EXPLORING THE FEASIBILITY OF USING COGNITIVE BEHAVIOURAL THERAPY FOR INSOMNIA TO IMPROVE PERCEIVED COGNITIVE IMPAIRMENT IN SURVIVORS OF BREAST CANCER

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Abstract

Objectives: The prevalence of both insomnia and cognitive impairment in survivors of breast cancer is well documented. Although there are currently effective treatments for insomnia, very few, if any, treatments are effective for improving cognitive impairment. This study evaluated the feasibility and acceptability of using Cognitive Behavioural Therapy for Insomnia (CBT-I), a gold-standard insomnia intervention, for the secondary benefit of improving perceived cognitive impairment (PCI) in survivors of breast cancer.

Methods: We recruited 10 female survivors of breast cancer who resided in St. John's, Newfoundland. Participants underwent 7 weekly sessions of CBT-I treatment and completed questionnaires to assess cognitive functioning, sleep, and psychological wellbeing at baseline, 2 months (post-treatment), and 3- and 6-months following treatment, for a total study time of 8 months. Repeated measures ANOVAs with pairwise comparisons were conducted to determine changes in symptomology.

Results: Out of 45 participants screened, 10 were both eligible and enrolled, for a recruitment feasibility rate of 22%. The intervention was highly acceptable with 100% of enrolled participants completing treatment. There were statistically significant improvements in PCI [$p < .001$, $\eta_p^2 = .546$], insomnia [$p < .001$, $\eta_p^2 = .739$], fatigue [$p = .004$, $\eta_p^2 = .379$] and depression [$p = .03$, $\eta_p^2 = .276$], over the 8-month study period. Pairwise comparisons revealed significant decreases in PCI from baseline to post treatment [$p = .006$], 3 months [$p = .003$] and 6 months [$p = .002$].

Conclusions: CBT-I seems to be an acceptable and potentially efficacious option for improving PCI in survivors of breast cancer, but future adequately powered randomized controlled trials are needed to confirm these preliminary results. In order for such trials to recruit the required sample size, they will likely need to screen 5 times the number of participants needed.

Keywords: Insomnia, mental health, anxiety, depression, cognitive impairment, memory, attention, concentration, sleep

General Summary

Insomnia and issues with attention, memory and concentration are common among survivors of breast cancer. Although there are currently effective treatments for insomnia, very few, if any, treatments are effective for improving reports of attention, memory and concentration difficulties. This study evaluated how common these symptoms were together in survivors of breast cancer. Additionally, we determined if survivors of breast cancer were accepting of using the primary treatment for insomnia Cognitive Behavioural Therapy for Insomnia (CBT-I) to potentially improve complaints of attention, memory and concentration. We recruited 10 female survivors of breast cancer who resided in St. John's, Newfoundland. Participants underwent 7 weekly sessions of CBT-I treatment and completed questionnaires to assess attention, memory, concentration, sleep, and mood at baseline, 2 months (post-treatment), and 3- and 6-months following treatment, for a total study time of 8 months. Out of 45 participants screened, 10 had insomnia and issues with attention, memory and concentration. This means 22% of cancer survivors interviewed, displayed both insomnia and issues in these areas. CBT-I was highly accepted with 100% of enrolled participants completing the full treatment. There were significant improvements in self-reports of attention, memory and concentration, insomnia, fatigue, and depression over the 8-month study period. These improvements were maintained after treatment. CBT-I seems to be an acceptable and potentially effective option for improving reports of issues with attention, memory and concentration in survivors of breast cancer, but future studies are needed to confirm these results.

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Exploring the Feasibility of Cognitive Behavioural Therapy for Insomnia on Perceived Cognitive Impairment in Survivors of Breast Cancer

Breast cancer is one of the most commonly diagnosed malignancies in Canada with 1 in 8 women developing it in their lifetime (Canadian Cancer Statistics Advisory Committee, 2019). In 2019, breast cancer contributed to 25% of diagnosed cases of cancer in Canada (Canadian Cancer Statistics Advisory Committee, 2019). This is troublesome as Newfoundland and Labradorean women have one of the highest incidence and mortality rates for breast cancer across the country (Canadian Cancer Statistics Advisory Committee, 2019). Although prevalent, mortality due to breast cancer has decreased dramatically over the last three decades. In North America, breast cancer mortality has decreased by 34% with a more substantial decrease noted in Canada (48%; Canadian Cancer Statistics Advisory Committee, 2019). Predictions suggest that there will be a further 10% decrease in mortality from 2012 to 2020 (Carioli et al., 2018; DeSantis et al., 2014). Such decreases in breast cancer mortality can be attributed to improved management of the disease, earlier diagnosis, and advances in treatment (Carioli et al, 2018). Although a decrease in mortality rate is positive, many survivors of breast cancer struggle to resume normal functioning following treatment. Common long-term side effects include cognitive impairment (Janelsins et al., 2014), changes in mood (Carreira et al., 2018), and fatigue (Bardwell & Ancoli-Israel, 2008) that can individually and cumulatively have a negative impact on a patient's quality of life (Argyriou et al., 2011). All of these symptoms have been associated with insomnia (Dirksen & Epstein, 2008; Fortier-Brochu et al., 2012). This study evaluated the feasibility and acceptability of using a psychosocial intervention designed to treat insomnia to improve associated symptoms in survivors of breast cancer.

Cognitive Impairment in Breast Cancer

Based on neuropsychological assessments, approximately 30% of women with breast cancer report a decline in a variety of cognitive domains prior to treatment, while up to 75% report cancer-related cognitive impairments during their treatments (Janelsins et al., 2014). Furthermore, up to 35% of these women continue to experience cognitive difficulties for months or years following their treatments (Janelsins et al., 2014). A number of potential factors have been suggested to contribute to the cognitive impairment experienced by women with breast cancer including biological factors related to the disease (e.g., increased cytokine levels; Korkaya et al., 2011), physical effects of cancer treatments (e.g., chemotherapy, radiotherapy, and endocrine therapy; Ahles & Saykin, 2007; Janelsins et al., 2014), the psychological burden of the disease (e.g., anxiety, depression, fatigue and disrupted sleep; Argyriou et al., 2011; Bedillion et al., 2019), as well as life disruptions due to treatment (e.g., ability to return to work; Bradley et al., 2004; Myers, 2012). This literature review will focus on the factors associated cognitive impairment with the most empirical investigation to date: the effects of cancer treatments and the psychological burden of cancer.

Cancer Diagnosis and Cognitive Impairment

Prior to 2004 when prospective and longitudinal studies started to emerge, it was believed that chemotherapy was the sole contributor to cognitive decline in those with cancer (Hermelink, 2015). Wieneke and Dienst (1995) conducted a cross-sectional study in 28 women with breast cancer to assess the effects of chemotherapy on cognitive functioning using a battery of neuropsychological tests. Although approximately 75% scored within the moderately impaired range on one or more of the test measures, these studies were not prospective and only looked at the effects of chemotherapy on women with breast cancer who had already undergone treatment and failed to measure cognitive impairment prior to the initiation of treatment. More recently, a

prospective, multicenter longitudinal study assessed the cognitive functioning of women with breast cancer prior to chemotherapy and found that about one-third experience pre-existing cognitive deficits prior to treatment (Hermelink et al., 2007). Therefore, without taking into account cognitive functioning prior to treatment, pre-existing cognitive impairments may have been misattributed to the effects of chemotherapy in the past literature. These findings suggest that the diagnosis as well as the neurotoxic effects of treatment seem to have implications on cognitive functioning within this population (Hermelink, 2015).

Chemotherapy and Cognitive Impairment

In women with breast cancer, chemotherapy-induced cognitive impairment—commonly referred to as "chemo brain"—is a common but under-recognized side effect (Argyriou et al., 2011). Estimates suggest that 16-75% of women with breast cancer who receive standard to high doses of chemotherapy will report some level of cognitive dysfunction (Tchen et al, 2003; Wieneke & Dienst, 1995). Meta-analyses of neuropsychological studies have found only small differences in verbal ability and visuospatial ability domains following standard chemotherapy regimens in women with breast cancer compared to controls and pre-chemotherapy baselines (Jim et al., 2012). However, a more recent meta-analysis of 27 studies and a total of 81 independent neuropsychological measures compared 1562 women with breast cancer who had undergone adjuvant chemotherapy treatment to 2799 controls consisting of women with breast cancer who did not receive adjuvant chemotherapy and healthy participants (Ono et al., 2015). Despite using differing methodological approaches, the results demonstrated consistent associations between adjuvant chemotherapy and cognitive impairment in a variety of domains including attention, executive function, information processing speed, motor function/speed, language, visuospatial ability/skill, short-term memory and long-term memory (Ono et al., 2015). Although these results are conflicting with regard to the exact cognitive processes chemotherapy

affects, it seems that memory, processing speed, and executive function are the most cognitively vulnerable, and are the processes most agreed upon within the literature (Correa & Ahles, 2008; Wefel et al., 2011; Wefel et al., 2008).

A plausible explanation for the differing results on the cognitive processes affected by chemotherapy could be attributed to differing types of breast cancer, which require varying degrees of chemotherapy treatment. Those in different stages of breast cancer display various tumour subtypes and require differing intensities and durations of chemotherapy treatments (Seah et al., 2014). A significant negative relationship is present between the duration of treatment and cognitive functioning and this relationship seems to be dose dependent (Hodgson et al., 2012). Those undergoing longer and more intense chemotherapy treatments seem to be at an increased risk for deterioration in cognitive functioning. Van Dam and colleagues (1998) examined the level of cognitive impairment associated with varying dosages of adjuvant chemotherapy in breast cancer patients. Patients treated with high-dose chemotherapy appeared to be at an 8.2 times heightened risk of developing cognitive impairment compared to healthy controls. Furthermore, those who had undergone a higher dosage experienced more adverse cognitive functioning consequences (34%) compared to patients who had taken standard doses (17%). Further supporting the neurotoxic effects of chemotherapy on cognitive processes, women with breast cancer who had completed chemotherapy at least one-year prior show less cognitive deficits compared to those who were currently undergoing adjuvant chemotherapy (Brezden et al., 2000). Therefore, based on the current literature, it seems that cancer treatments may contribute to impairments in cognitive functioning and this relationship is dependent on factors such as cancer type and the associated duration and dosage of treatments.

Hormonal Therapies and Cognitive Impairment

In addition to chemotherapy, hormonal therapies also appear to have a negative impact on cognitive functioning, particularly for women with breast cancer. Jenkins et al. (2006) examined this relationship in a prospective study and found that after 6 months following chemotherapy treatment, women with breast cancer who had experienced treatment-induced menopause were 2.6 times more likely to show a decline in cognitive impairment compared to the postmenopausal women. There is evidence that deficits in attention, memory and concentration appear when women are deprived of estrogen earlier than normal due to ovarian suppression following chemotherapy and hormonal therapy (Bender et al., 2001). Estrogen is one of the female reproductive hormones that has neurological protective effects and increases synaptogenesis in brain regions important for memory (Yaffe et al., 1998). Therefore, hormonal restriction therapies that decrease these reproductive hormones may be contributing to the cognitive deficits seen within this population (Bender et al., 2001). Further evidence of this relationship is apparent through improved scores of learning and memory in postmenopausal women who are undergoing hormonal replacement therapy to counteract the negative effects of reproductive hormone deprivation (Henderson et al., 1994; Robinson et al., 1994). Evidence also suggests that the cognitive impairment experienced by women with breast cancer may not always persist. Out of 50% of breast cancer survivors displaying cognitive dysfunction following chemotherapy, approximately 25% taking anti-estrogen hormonal therapies such as tamoxifen show improvements in cognitive dysfunction 2 years following chemotherapy treatment (Fan et al., 2005). A possible explanation for these improvements during hormonal therapies may be attributed to neuroplasticity occurring following invasive treatments. Unfortunately, 25% of these women taking anti-estrogen hormonal therapies still show signs of at least mild cognitive

impairment (Fan et al., 2005) suggesting neuroplasticity following invasive cancer treatments may not be enough to restore cognitive processes.

