐ Other medical conditions. Please specify: _____
- ☐ None

15. Are you currently taking any prescription medication? _____
a. If yes, what are they? _____

16. Are you currently taking any over the counter medication? _____
    b. If yes, what are they, purpose and dose? _____
17. Are you currently taking any herbal medication (Ginkgo Biloba, Melatonin, etc.)? _____
    c. If yes, what are they, purpose and dose?_____
18. Do you smoke? _____
    d. If yes, how many cigarettes do you typically smoke per day? _____
19. How many alcoholic beverages (e.g. a single beer, one glass of wine) do you typically consume per week? _____
20. During a typical week, how many hours have you spent participating in physical activities? (ex. jogging, sports, etc.) _____
21. Approximately how many cups of coffee do you drink per day? _____
22. What gender do you identify with?
    a. Male
    b. Female
    c. Other

    Preferred pronouns: _____
23. If female, when was your last menstrual period? (M/Y) _____
24. If female, have your menstrual periods stopped permanently? _____
    a. If yes, why did your menstrual periods stop?
        a. Natural menopause (periods stopped by themselves)
        b. Both ovaries were removed (oophorectomy)
        c. Hysterectomy (uterus or womb removed), and at least one ovary was removed
        d. Chemotherapy or Radiation
        e. Hormonal therapy (for example, Lupron)
        f. Other, please specify: _____
25. When did your insomnia start? (M/Y) _____
26. How did cancer impact your insomnia?
    a. My cancer diagnosis or treatment caused my insomnia
    b. My cancer diagnosis or treatment had no impact on my insomnia
    c. My insomnia became worse after my cancer diagnosis or treatment
    d. My insomnia symptoms improved after my cancer diagnosis or treatment
27. Would you like to receive results from the study? _____
    a. If yes, would you prefer to receive this by email or mail? _____

Appendix B

Multidimensional Fatigue Symptom Inventory – Short Form

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

20. I am unable to concentrate	0	1	2	3	4
21. I feel depressed	0	1	2	3	4
22. I feel refreshed	0	1	2	3	4
23. I feel tense	0	1	2	3	4
24. I feel energetic	0	1	2	3	4
25. I make more mistakes than usual	0	1	2	3	4
26. My body feels heavy all over	0	1	2	3	4
27. I am forgetful	0	1	2	3	4
28. I feel tired	0	1	2	3	4
29. I feel calm	0	1	2	3	4
30. I am distressed	0	1	2	3	4

Appendix C

Insomnia Severity Index

1. Please rate the current (i.e., **last 2 weeks**) severity of your insomnia problem(s).

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

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

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

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

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

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

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

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

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

Appendix D

The Functional Assessment of Cancer Therapy - Cognitive Function (FACT-Cog)

Below is a list of statements that other people with your condition have said are important.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
I have had trouble forming thoughts	0	1	2	3	4
My thinking has been slow	0	1	2	3	4
I have had trouble concentrating	0	1	2	3	4
I have had trouble finding my way to a familiar place	0	1	2	3	4
I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
I have had trouble remembering new information, like phone numbers or simple instructions.....	0	1	2	3	4
I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
I have had trouble finding the right word(s) to express myself	0	1	2	3	4
I have used the wrong word when I referred to an object	0	1	2	3	4

I have had trouble saying what I mean in conversations with others	0	1	2	3	4
I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
I have forgotten names of people soon after being introduced	0	1	2	3	4
My reactions in everyday situations have been slow	0	1	2	3	4
I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
My thinking has been slower than usual	0	1	2	3	4
I have had to work harder than usual to express myself clearly	0	1	2	3	4
I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have been able to concentrate	0	1	2	3	4
I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
My mind is as sharp as it has always been	0	1	2	3	4
My memory is as good as it has always been	0	1	2	3	4
I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
I am able to keep	0	1	2	3	4

track of what I am doing, even if I am interrupted					

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have been upset about these problems	0	1	2	3	4
These problems have interfered with my ability to work	0	1	2	3	4
These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
These problems have interfered with the quality of my life	0	1	2	3	4

Appendix E

Hospital Anxiety and Depression Scale

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
□	3	Most of the time	3	□	Nearly all the time
□	2	A lot of the time	2	□	Very often
□	1	From time to time, occasionally	1	□	Sometimes
□	0	Not at all	0	□	Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0	□	Definitely as much	□	0	Not at all
1	□	Not quite as much	□	1	Occasionally
2	□	Only a little	□	2	Quite often
3	□	Hardly at all	□	3	Very often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
□	3	Very definitely and quite badly	3	□	Definitely
□	2	Yes, but not too badly	2	□	I don't take as much care as I should
□	1	A little, but it doesn't worry me	1	□	I may not take quite as much care
□	0	Not at all	0	□	I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0	□	As much as I always could	□	3	Very much indeed
1	□	Not quite so much now	□	2	Quite a lot
2	□	Definitely not so much now	□	1	Not very much
3	□	Not at all	□	0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
□	3	A great deal of the time	0	□	As much as I ever did
□	2	A lot of the time	1	□	Rather less than I used to
□	1	From time to time, but not too often	2	□	Definitely less than I used to
□	0	Only occasionally	3	□	Hardly at all

D	A		D	A	
		I feel cheerful:			**I get sudden feelings of panic:**
3	□	Not at all	□	3	Very often indeed
2	□	Not often	□	2	Quite often
1	□	Sometimes	□	1	Not very often
0	□	Most of the time	□	0	Not at all

		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
□	0	Definitely	0	□	Often
□	1	Usually	1	□	Sometimes
□	2	Not Often	2	□	Not often
□	3	Not at all	3	□	Very seldom