Perceived Cognitive Impairment in Breast Cancer

The relationship between cognitive impairment and breast cancer appears to be stronger when assessed with subjective self-report measures of cognitive function compared to objective assessments (Ono et al., 2015; Hodgson et al., 2012; Hutchinson et al., 2012; Jean-Pierre et al., 2014). Due to the inconsistency regarding the cognitive domains that seem to be affected by chemotherapy using objective cognitive measures, researchers have suggested that "chemo brain" may largely be a subjective experience (Hermelink, 2015). While this may lead some to dismiss or minimize its significance, Savard and Ganz (2016) have suggested that the subjective experience of cognitive impairment is as, or more, important than an objective classification. Investigating the emotional component of cognitive decline is important as 50% of cancer survivors experience perceived cognitive impairment (PCI) and report it is one of the largest barriers to resume normal functioning (Boykoff et al., 2009; Janelsins et al., 2014; Schmidt et al., 2016). It is also arguable that an individual's perception of their cognitive impairment is essential when trying to measure the impact of interventions that focus on improvements in quality of life (Basch, 2016). Subjective perceptions, which can be reliably measured using validated instruments, allow us to observe the impact that declines in cognitive performance have on an individual's daily functioning (Basch, 2016). With such valuable information, it may be more meaningful to target how the patient feels about their cognitive performance rather than just objective measurements, which fail to assess the emotional component of cognitive impairments. Such cognitive complaints are associated with a variety of additional symptoms such as decreased quality of life, daily functioning impairment, emotional distress, fatigue, psychological distress and stress (Argyriou et al., 2011; Bedillion et al., 2019; Boykoff et al., 2009; Hutchinson

et al., 2012; Moon et al., 2011). PCI can also negatively impair performance at work or ability to return to work (Boykoff et al., 2009; Munir et al., 2010). This can cause prolonged leaves of absence or early onset retirement which has significant consequences for both the individual and society (Boykoff et al., 2009; Munir et al., 2010).

Treatment for Perceived Cognitive Impairment

Although PCI seems to be highly prevalent in cancer patients, there are few effective treatments (Jean-Pierre et al., 2014; Joly et al., 2015). Cognitive rehabilitation programs and physical exercise/mental stimulation are the most common intervention strategies. Based on a methodological review, cognitive interventions have reported some benefits for attention, memory, functional communication, and executive functioning, but they can vary substantially based on the technique used (Jean-Pierre et al., 2014; Kesler et al., 2013). Cognitive rehabilitation programs aim to reduce cognitive dysfunction and improve quality of life through psycho-education and cognitive-behavioural strategies. One feasibility study found improvements in overall cognitive function, perceived cognitive function, social functioning, and decreased levels of psychological distress in survivor of cancer populations which were maintained for three months following cognitive rehabilitation treatment (Schuurs & Green, 2013). However, this study lacked statistical power, failed to randomly assign participants to groups, and also had a larger number of cancer survivors in their intervention group. As such, the treatment effects could have been inflated and the effectiveness of cognitive rehabilitation within this population requires further investigation.

Physical exercise/mental stimulation to improve cognitive impairment has also been investigated. A randomized controlled trial of 81 women with breast cancer evaluated the effectiveness of exercise and meditation on subjective cognitive function (Oh et al., 2011).

Although significant improvements were noted in perceived cognitive impairment, the mean difference out of a 5-point scale was slight (MD= 4.70) and would not constitute a clinically meaningful change of 5.9 (Bell et al., 2018). This study also did not follow up on their participants to ensure treatment effects were maintained and therefore, the effectiveness of this intervention remains inconclusive.

In addition to cognitive and physical activity interventions, medications such as modafinil, methylphenidate, gingko biloba, and donepezil + vitamin E have been investigated. Methylphenidate (Ritalin) is a pharmaceutical commonly used to treat attention-deficit hyperactive disorder, narcolepsy, and cognitive decline in patients with brain tumors. However, a double-blind, placebo-controlled trial of 57 women with breast cancer undergoing adjuvant chemotherapy found no significant differences on objective or subjective cognitive impairment in those who had taken 5-10 mg twice daily of methylphenidate over the course of treatment compared to placebo (Mar Fan et al., 2008). Overall, methylphenidate seems to alleviate cancer-related fatigue but has no effect on chemotherapy-induced cognitive impairment (Argyriou et al., 2011; Minton et al., 2010). Based on double-blind randomized controlled trials, gingko biloba and donepezil, which are used to treat cognitive impairment in other chronic disease populations, are ineffective as well (Barton et al., 2013; Jatoi et al., 2005). Preliminary evidence from a randomized controlled trial suggests that modafinil may be beneficial in improving cognitive functioning in women with breast cancer following chemotherapy (Kohli et al., 2009), although these effects have not been consistent across studies (Davis et al., 2013). Overall, medications for reducing cognitive impairment in survivors of breast cancer have not demonstrated much promise (Argyriou et al., 2011; Hines et al., 2014; Joly et al., 2015).

Although cognitive, behavioural, and pharmaceutical treatments have been investigated for the treatment of PCI in individuals with cancer, no one treatment has emerged as an agreed upon standard. As such, we need to continue to examine other potential treatment options that take into account factors that may be contributing to PCI such as sleep, fatigue, and mood disturbance.

Protective Effect of Sleep on Cognitive Impairment

Sleep plays an important role in neuroplasticity and allows us to repair and restore the micro injuries that occur in our brain on a daily basis (Karren et al., 2013). The benefits of sleep on neuroplasticity can be observed while examining sleep-deprived individuals. Over 50% of those diagnosed with a sleep disorder that prevents REM sleep (REM Behaviour Disorder) have been found to later develop dementia or Parkinson disease, demonstrating the therapeutic properties of sleep on cognition (Postuma et al., 2010). Similarly, sleep deprivation is a common symptom in about 50% of clinical and community-based samples of Alzheimer's disease and has been linked to memory deficits within this population (Qiu et al., 2009; Vitiello & Borson, 2001; Walker, 2017). This relationship is further supported by animal models that have restrained rats to four hours of sleep per night for eight weeks and found a significant decline in their learning and memory tasks compared to controls (Dimeco et al., 2014). Sleep also allows us to integrate our experiences by organizing memories and incorporating the day's experience into our worldview during a restful state (Karren et al., 2013). Poor sleep quality in humans has negative impacts on a variety of additional cognitive functions such as attention, memory, executive function, and behavioural alertness (Banks & Dinges, 2007), cognitive issues which are similarly reported in women with breast cancer (Argyriou et al., 2011; Hines et al., 2014). These results are quite troublesome as one of the most frequent reasons survivors of cancer visit their general practitioner is due to sleep difficulties (Heins et al., 2013). Although it has yet to be empirically

demonstrated, good sleep may act as a protective agent against the neurotoxic effects of cancer treatments on cognitive functioning in women with breast cancer.

Insomnia in Breast Cancer

Insomnia is defined as difficulty falling and/or staying asleep more than three nights a week and ongoing for at least 3 months despite adequate opportunity for sleep (American Psychiatric Association, 2013). In order to be categorized as a disorder, the presented sleep issues must cause distress and significantly impact daily functioning. Insomnia is a prevalent and frequently overlooked experience associated with breast cancer onset and treatment (Palesh et al., 2013; Savard & Savard, 2013). Women with breast cancer have a significantly higher risk (between 42-69%) for developing insomnia compared to adults with other cancer types (Heins et al., 2013; Savard et al., 2011). Large-scale epidemiological studies demonstrate that approximately 60% of women treated for breast cancer experience insomnia, which can persist for years if not treated appropriately (Palesh et al., 2010; Savard et al., 2011). A variety of hypotheses have been proposed regarding the association between insomnia and cancer including biological factors such as treatment-induced circadian disruption, psychological factors such as depression, and treatment side effects such as hot flashes (Desai et al., 2013; Liu et al., 2013; Savard et al., 2009; Stepanski et al., 2009). Although no one cause has been determined, most patients report that their insomnia either began with or shortly followed their diagnosis, suggesting that poor sleep is more overwhelming than the cancer treatments themselves (Fleming et al., 2010). Insomnia negatively impacts work performance for survivors of cancer, corresponding to 7.8 fewer workdays and a loss on average of $2,280 in income per person per annum (Kessler et al., 2011). Therefore, not only is PCI associated with burdens to both the individual and society, but insomnia shows a similar association as well. Although it is apparent a relationship is present between cognitive impairment and insomnia in women with breast

cancer, the relationship has not been well studied and research is lacking on validated treatment options for both.

Treatment Options for Insomnia

Current treatment options for insomnia include both behavioural and pharmaceutical based therapies. In the United States, 11 pharmaceuticals have been approved to treat insomnia, although none of these have been specifically tested for efficacy and safety in those with cancer (Fiorentino et al., 2011). Although pharmaceutical treatments have been found to improve sleep onset, many patients report large tolerance effects and poor quality of sleep, as well as increased severity of insomnia, fatigue, and pain from cessation. Therefore, behavioural therapies are frequently preferred due to much lower side effects.

Cognitive Behavioural Therapy for Insomnia. Cognitive Behaviour Therapy for Insomnia (CBT-I) is recommended by the American Academy of Sleep Medicine as the primary treatment for chronic insomnia (Boykoff et al., 2009; Joly et al., 2015). CBT-I has consistently been found to be more effective in treating insomnia both in the short and long term when compared to sleep aids such as benzodiazepines (Mitchell et al., 2012). CBT-I is a multi-component weekly intervention that combines principles from stimulus control and sleep restriction with formal cognitive restructuring in order to target hyper-arousal, dysfunctional behaviours, and maladaptive thoughts, beliefs and attitudes associated with insomnia. The five main components of CBT-I are: sleep restriction, stimulus control, cognitive restructuring, relaxation training, and sleep hygiene. Sleep restriction promotes consolidation of sleep periods through a build-up of sleep drive by restricting the time spent in bed as close as possible to the time actually spent sleeping. A sleep efficiency percentage is then calculated (amount of time spent sleeping divided by the amount of time in bed). When an individual achieves 85% sleep efficiency, their prescribed time in bed is increased. This continues until the patient can achieve

adequate sleep quantity and quality with little to no disturbances. Stimulus control is designed to condition the body to associate the bed with sleepiness and to avoid the association of the bed with wakefulness. This technique is aimed at breaking perpetuating behaviours that contribute to insomnia such as going to bed too early and "trying' to sleep. Cognitive restructuring addresses dysfunctional beliefs and thoughts that maintain and exacerbate behaviors which perpetuate insomnia symptoms. With the assistance of the therapist, the patient monitors these thoughts and beliefs, assesses their validity, and if necessary, replaces them with accurate and/or less distressing cognitions advantageous to the sleep process. Lastly, relaxation training targets cognitive and physiological arousal that exacerbates insomnia and sleep hygiene promotes ideal sleep behaviours and environmental conditions.

A systematic review and meta-analysis of the efficacy of CBT-I in cancer patients found significant improvements indicated by moderate to large effect sizes (Cohen's *d*) in sleep efficiency ($d = 0.53$), sleep latency ($d = 0.43$), and amount of time awake during the night ($d = 0.41$). Significant improvements were also present in insomnia severity indicated by a large effect size ($d = 0.77$) and these effects were maintained for up to 6 months (Johnson et al., 2016). Importantly, the effects of CBT-I were noted across differing delivery modalities (individual, group, online and video), durations of the intervention, as well as a variety of cancer diagnoses/stages. This indicates that CBT-I not only produces significant and durable changes in insomnia severity but also is effective in reducing insomnia symptoms in a heterogeneous sample of cancer patients.

Fatigue in Breast Cancer

In addition to insomnia, approximately 33% of women with breast cancer will experience persistent fatigue, which can continue into their survivorship for up to 10 years if not treated

appropriately (Bardwell & Ancoli-Israel, 2008). Cancer-related fatigue differs from daytime sleepiness and is described as '...a subjective state of overwhelming and sustained exhaustion and decreased capacity for physical and mental work that is not relieved by rest.' (Cella et al., 1998, p. 369). Cancer-related fatigue often appears as a cluster of symptoms with insomnia, pain and depression making it an important symptom to take into consideration when targeting symptoms that often co-occur (Bardwell & Ancoli-Israel, 2008; Donovan & Jacobsen, 2007). Fatigue related to cancer is often present with subjective cognitive complaints in survivors of breast cancer as well. Li and colleagues (2015) conducted a cross-sectional observational study on 204 women with breast cancer to examine the effect of psychological functioning on PCI following chemotherapy. It was found that Post Traumatic Stress Disorder symptoms and fatigue independently accounted for PCI while controlling for age, education, anxiety and depression. Possible explanations for the association between fatigue and PCI may be due to the neurological implications of invasive treatments. Robust evidence suggests inflammatory processes are triggered and/or worsened by the cancer treatments and therefore can lead to symptoms of both fatigue and cognitive dysfunction (Joly et al., 2019). These findings support the need to account for not only insomnia when trying to improve subjective cognitive complaints but cancer-related fatigue as well.

Mood Disturbance in Breast Cancer

Similarly, to insomnia and fatigue, psychological functioning is often impacted following the stressful news of a cancer diagnosis (Palesh et al., 2013). A population-based epidemiological study of 53,258 found that women with breast cancer are at a 1.33 heightened risk of reporting levels of mood disturbance including an increased risk of anxiety, depression and suicide compared to a matched control cohort (Carreira et al., 2018; Hung et al., 2013). Hartung and colleagues (2017) examined the prevalence of depression in a multi-center

epidemiological study and reported those with cancer are five times more likely to display depressive symptoms compared to the general population. Depression has been identified as the most common mood disturbance symptom in women with breast cancer, although anxiety symptoms are prevalent as well (Fiorentino et al., 2011). Based on clinical questionnaires, the prevalence of anxiety and depression in women with breast cancer is 19% and 17%, respectively (Lueboonthavatchai, 2007). A longitudinal study of 222 women with breast cancer found that women were most vulnerable within the first three months after a diagnosis, with about half of those with breast cancer having at least one period of anxiety and depression within this time frame (Burgess et al., 2005).

Mood Disturbance and Insomnia

Mood disturbance is also associated with insomnia in women with breast cancer, with both often co-occurring, exacerbating the other, and affecting the patient's quality of life (Fiorentino et al., 2011; Redeker et al., 2000). A meta-analysis of 16 studies investigated the relationship between depression and insomnia in those with cancer who were undergoing mixed treatment modalities (Donovan & Jacobsen, 2007). A moderate correlation was observed between insomnia and depression (r = .45). Fatigue also seemed to be influencing this relationship with significant associations between insomnia and fatigue (r = .34) and depression and fatigue (r = .55). Although there is an abundance of support for the relationship between insomnia and anxiety symptoms, very little research has been conducted on this interaction within breast cancer patients. Most reports include the more generalized term mood disturbance, which includes depression as well. Regardless, the relationship between insomnia and mood disturbance is of particular concern for this population as a bidirectional relationship seems to be present, with each negatively affecting the other (Glidewell et al., 2015). As a result, women with breast cancer who experience one of these symptoms are at a heightened risk for the other

as well. Examining clusters of symptoms experienced by breast cancer survivors such as anxiety, depression, fatigue, and insomnia are important to take into consideration as they may provide evidence to why treatment modalities to treat cognitive impairments have been previously unsuccessful.

Mood Disturbance and PCI

Hutchinson et al. (2012) proposed that the differences in objective and subjective cognitive impairment are due, in part, to the influence of psychological distress. Subjective cognitive complaints have been consistently correlated with varying measures of psychological distress including depression and anxiety symptoms (Hutchinson et al., 2012). Bedillion and colleagues (2019) examined whether depression mediated the effect of cancer treatment on PCI in survivors of breast cancer in a cross-sectional survey of 317 patients who had received all adjuvant treatments less than 10 years prior. Women completed self-report questionnaires examining PCI, depressive symptomology, and physical activity. Depression partially mediated the relationship between the effects of treatment on PCI, indicating that depression was partially contributing to participants' PCI following treatment. In addition, physical activity acted as a moderator on this relationship with increases in physical activity being correlated with lower depressive symptomology and therefore lower PCI. Therefore, it appears the effect of depression needs to be taken into consideration when examining treatment options for PCI as improvements in one may yield improvements in the other.

In addition to depression, Moon and colleagues (2011) examined whether PCI was related to general mood disturbance in a cross-sectional survey of 118 women with breast cancer who had either undergone or were currently undergoing chemotherapy. Using self-report questionnaires, mood disturbance was significantly associated with PCI, with those who had

higher scores of mood disturbance reporting higher levels of PCI. With such findings, a strong relationship seems apparent between psychological distress and PCI. Therefore, in addition to depression, anxiety should also be taken into consideration when investigating treatment modalities to improve PCI to capture differing measurements of mood disturbance.

Treatment of Cognitive Impairment, Insomnia, Fatigue and Mood Disturbance

Based on the presented evidence, cognitive impairments in breast cancer survivors cannot be associated to a singular cause (See Figure 1, pg. 69). Rather, there seem to be interactions among the cancer treatments (e.g., chemotherapy, hormonal restriction therapies), psychological side effects of these treatments (e.g., depression, anxiety, and fatigue), sleep disturbance associated with treatments that can develop into insomnia, as well as physical side effects of the treatments (e.g., hot flashes, pain, and fatigue). All of these taken together can lead to the development and maintenance of cognitive impairments and are therefore important to consider when investigating effective treatment options. Current research shows that in addition to insomnia, CBT-I can also reduce clinical levels of fatigue, anxiety, and depression related to cancer treatments (Fleming et al., 2014). Due to the high co-occurrence of psychological distress and insomnia, many treatment programs designed to decrease one tend to have a positive influence on the other symptoms as well (Dirksen & Epstein, 2008; Kim et al., 2018). CBT-I in particular has been found to be an effective treatment for improving levels of psychological distress compared to other treatment options. Garland and colleagues (2014) evaluated the effectiveness of both CBT-I and Mindfulness-Based Stress Reduction (MBSR) therapy on improving insomnia, mood and stress symptoms in cancer survivors. Using a partially blinded, randomized trial with 111 survivors of cancer experiencing insomnia, they found both MBSR and CBT-I significantly improved insomnia severity, stress level and mood disturbance although, the effects of CBT-I were more rapid and durable over time.

Preliminary research suggests that CBT-I may also improve PCI in individuals without cancer. A systematic review of 18 studies investigating the impact of CBT-I on cognitive functioning in those with insomnia and found small to moderate effects of CBT-I in treating subjective cognitive impairment (Herbert et al., 2018). Although these results are promising, they were not conducted in survivors of cancer and require additional research using subjective and objective measures of cognitive functioning, and controlling for confounding variables (Hines et al., 2014). In summary, insomnia, mood disturbance, and cancer treatments have been associated with PCI, putting survivors of cancer experiencing insomnia symptoms at an increased risk for the of development of PCI and making research on the treatment of insomnia in cancer survivors a priority for clinicians, researchers, and patients (Vardy et al., 2008).

Objectives of the Current Study

The current study will assess the feasibility, acceptability, and preliminary effectiveness of using the 'gold standard' non-pharmacological intervention for insomnia (CBT-I) to improve PCI in survivors of breast cancer. This will allow us to determine the feasibility for subsequent randomized controlled trials. To inform future research, we will use both subjective and objective measures of cognitive impairment as well as examine co-morbid symptomology. Should the intervention be feasible and acceptable, it could open up new treatment possibilities for PCI, a condition with few effective treatment options. In addition, this therapy could potentially improve a cluster of psychological symptoms associated with breast cancer treatments therefore providing a more cost-effective treatment for the patient. Lastly, an effective intervention would provide justification and important pilot data for larger randomized controlled trials. The specific objectives of this study are:

1. Estimate the feasibility of recruitment of survivors of breast cancer who report both insomnia and cognitive impairments.

2. Collect pilot data on the acceptability of the intervention and completion of the study protocol (including documentation of incomplete data and drop-outs).
3. Estimate the effect of CBT-I on PCI and related symptoms (objective cognitive impairment, insomnia, sleep efficiency, fatigue, depression and anxiety) and assess whether any changes observed are durable up to 6 months post-treatment.

Methods

Participants

Participants were deemed eligible if they: were diagnosed with stage I-III breast cancer; were English speaking; had received and completed all adjuvant treatments for non-metastatic breast cancer at least 12 months prior to study entry but no more than 5 years (continued maintenance or hormonal treatments were acceptable); reported dissatisfaction with their memory, concentration, and/or attention as indicated by a score of "quite a lot" or "always" on at least one of the two items used to assess concentration and memory (questions 20 and 25) on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30; Aaronson et al., 1993); met the DSM-5 criteria for insomnia disorder determined as difficulty falling and/or staying asleep more than three nights a week and ongoing for at least 3 months despite adequate opportunity for sleep (American Psychiatric Association, 2013) and had a score >8 on the Insomnia Severity Index; and resided in the metro area of St. John's, NL. Participants were excluded from the study if they had severe cognitive impairments as indicated by a score of < 23 on the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005), another untreated sleep disorder such as obstructive sleep apnea, previous experience with CBT-I, a major sensory deficit, a neurologic or major medical condition known to affect cognitive function, a history of inpatient psychiatric hospitalization, a history of cranial radiation, a change in psychotropic medications less than six weeks prior to study entry, an Eastern Cooperative

Oncology Group (ECOG) performance score greater than two (Oken et al., 1982) or a life expectancy of less than five years.

Procedure

The primary means of recruitment was through self-referral. Participants were made aware of the study through study information posted at the Dr. H. Bliss Murphy Cancer Centre and community organizations, referrals from medical professionals working for both the Cancer Centre and Eastern Health, information provided at community events directly related to targeted participants, and information posted through social media platforms. All interested participants were directed to our website for additional information and provided with an email and phone number to contact a research assistant to obtain additional details regarding the study. Interested participants underwent two screening processes. If those who were interested met all eligibility criteria that could be determined via a telephone interview, they were further screened in person. Those who were deemed eligible were enrolled in the study. Participants received 7 individual sessions of CBT-I with one individual therapist who oversaw all participants over the course of 8 weeks. At the end of each treatment session, participants were given a sleep diary to complete for the following week that was reviewed and used by the therapist to tailor treatments. A detailed week-to-week description of the CBT-I protocol is provided in Appendix A (pg. 74). Participants also underwent assessments at five different time points by one single research assistant besides the therapist: baseline, mid-treatment (4 weeks), post treatment (8 weeks), a 3 month follow up and a 6 month follow up. See Figure 2 (pg. 70). The total study time was 12 hours over an 8-month period for assessments and treatment. Ethical approval for this study was obtained from the Health Research Ethics Board of Memorial University (See Appendix B pg. 78)

Measures

A medical history and demographics questionnaire developed for this study was used to obtain demographic information (e.g., sex, age, ethnic background, education, marital status, employment status), medical history (e.g., type of cancer, date of diagnosis, treatment details), psychiatric history and current medication use. Each assessment included measures of cognitive function, sleep, fatigue, anxiety and depression.

Subjective Cognitive Function

The Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog) version 3 is a 37 item self-report questionnaire that measures four different aspects of cognition in the past week: perceived cognitive impairments (PCI), impact on quality of life, comments from others and perceived cognitive abilities (Jacobs et al., 2007; Von Ah & Tallman, 2015). For the purposes of this study, the PCI subscale score of the FACT-Cog was used to capture subjective cognitive impairment (See Appendix C, p. 80). Responses to each question range from 0 to 4 with 0 indicating "never" and 4 indicating "several times a day." Negatively worded items are reverse scored to create subscale scores, with higher scores reflecting fewer cognitive problems and better quality of life. Scores on the PCI subscale range from 0 to 72. A change of 5.9 points has been established as clinically meaningful change on the FACT-Cog PCI subscale (Bell et al., 2018). The FACT-Cog has been validated specifically for women with breast cancer and has been found to be a reliable measure with a Cronbach alpha of 0.86 for the total score, and the subscale scores ranging from 0.77 to 0.86 (Lai et al., 2009; Wagner et al., 2009).

Objective Cognitive Function

Verbal Learning and Memory: The Hopkins Verbal Learning Test-Revised (HVLT-R) is a brief assessment of verbal learning and memory, specifically immediate recall, delayed recall, and delayed recognition (Brandt, 1991). Each form consists of 12 nouns, with four words drawn

from three semantic categories and requires participants to recall the words read aloud by a trained assessor. Four different forms were used at each of the assessment time points. For the purpose of this study, delayed recall scores presented as a recall percentage were used to determine cognitive functioning in verbal learning and memory. The HVLT-R has six alternative forms making it suitable for repeated testing (Brandt & Benedict, 2001), has high test-retest reliability and has been well established with regards to its construct, concurrent and discriminant validity.

Verbal Fluency and Executive Functioning: The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency, cognitive and motor speed, and executive functioning performance such as cognitive flexibility, strategy utilization, interference suppression, and response inhibition (Lezak et al., 2004). The test requires participants to say as many words they can think of as quickly as they can that begin with a certain letter of the alphabet (avoiding proper nouns and words with different suffix) in a one-minute interval. Scores are adjusted based on age and education. For the purpose of this study, adjusted scores were used to determine change in cognitive functioning. The COWAT has two alternative forms which were used at baseline and 6 months, making it suitable for a repeated testing. Results are compared against normative data.

Divided Attention and Processing Speed: The Colour Trails Test (CTT) is a widely used measure of executive function (D'Elia et al., 1996; Maj et al., 1993) Successful performance requires a wide range of mental abilities such as mental flexibility, visual scanning, and motor function. The test has two forms, one where participants are required to work as quickly as they can to connect numbered circles in order and another that does the same but switches the colour of the circles each time. The second form is a measure of divided attention and processing speed

and the completion time in seconds was used to calculate change in cognitive functioning in this study. It has the same sensitivity and specificity as the original Trail Making Test and presents age- and education- corrected normative data collected from a sample size of 1528 participants (Lezak et al., 2004). The CTT has four alternative forms which were used during each assessment making it suitable for repeated testing. It has demonstrated adequate test-retest reliability and has excellent concurrent validity with the original Trail Making Test (D'Elia et al., 1996; Elkin-Frankston et al., 2007).

Insomnia and Sleep Continuity

The Insomnia Severity Index (ISI) is a self-report measure that consists of 7 items designed to assess the severity of insomnia symptoms, the impact on daytime functioning, and the amount of associated distress within the last two weeks (See Appendix D, p. 82; Bastien et al., 2001). Items are scored on a Likert-scale of 0-4, with the highest possible score of 28. Scores of 0-7 are classified as no clinically significant insomnia, 8-14 as sub-threshold insomnia, 15-21 as clinical insomnia of moderate severity, and 22-28 as severe clinical insomnia. A change of 8.4 points has been established as clinically meaningful change on the ISI (Morin et al., 2011). The ISI has demonstrated internal consistency, reliability, construct validity, specificity and sensitivity in a representative sample of 1670 individuals living with cancer (Savard et al., 2005).

The Consensus Sleep Diary (CSD) is a self-report measure of sleep pattern and quality for each night for 7 consecutive days (Carney et al., 2012). The CSD was used to record nightly sleep-onset latency, wake after sleep onset, total sleep time, time in bed, number of awakenings, sleep quality and terminal wakefulness, which was then averaged over the 7 days. As a summary score, sleep efficiency percentages were calculated by dividing the amount of time spent in bed for the week by the amount of time actually spent sleeping for the week multiplied by 100% to

gain a percentage score. A sleep efficiency of above 85% is considered good. Sleep diaries are a reliable and valid self-report of nightly insomnia symptoms (Maich et al., 2016).

Sleep-wake activity was monitored using an actigraph, which is a watch that participants wear for 7 consecutive days. The actigraph monitors movement using an accelerometer to assess sleep-wake cycles by measuring sleep efficiency, sleep latency, total sleep time, and number and frequency of awakenings (Vallieres & Morin, 2003). To allow for comparison with sleep diaries, we used sleep efficiency percentages as a summary variable. The Micro Motionlogger brand has a 95% sensitivity, a 65% specificity, and a 90% agreement with polysomnographic data (Rupp & Balkin, 2011).

Fatigue

The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) is a 30 item self-report measure of the physical and psychological aspects of fatigue on 5 subscales (general, emotional, physical, mental and vigor) and a total fatigue score (Stein et al., 2004). The MFSI-SF reports symptoms of fatigue for a one-week period. For the purposes of this study, the total fatigue score was used. The total MFSI-SF score range from -24 to 96 with larger scores indicating more fatigue. A minimal clinically important difference has been identified as 10.79 for the MFSI-SF (Chan et al., 2018). The MFSI-SF has been validated in a sample of cancer patients compared to a healthy population (Stein et al., 2004) and has an internal consistency based on Cronbach alpha of 0.87 for the total score in breast cancer patients (Donovan et al., 2015;

Mood Disturbance

The Hospital Anxiety and Depression Scale (HADS) is a self-rated instrument with 14 items and two subscales: one for depressive symptomology and one for anxiety symptomology in the past week (Bjelland et al., 2002). Each item is scored from 0 to 3 and totalled. Established

cutoffs are: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety. A minimal important difference for the HADS anxiety and depression scores has been determined as 1.3 and 1.4 points, respectively (Puhan et al., 2008). The HADS has been validated and used extensively in individuals with cancer showing reliability, specificity and sensitivity (Uchino et al., 2011). Cronbach's alpha of the HADS-A and HADS-D sub-scales in breast cancer patients are 0.79 and 0.87 respectively (Rodgers et al., 2015).

Treatment Acceptability

The Credibility/Expectancy Questionnaire (CEQ) is a self-report 6-item measure that evaluates the participant's perception of treatment effectiveness after the intervention has been described in detail prior to starting the treatment (Devilly & Borkovec, 2000). Items 1-3 and 5 are measured on a 9-point Likert scale. Items 4 and 6 are measures on a percentage scale of 0-100. The questions investigate how logical the treatment appears, how successful they think it will be, how likely they would be to recommend it to a friend, how much improvement they think they will make, how much they feel the treatment will improve symptoms, and how much improvement they feel will occur by the end of treatment. The scale is interpreted by creating an overall credibility factor (taking the mean of questions 1 to 3) and an expectancy factor (question 4). For the purposes of this study we adjusted the questionnaire to specify how much improvement they think/feel they will make in regard to their insomnia and cognitive functioning. The CEQ has demonstrated high internal consistency within each factor and good test-retest reliability (Devilly & Borkovec, 2000). The expectancy factor single question maintains the high degree of face validity and is the most commonly used indicator of treatment outcome expectancy in psychotherapy and clinical trial research (Borkovec & Mathews, 1988; Borkovec et al., 2002; Constantino et al., 2011; Delsignore & Schnyder, 2007; Westra et al., 2011)

Treatment Details

Participants met for their individualized sessions with a trained doctoral student therapist at the psychology clinic. To ensure treatment consistency, a single therapist administered all sessions. The therapist was trained and supervised by a clinical psychologist with extensive experience delivering the intervention and providing supervision. The training consisted of teaching from a manualized CBT-I protocol developed by the clinical psychologist o effectively deliver CBT-I in the context of cancer and other chronic conditions. The supervision involved weekly case meetings for audiotape review to ensure adherence to CBT-I protocol. Each treatment sessions lasted approximately one hour. See Appendix A (pg. 74) for daily intervention breakdown.

Sample Size

The intended sample size was 30, which was estimated by a power calculation for pilot trials in clinical and translational research and based on previous studies with this patient population (Janelsins et al., 2014; Moore et al., 2011). It is recommended that single-arm clinical pilot studies aimed at testing the efficacy of an intervention that are being subsequently tested in larger trials to keep levels of type I error rates around 10–25% and type II error rates low ($\beta \leq$ 10%). Our sample size estimate was based on our primary outcome of PCI using the FACT-Cog. A change of 5.9 points has been established as clinically meaningful change on the FACT-Cog PCI subscale (Bell et al., 2018). Based on the primary outcome being continuous, this trial was powered using a dependent samples t-test score at post-treatment. Using a beta of 0.90 and a two-sided alpha of 0.25, 25 participants were needed to detect an effect size of 0.5. Due to the pilot trial nature of this study, we adjusted for a potentially large attrition rate of 20% from previous studies, resulting in a desired sample of 30 participants.

Data Collection

Questionnaires were filled out during each assessment and later entered into SPSS statistical software for future data analysis. Sleep diaries and actigraphs were collected one week following each assessment/treatment session and immediately downloaded and entered into SPSS. To minimize missing data, all surveys were checked upon completion. If missing data was identified the same day, participants were contacted via telephone to indicate unanswered questions.

Quantitative Data Analysis

Descriptive statistics were used to characterize the sample and are presented in Table 1 (pg. 65). Due to the exploratory nature of the present research, and the problematic interpretation of p values in small samples, effect sizes of partial eta squared (0.01 small, 0.09 medium and 0.25 large) were reported in addition to p values with significance level set at $p < .05$. Since this research is not aimed at hypothesis testing, no corrections were made for multiple comparisons. Data analysis was conducted in line with the study objectives:

1. Feasibility of Recruitment- The feasibility of conducting a longitudinal study with survivors of breast cancer was assessed by: the number of patients screened as identified by a research assistant and the number who both consented and completed the baseline assessment package. Reason for patient ineligibility is also reported.
2. Acceptability of Research Protocol and Intervention- Participants who consented and completed their baseline assessment were included in the final sample. Treatment acceptability was calculated using range of values (mean and standard deviation) for the CEQ. Completion rates were calculated based on the proportion of participants who completed the questionnaire packages at each time point. Reason for study withdrawal was indicated.

3. Treatment Effect and Durability - Range of values (mean and standard deviation) for all questionnaires was reported for the total scores at each time point. To investigate the impact of CBT-I treatment, a repeated measures analysis of variance (ANOVA) was performed for four assessment points (baseline, post-treatment, 3 month and 6 month follow-up) for each individual measure of cognition, insomnia, sleep, fatigue, and mood. Follow-up pairwise comparisons between data collection points were calculated to see where exactly the differences lay. Normative data based on age, sex and education demographics were used to examine objective cognitive function (Benedict et al., 1998; Loonstra et al., 2001; Ruff et al., 1996).

Missing Data

To determine the amount of existing missing data in our data set, a missing values analysis was conducted using SPSS. Due to the longitudinal data we were able to collect from participants, this method also imputed missing values with estimated values using estimated means methods to account for all missing data variables throughout the study. Multiple imputation methods were deemed unnecessary given the small sample size and low percentage of missing data.

Results

Objective 1: Feasibility of Recruitment

The primary objective of this pilot study was to estimate the feasibility of recruiting women who have survived breast cancer who report both insomnia and cognitive impairments for treatment of insomnia using CBT-I. Patient screening began in November 2018 and continued until September 2019. Due to the low number of participants who were interested in participating in the study and who also met the treatment criteria, we changed our eligibility requirement within the patient screening timeframe from participants having to have completed

treatment 12 months prior to 3 months prior but no more than 5 years. This increased the recruitment rate but not near our target sample size. Recruitment continued until the potential participant pool had been exhausted with no new identifiable cases.

A total of 45 survivors of cancer were screened for eligibility. Of these patients, 78% were excluded due to ineligibility. Geographical location of residence preventing treatment attendance was the primary reason for exclusion (27%), followed by no cognitive impairments (20%), male gender (17%), having completed all adjuvant cancer treatments more than 5 years prior (10%), a diagnosis of an alternative cancer to breast (10%), having previous experience with CBT-I (7%), a diagnosis of untreated obstructive sleep apnea (7%), and no present insomnia symptoms (3%). This left 15 patients who were potentially eligible for the study. We were able to successfully recruit 67% of these 15 patients to enrol in our study (five participants were unresponsive following initial contact). This resulted in a final sample of 10 survivors of breast cancer who consented to participate. With 45 participants screened and 10 being both eligible and completing baseline, this gave our study a recruitment feasibility of 22%. Detailed recruitment data (number of participants screened, eligible, consented, and dropouts) and reason for ineligibility are reported in Figure 3 (pg. 71).

Objective 2: Acceptability of Research Protocol and Intervention

Patient demographics are presented in Table 1 (p. 65). Women were an average age of 50.8 (SD 6.84) with 18.2 (SD 3.62) years of education. Most of the women were either in a committed relationship or married (80%). The sample was predominantly diagnosed with stage II breast cancer (70%) and the time since diagnosis was on average 43.2 months (SD 18.2). About 60% of the women believed their cancer diagnosis or treatments caused their insomnia and the other 40% believed their insomnia worsened after diagnosis/treatment.

Treatment credibility and expectancy were determined prior to treatment using the Credibility/Expectancy Questionnaire (CEQ). See Table 2 (p. 67). Regarding credibility, when asked “At this point, how logical does the therapy offered to you seem?” the sample mean was 8.10 (SD 1.10) out of a possible 9 (very logical). Regarding expectancy, when asked “At this point, how successful do you think this treatment will be in reducing your insomnia and cognitive impairment symptoms?”, the sample mean was 7.70 (SD .95) out of a possible 9 (very useful). Participants were highly confident they would recommend this treatment to a friend who experiences similar problems (Mean: 7.80 out of 9). By the end of the therapy period, participants expected their insomnia and cognitive impairment symptoms would improve by more than 70%. The overall credibility factor for this therapy for improving insomnia and cognitive impairment symptoms was rated at 7.87 out of 9 (87.4%) and the expectancy factor was 71%.

The second objective was to determine if participants were able to complete the study protocol. Missing values analysis revealed that the percentage of missing data from questionnaire packages throughout the duration of the study was 6.98%. The majority of missing data came from a single participant (41%) who did not complete two assessment packages, a participant who did not complete one assessment package (21.8%) as well as some adherence issues with the consensus sleep diaries (10.42%) and actigraphs (12.92%). Due to the COVID-19 pandemic, actigraphy and CTT (6.77%) information was not accessible from two 6-month follow-up patient assessments that had to be conducted online.

Adherence was calculated based on the number of participants who completed the assessment packages at all time points as well as those who completed treatment. A total of 50 assessments were expected and 47 were actually completed, resulting in a response rate of 94%

for the full duration of the study. There was a downward trend in the number of assessments completed over the course of 8 months. At baseline and post-treatment, 100% of the assessments were completed, followed by 90% at 3 months and 80% at 6 months (See Figure 4, p. 72). As for the CBT-I treatment adherence 100% of participants who enrolled in the study completing all 7 sessions of the treatment.

Attrition was defined as withdrawal from the study at any time point. The attrition rate for this study was 20%. One participant withdrew from the study following the post-treatment assessment due to emotional instability following the death of a family pet. Another participant was unresponsive to communications following the 3-month follow-up assessment. Missing values analysis imputation method was used for missing values.

Objective 3: Treatment Effects and Durability

To provide preliminary estimates for future randomized controlled trials, our third objective was to determine if scores on measures of PCI, objective cognitive impairment, sleep, fatigue and mood were associated with changes in insomnia symptomology following CBT-I treatment. A repeated measures analysis of variance (ANOVA) with pair-wise comparisons was performed at baseline, post-treatment, 3 months and 6 months for each of the symptoms, respectively. Results for the ANOVAs are presented in Table 3 (p. 68).

At baseline, participants scored within the higher range of the PCI subscale [Mean: 28.6] with a range of 0 to 72. There was a large effect size and significant main effect of time for PCI over 8 months [$F(3,27) = 10.81$, $p < .001$, $\eta_p^2 = .546$]. Pairwise comparisons revealed that there was a significant decrease in PCI from baseline to post treatment [Mean: 28.6 to 43.1; $p = .006$], 3 months [Mean: 28.6 to 41.6; $p = .003$] and 6 months [Mean: 28.6 to 43.6; $p = .002$]. These changes represent both a statistically significant change and clinically meaningful change of

more than 5.9 points following treatment. PCI at post treatment was not significantly different than at 3 months [Mean: 43.1 to 41.6; $p = .632$] or 6 months [Mean: 43.1 to 43.6; $p = .748$] indicating that these changes were maintained at follow-up. There appeared to be no significant differences between PCI at 3 months and 6 months [Mean: 41.6 to 43.6; $p = .434$]. These results are presented in Figure 5 (p. 73).

To provide a more in-depth analysis of cognitive impairment, we wanted to determine if measures of objective cognitive impairment in addition to PCI were sensitive to changes in insomnia symptomology following CBT-I treatment. Three tests (The HVLT-R, COWAT, and CTT) were used to capture the multifaceted nature of cognitive impairment and were compared to normative data using age and educational level to categorize as cognitively impaired. There was a small effect size and no significant main effect of time on verbal learning and memory [$F(3, 27) = .238$, $p = .869$, $\eta_p^2 = .026$], a large effect size but no significant main effect of time on verbal fluency and executive functioning [$F(3, 27) = .254$, $p = .254$, $\eta_p^2 = .626$], and a large effect size but no significant main effect of time on divided attention and processing speed [$F(3, 27) = 2.37$, $p = .093$, $\eta_p^2 = .208$]. These findings suggest that although statistically significant changes weren't apparent in verbal learning and memory, verbal fluency and executive functioning, and divided attention and processing speed, there were small to large effects of time that may be of clinical significance. During baseline and throughout the duration of the study the average scores of each neuropsychological measure were within the non-cognitively impaired range.

At baseline, participants were in the moderate severity range of clinical insomnia [Mean: 19.4]. There was a large effect size and significant main effect of time for insomnia severity over 8 months [$F(3,27) = 25.48$, $p < .001$, $\eta_p^2 = .739$]. Pairwise comparisons revealed that there was a

significant decrease in insomnia severity from baseline to post treatment [Mean: 19.4 to 7.1; $p <$ .001] which also represented a clinically meaningful change of > 8.4 point reduction. Significant improvements were also noted in 3 months [Mean: 19.4 to 9.2; $p < .001$] and 6 months [Mean: 19.4 to 12.1; $p = .002$]. While effects were largely maintained, there was some rebound of insomnia symptoms at 3 months [Mean: 7.1 to 9.2; $p = .076$] and 6 months [Mean: 9.2 to 12.1; $p = .067$].

Baseline scores revealed participants scored in the normal and slightly below normal range for subjective sleep efficiency and objective sleep efficiency, respectively [Mean: 84.6, 78.8]. There was a large effect size but no significant main effect of time for either subjective sleep efficiency [$F(3,27) = 1.36$, $p = .275$, $\eta_p^2 = .132$] or objective sleep efficiency [$F(3,27) = 1.45$, $p = .249$, $\eta_p^2 = .139$] over 8 months. This suggests that statistically significant changes weren't apparent in sleep efficiency however, there were large effects of time that may be of clinical significance.

Based on the range of -24 to 96, participant's baseline fatigue was in the moderate range [Mean: 43.0]. There was a large effect size and significant main effect of time for fatigue over 8 months [$F(3,27) = 5.49$, $p = .004$, $\eta_p^2 = .379$]. Pairwise comparisons revealed that there was a significant decrease in fatigue from baseline to post treatment [Mean: 43.0 to 24.4; $p = .036$], 3 months [Mean: 43.0 to 21.5; $p = .010$] and 6 months [Mean: 43.0 to 25.0; $p = .042$]. These changes also represent a clinically meaningful change of 10.79 points. Fatigue at post treatment was not significantly different than at 3 months [Mean: 24.4 to 21.5; $p = .548$] or 6 months [Mean: 24.4 to 25.0; $p = .875$] suggesting decreases in fatigue were maintained at follow-up. There was no significant difference between fatigue at 3 months and 6 months [Mean: 21.5 to 25.0; $p = .402$].

At baseline, participants were in the subclinical range for depression [Mean: 7.9]. There was a large effect size and significant main effect of time on depression over 8 months [$F(3,27) = 3.44$, $p = .031$, $\eta_p^2 = .276$]. Pairwise comparisons revealed that there were no significant differences between baseline and post treatment [Mean: 7.9 to 5.3; $p = .101$] or baseline to 3 months [Mean: 7.9 to 5.4; $p = .061$], although significant decreases were apparent in depression from baseline to 6 months [Mean: 7.9 to 4.4; $p = .035$]. However, change in depression from baseline, post-treatment, 3 months and 6 months represents a clinically meaningful change of 1.3 points. At post treatment depression was not significantly different than at 3 months [Mean: 5.3 to 5.4; $p = .929$] or 6 months [Mean: 5.3 to 4.4; $p = .337$] indicating that changes in depression were maintained at follow-up. There were no significant differences between depression at 3 months and 6 months [Mean: 5.4 to 4.4; $p = .204$]. At baseline, participants scored within the subclinical range for anxiety [Mean: 10.10]. There was a large effect size but no significant main effect of time on anxiety over 8 months [$F(3,27) = 2.34$, $p = .095$, $\eta_p^2 = .207$]. However, a clinically meaningful change of 1.4 points was apparent in anxiety from baseline [Mean: 10.1], post-treatment [Mean: 8.4], 3 months [Mean: 7.7] and 6 months [Mean: 7.6]. This suggests that although statistically significant changes weren't apparent in anxiety, there were large effects of time on anxiety that were clinically significant.

In summary, baseline scores revealed participants entered the study with high levels of PCI, normal levels of cognitive functioning, moderately severe levels of insomnia, below normal levels of objective sleep efficiency, normal levels of subjective sleep efficiency, moderate levels of fatigue, and subclinical levels of depression and anxiety. Over the course of 8 months, there were statistically significant improvements in PCI, insomnia, fatigue and depression. Following treatment, improvements in PCI, insomnia and fatigue were all maintained at 3 and 6 months.

More importantly for this study, there were clinically significant improvements in PCI, insomnia, fatigue, depression and anxiety over 8 months. Lastly, there were large effect sizes over time for PCI (ES = .546), verbal fluency and executive functioning (ES = .626), divided attention and processing speed (ES = .208), insomnia (ES = .739), subjective sleep efficiency (ES = .132), objective sleep efficiency (ES = .139), fatigue (ES = .379), depression (ES = .276) and anxiety (ES = .207).

Discussion

This study assessed the feasibility, acceptability, and the preliminary effectiveness and durability of using CBT-I to reduce PCI in survivors of breast cancer. Regarding feasibility, the results indicated that out of 45 participants screened, 15 reported both insomnia and perceived cognitive impairment as well as met all other eligibility criteria, with 10 who enrolled. This provides 22% recruitment feasibility for this project, which indicates future randomized control trials will have to recruit approximately five times (80%) their intended sample size to obtain participants who are both interested and eligible. These findings will be very informative to subsequent designs as they can expect to recruit a much larger sample of interested participants than might have been previously expected. The literature states that insomnia affects approximately 60% of survivors of breast cancer (Savard et al., 2011) and cognitive impairments are reported in approximately 50% (Janelsins et al., 2017) but to our knowledge, this was the first study to estimate the prevalence of both insomnia and cognitive impairments (problems with attention, memory and concentration) in survivors of breast cancer. Based on our findings, about 20% of survivors of breast cancer report issues with both insomnia and cognitive impairments, although future research should be conducted to identify the prevalence based on cancer stage, previous treatments, and underlying conditions.

The second aim of this study was to determine the acceptability of both the research project and the intervention for participants. Patient's scores on the Credibility/Expectancy Questionnaire prior to treatment and adherence to study protocols were used as a proxy indicator of acceptability. No clear theoretical framework for acceptability was followed (e.g., Sekhon et al., 2017), and therefore some facets of acceptability may have been missed (e.g., affective attitude, ethicality, intervention coherence, opportunity costs, and self-efficacy). Prior to the intervention, participants on average thought the treatment was credible and expected positive outcomes. Participants were adherent to the treatment with 100% of participants who enrolled in the study completing the treatment. The completion rate of the intervention was higher than previous studies, where only 83% of survivors of cancer who had enrolled completed the 7-week intervention (Kamen et al., 2019). A plausible explanation for our large adherence rate to treatment could be the role of social support. Psychosocial factors such as social support predict both the adherence and response to CBT-I treatments, with those who have stronger social support networks being more likely to maintain improvements of the therapy (Kamen et al., 2019). More positive partner statements are also associated with better treatment outcomes of the Insomnia Severity Index (Ellis et al., 2015). This explanation seems plausible as 80% of our sample were either married or in a committed relationship throughout the course of our study. Future studies should investigate the role of social support in treatment adherence as well as other social environment factors that may be contributing to the acceptability of the therapy such as the effects of co-sleeping, parenting, and other life events. Adherence to the assessments also seemed to be quite high based on the low frequency of dropouts (20%) from the study. This resulted in 47 out of 50 assessments being completed, a response rate of 94% for the full duration

of the study. These results build on existing evidence of low attrition rates (~15%) in CBT-I studies in women with breast cancer (Zhou et al., 2017).

The third objective investigated if measures of PCI were sensitive to change following CBT-I treatment. A strong effect size of the treatment was noted for improvements in PCI, with changes being both clinically and statistically significant. These effects were largely maintained at 3 and 6 months, which indicates, that CBT-I may be successful in not only improving insomnia severity but also potentially PCI as well. However, prior to study initiation participants indicated they were very optimistic about the treatment and felt better about their cognitive performance following treatment. Expectancy effects may explain the improvements in PCI as there was no control group to account for such biases. This pilot trial is the first study to provide preliminary evidence of large effects of CBT-I on subjective cognitive impairment in survivors of breast cancer in particular. Our results are consistent with 14 other studies that were conducted in individuals with insomnia who did not have cancer that found small to moderate effect sizes of CBT-I on subjective cognitive impairment (Herbert et al., 2018). These results demonstrate promise of CBT-I as a plausible treatment for cognitive difficulties experienced following a cancer diagnosis and provide hope for future studies.

We were also interested in whether measures of objective cognitive impairment in addition to PCI were sensitive to improvements in insomnia symptomology following CBT-I treatment. There were no statistically significant improvements in verbal learning and memory, verbal fluency and executive functioning and, divided attention and processing speed. Importantly, participant's mean score based on age, sex and education were within the average range for verbal learning and memory, verbal fluency and executive functioning and, divided attention and processing speed at baseline which would make it difficult to demonstrate

improvements. These results are consistent with previous literature that has found inconsistencies between patient reports and neuropsychological cognitive measures (Hermelink, 2015). Our findings support the idea that the "chemo brain" may largely be a subjective experience with a strong emotional component involved (Hermelink, 2015). Previous literature has found PCI influences overall subjective wellness in cancer patients. With improvements in insomnia, fatigue, depression and anxiety in addition to subjective cognitive impairments noted in our study, the "chemo brain" being more of a subjective experience seems very plausible. These findings are consistent with other studies that have been conducted and found no significant improvements in objective cognitive functioning following CBT-I (Herbert et al., 2018). However, participants could have simply been having cognitive difficulties in areas that were not measured by our neuropsychological instruments. Although, there have been very few studies conducted to investigate the effectiveness of this therapy on cognitive functioning and like ours, the existing studies lacked power given the small sample sizes. Therefore, based on our sample size it is important to emphasize the large effect size of verbal fluency and executive functioning, and divided attention and processing speed that were noted over 8 months. Further research is warranted on this topic before deeming CBT-I as ineffective in improving cognitive impairment, with samples that show larger impairments at baseline.

Consistent with previous findings (Johnson et al., 2016), clinical and statistical improvements in insomnia severity were noted with large effect sizes in survivors of breast cancer following CBT-I treatment and scores remained lower than baseline at 3 and 6 months following treatment; however, there was an linear increase in insomnia severity following treatment. A plausible explanation for this could be adherence to therapeutic recommendations following treatment. Manber et al. (2011) notes that better adherence to CBT-I treatment is

associated with lower insomnia scores following treatment. In particular, patients report that adhering to the behavioural recommendations of CBT-I can be quite difficult (Matthews et al., 2013). These guidelines can be especially challenging to follow long-term as pleasant experiences such as sleeping in on weekends is not recommended in order to keep a consistent sleep and wake time and involves a large lifestyle change (Matthews et al., 2013). Where this study did not provide any incentive following treatment and no therapist to hold the patient accountable, it may have been harder for them to adhere to the treatment recommendations. This theory would explain the weakening of treatment effect over time, as without continued support from the therapist, patients may stop engaging in behaviours that are beneficial for sleep. Based on Spielman's 3 P model (Spielman et al., 1987), what tends to predominately feed insomnia symptoms are perpetuating factors. These are behaviours those experiencing sleep difficulties following a precipitating event (e.g., stressful life event) do to compensate for loss of sleep (e.g., napping). Therefore, reinstating these perpetuating factors would increase the likelihood of insomnia symptoms returning.

We did not observe a significant increase in either subjective or objective sleep efficiency. Although our findings were not statistically significant, our effect size was in line with previous research, showing large treatment effects of CBT-I on sleep efficiency (Johnson et al., 2016). It is possible that adherence may be to blame for the lack of significant findings as most of the missing data in the individual questionnaires were from sleep diaries and actigraphs. For the sleep diaries in particular, perhaps inaccurate recording of daily sleep impaired the utility of the data obtained. This would explain the lack of variability in sleep diary sleep efficiency scores throughout the course of the study. This theory would also provide support for why there seemed to be inconsistencies between subjective and objective measures of sleep efficiency in

survivors of breast cancer with insomnia, which is consistent with the literature (Moore et al., 2015). These results also support our use of both an objective and subjective sleep efficiency measures in order to provide a more reliable measurement. Although statistically significant improvements were not apparent throughout the duration of the study, there were large effect sizes in sleep efficiency that provide optimistic preliminary evidence for future studies.

In addition to insomnia symptoms, fatigue had also significantly decreased with a large effect size over 8 months, with improvements in fatigue following treatment being maintained 3- and 6-months following treatment. These findings are consistent with Fleming et al (2014) who found CBT-I effectively reduced clinical levels of fatigue related to cancer treatments as well. This is unsurprising as you would expect treatment programs designed to decrease insomnia would also yield improvements in highly co-occurring symptoms as well, especially those related to day-time functioning (Kim et al., 2018).

The current results indicate that depression symptomology significantly decreased over the course of 8 months but there were no apparent differences following treatment compared to baseline. Interestingly, there were also no statistically significant changes in anxiety symptomology over the course of the study. This is inconsistent with previous literature which has found CBT-I to be very effective in decreasing insomnia, depression and anxiety symptomology particularly in survivors of breast cancer (Fleming et al., 2014; Garland et al., 2014). However, once scores had decreased following treatment, they remained consistently in the non-significant range. There also appeared to be large effect sizes and clinically meaningful changes in both anxiety and depression throughout the study. A possible explanation for these results is that participants did not show high levels of depression or anxiety at baseline, scoring in the subclinical range. With a range of scores between 0-10 out of a possible range of 0-21,

achieving statistical significance is difficult given the size of our current sample. Based on the large effect sizes and clinical significance, CBT-I demonstrates promise for reducing mood disturbance in the population in subsequent research.

Strengths and Limitations

This study was the first of its kind to test whether we could improve the commonly reported symptom of "chemo brain" in survivors of breast cancer using CBT-I. The primary strength of this study was its ability to provide valuable information for stronger future research designs. Given the small sample size and detection of improvement in PCI, our results show promise for future randomized controlled trials. Secondly, the current study used the best available measures of symptoms. Subjective measures were used to determine psychological well-being symptoms which are best assessed by self-report (Haberer et al., 2013) while subjective and objective measures of insomnia, sleep and cognitive functioning were used, giving us confidence in the accuracy of the results (Aili et al., 2017; Savard & Ganz, 2016; Morin, 2003).

There were also a number of limitations to our study, the first being the small sample size. With such a small sample, it is difficult to obtain representativeness from the population making it hard to determine generalizability as well as draw any firm conclusions from the results. However, this is not the purpose of a feasibility study. Future studies should try to obtain a larger, more heterogeneous sample, including those living in rural communities as well. A small sample size also decreased the power of our study but we were still able to find significant differences with a low powered study. To adapt to the small sample limitation, we also reported effect sizes and clinically meaningful change scores. As well, given the number of statistical tests performed to evaluate preliminary efficacy, future studies should correct for alpha-spending

function, which was no appropriate given the exploratory nature of this study. Secondly, due to the single arm design of this study with no control group, we are unable to rule out the effect of time on patients PCI. Improvement in PCI could have been attributed to time effects rather than the treatment provided. Control conditions are also the principle method used to ensure internal validity by removing overlapping variance of unwanted variables in experimental research. Selection biases therefore may have occurred as well with self-selected highly motivated women may have led to larger improvements following CBT-I treatment. As well as a possible demand characteristic may have been present with participants expecting to notice improvements given the high expectancy effects at pre-intervention. Specifically, in the treatment of insomnia, meta-analyses indicate a reliable placebo effect (Yeung et al., 2018). Experimenter effects are important to consider as well given a systematic review that examined 146 meta-analyses that included 1,346 trials reported that a lack of blinding within trials resulted in a 25% exaggeration in the effect sizes of subjective outcomes (Wood et al., 2008). Although future randomized controlled trials will be able to control for some of these confounds, future studies should potentially include a healthy control group as well to rule out practice effects on measures that do not have multiple forms suitable for repeated testing (Wefel et al., 2011). Of particular concern is the potential impact of administering numerous instruments to a population vulnerable to attention/concentration/memory problems. This may have led to incorrect recall of symptoms as well as potential fatigue effects that could bias the results. However, neuropsychological tests were spaced out between self-report questionnaires to limit this effect. This study was also unable to control for potential confounds such as mood or stress on PCI due to the small sample size. Subsequent designs should control overlapping variance to increase the accuracy of the results. The amount of missing data was also of concern as missing value analysis was conducted

to estimate scores based on previous data. Future studies should try to limit missing data as much as possible to conserve reliability of their findings. Lastly, this non-experimental research design provides the inability to infer causation. Although we have identified that a relationship exists between improvement in insomnia and PCI, this relationship is purely correlational. The two may simply coexist but the extensive literature suggests that improvement in one may have an indirect effect on the other as well.

Conclusion

Our study was the first study to investigate the feasibility and acceptability of using a gold-standard treatment for insomnia on subjective cognitive complaints in this population. Although recruitment yielded difficulties, CBT-I was associated with improvements in not only PCI but also objective cognitive functioning, sleep efficiency, insomnia, fatigue, depression and anxiety. The current pilot trial has important implications for future studies investigating treatment modalities for the psychological well-being of survivors of cancer. Subsequent research should examine the effectiveness of this treatment on a larger scale with a more heterogeneous sample of women to determine its effectiveness.

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Table 1

Summary of Demographic Characteristics

	N	%
	10	**100**
Age		
Mean (SD)	50.8 (6.84)	
Range	(42-63)	
Race		
White	10	100
Non-white	0	0
Body Mass Index		
Underweight (< 18.5)	0	0
Normal weight (18.5 – 24.9)	3	30.0
Overweight (25 – 29.9)	5	50.0
Obese (> 30)	2	20.0
Years of Education		
Mean (SD)	18.2 (3.62)	
Range	(12-23)	
Employment		
Full-time	5	50.0
Part-time	2	20.0
Unemployed/Retired	3	30.0
Relationship Status		
Single	1	10.0
Committed relationship/Married	8	80.0
Divorced	0	0
Widowed	0	0
Other	1	10.0
Comorbid Health Conditions		
Obstructive Sleep Apnea (Treated)	2	20.0
Depression	1	10.0
Inflammatory conditions	6	60.0
Crohn's Disease	2	20.0
Bone Diseases (Osteoporosis/Osteopenia)	2	20.0
* Women could have more than one of these conditions		
Cancer Stage		
I	2	20.0
II	7	70.0
III	1	10.0
Months Since Treatment Completion		
Mean (SD)	9.6 (3.84)	
Range	(6-15)	
Months Since Cancer Diagnosis		
Mean (SD)	43.2 (18.2)	

Range	(24-84)	
Treatments		
Surgery	10/10	100
Chemotherapy	9/10	90.0
Radiation	8/10	80.0
Hormonal Therapy	8/10	80.0
Antibody Therapy	4/10	40.0

* Women could have received more than one of these treatments

Table 2

Credibility/Expectancy Questionnaire

	Mean(SD)	(Range)	%
	10		**100**
Question 1: At this point, how logical does the therapy offered to you seem?	8.10(1.10)	(6-9)	**100**
Question 2: At this point, how successfully do you think this treatment will be in reducing your insomnia and cognitive impairment symptoms?	7.70(.95)	(6-9)	100
Question 3: How confident would you be in recommending this treatment to a friend who experiences similar problems?	7.80(1.23)	(6-9)	100
Question 4: By the end of the therapy period, how much improvement in your insomnia and cognitive impairment symptoms do you think will occur?	71.0(19.7)	(20-90)	100
Credibility Factor (Questions 1-3)	7.87		100
Expectancy Factor (Question 4)	71.0		100

Table 3

Repeated Measures Analysis of Variance of Patient Symptoms

	Baseline	Post Treatment	3 Months	6 Months	Time Effect	Effect Size
	Mean(SD)	**Mean(SD)**	**Mean(SD)**	**Mean(SD)**	**F (df) [p]**	**η_p^2**
Perceived Cognitive Impairment (FACT-Cog)	28.60(14.01)	43.10(7.64)	41.60(11.62)	43.60(9.01)	**10.81 (3,27) [<.001]**	.546
Objective Cognitive Impairment						
Verbal Learning & Memory (HVLT-R)	92.50(17.97)	91.70(16.79)	88.30(32.28)	89.40(12.68)	.238 (3,27) [.869]	.026
Executive Verbal Functioning (COWAT)	42.00(10.10)	-	-	42.50(11.18)	.254 (3,27) [.254]	.626
Divided Attention & Processing Speed (CTT)	76.37(20.26)	66.97(17.88)	71.11(16.66)	66.87(11.03)	2.37 (3,27) [.093]	.208
Insomnia (ISI)	19.44(3.66)	7.10(3.81)	9.20(3.49)	12.10(3.93)	**25.48 (3,27) [<.001]**	.739
Objective Sleep Efficiency (Actigraphy)	78.84(12.25)	80.51(9.62)	81.94(10.79)	85.99(3.35)	1.45 (3,27) [.249]	.139
Subjective Sleep Efficiency (CSD)	84.60(7.03)	89.90(5.97)	80.32(17.41)	84.85(7.21)	1.36 (3,27) [.275]	.132
Fatigue (MFSI-SF)	43.00(18.81)	24.40(15.41)	21.50(12.59)	25.00(9.68)	**5.49 (3,27) [.004]**	.379
Depression (HADS-D)	7.90(3.45)	5.30(2.83)	5.40(1.84)	4.40(1.90)	**6.08 (3,27) [.036]**	.276
Anxiety (HADS-A)	10.10(4.36)	8.20(3.91)	7.70(1.70)	7.60(3.20)	2.34 (3,27) [.095]	.207

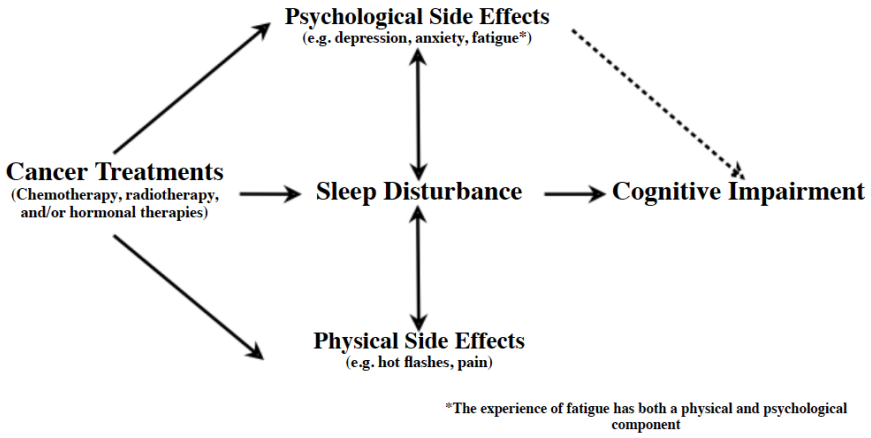

Figure 1. Treatment conceptual model. The interactions between cancer treatments, psychological side effects, sleep disturbance and physical side effects on cognitive impairment.

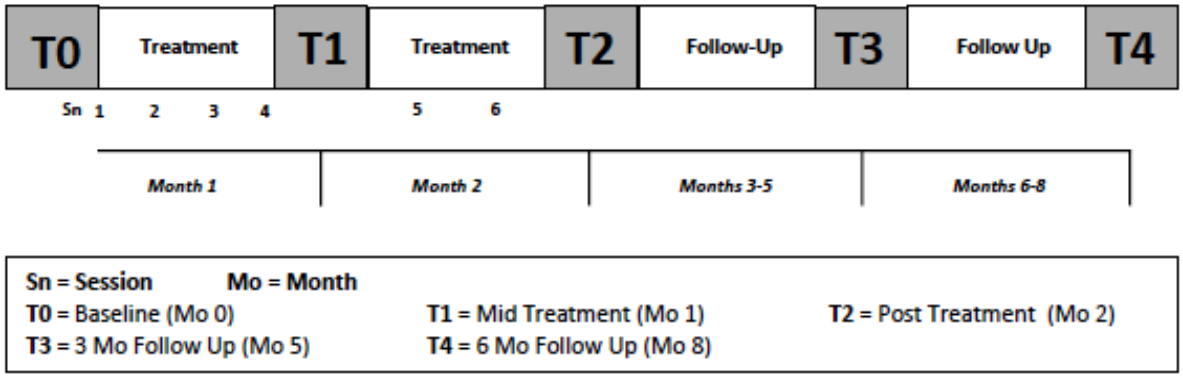

Figure 2. Study design.

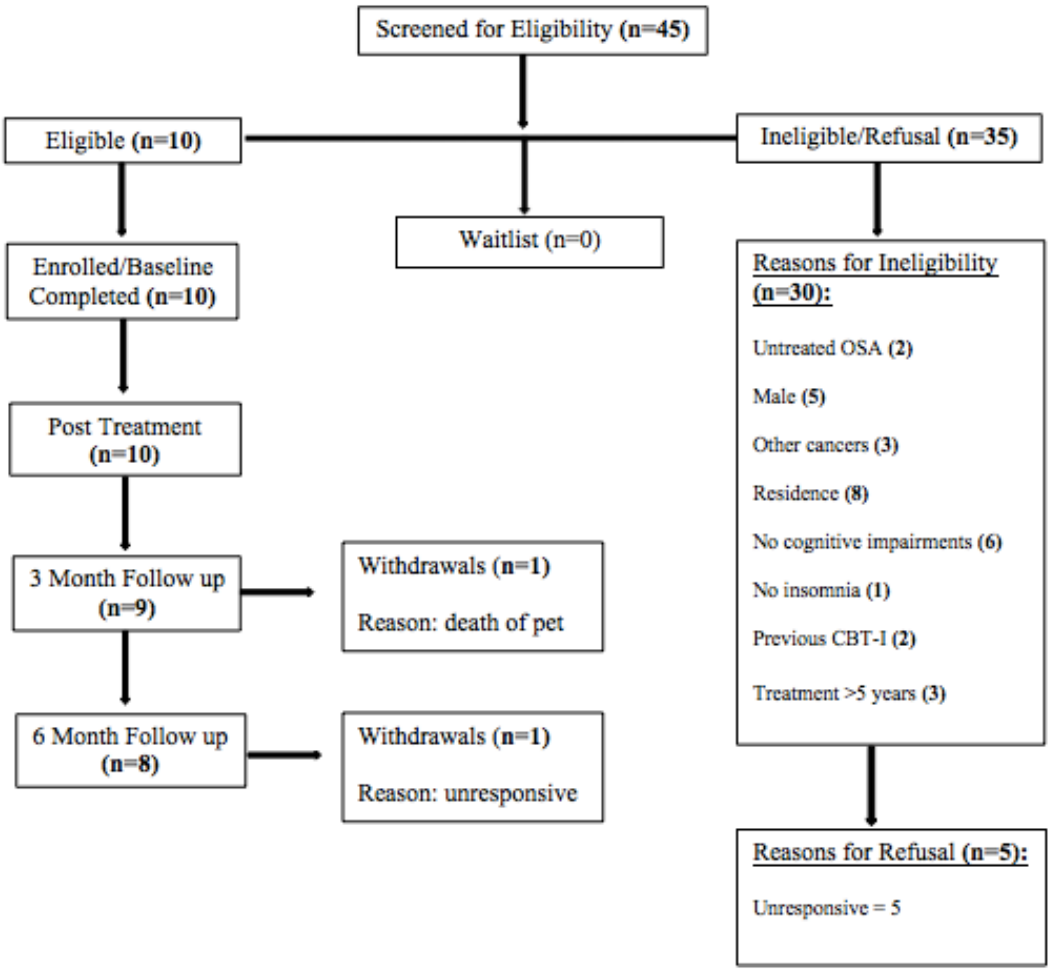

Figure 3. Recruitment flowchart of eligible participants. Feasibility of suitable women with breast cancer who reported both insomnia and cognitive impairments and acceptability of the research project including completion rates of questionnaire packages.

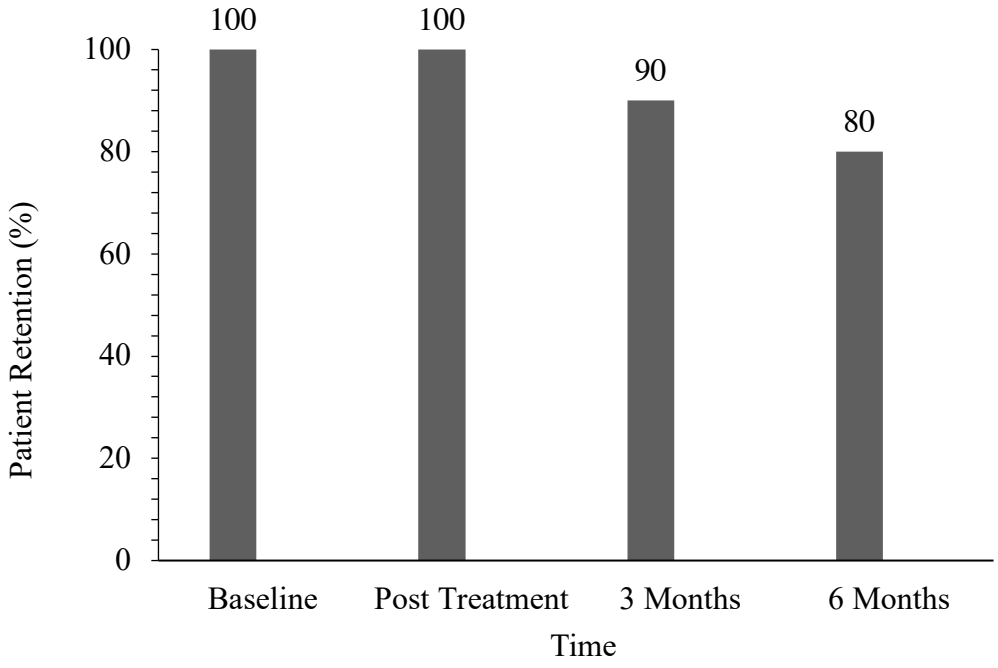

Figure 4. Acceptability of research study in survivors of breast cancer. All participants who enrolled in the study completed treatment. One dropout following treatment resulted in a decrease in retention at 3 and 6 months. Another dropout following 3 months resulted in decrease in retention at 6 months. Data was expressed as percentages.

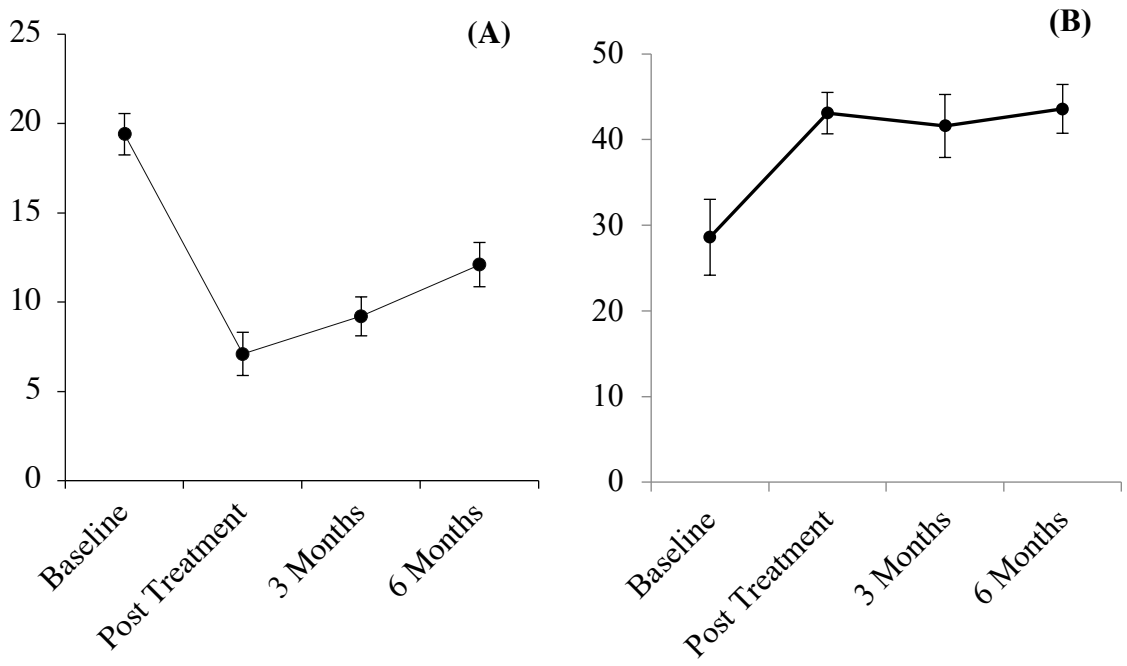

Figure 5. Change in insomnia and perceived cognitive impairment (PCI) following treatment. Comparison of insomnia (A) and PCI (B) symptoms at baseline, post treatment, 3 months and 6 months. Insomnia and PCI symptoms significantly improved following treatment and were maintained 6 months following treatment ($p < .001$). There were no significant differences between post-treatment, 3-month and 6-month scores for both insomnia and PCI. Higher ISI score indicates worse insomnia severity. Higher FACT-COG indicates better PCI. Data were expressed as means ± SEM

Appendix A

Weekly CBT-I Description:

Week One: Week one involved gaining information from participants with respect to medication use, medical problems, addressing any immediate concerns/problems with participation (e.g., adverse events, symptoms, illnesses, or new stressors), discussing the participant's sleep schedule and discussing motivation and general compliance issues of the therapy. Using this information, the therapist was able to formulate an impression of the type and subtype of insomnia and determine modifiable factors that relate to the predisposing, precipitating, perpetuating factors and conditioning relevant to the development and maintenance of insomnia. At the end of the session, the therapist gave the participant a sleep diary to fill out for the week, reinforcing its importance, and confirmed the next appointment the following week.

Week Two: Session two was more in depth with regards to the participant's sleep schedule and involved reviewing the sleep diary to identify any mismatch between the sleep opportunity and the sleep ability. By reviewing the patient's sleep diary from the previous week the therapist was able to calculate sleep onset latency, sleep efficiency (i.e., current sleep ability vs. hours spent in bed), total sleep time, wake after initial sleep onset, early morning awakenings and total time in bed. These scores were used to provide an individualized sleep program for the upcoming weeks. This allowed the therapist to introduce **sleep education** and explain the 4-P model of insomnia (modifiable factors that relate to the predisposing, precipitating, perpetuating factors and conditioning relevant to the development and maintenance of insomnia). The therapist then used this information to prescribe **sleep restriction** and **stimulus control therapy** while providing the rationale behind the prescription. This involved: 1.) Setting a strict wake up time for every day of the week, regardless of number of hours slept. 2.) Establishing a 60-90-minute relaxation buffer

zone before bed in dim light, avoiding the use of backlit devices. 3.) Setting a bedtime but only if sleepy and restricting the bed use to only sleep and sex. 4.) Encouraging to get out of bed and return to buffer zone if participant cannot fall or fall back to sleep within 15-20 minutes to again engage in relaxing activities. 5.) Try to deter participants from napping during the day. Similar to week one, the therapist gained information from participants with respect to medication use, medical problems, addressed any immediate concerns/problems with participation (e.g., adverse events, symptoms, illnesses, or new stressors) and discussed motivation and general compliance issues of the therapy. The session ended by reinforcing the importance of the sleep diary and new time to bed/time out of bed, providing the patient with a hard copy of the individualized sleep program and confirming the next appointment for the following week.

Week Three: Session three began with reviewing the patient's sleep diary from the previous week and calculating sleep variables. Same as previous weeks, the therapist identified changes to medication use, medical problems, addressed any immediate concerns/problems with participation (e.g., adverse events, symptoms, illnesses, or new stressors) and discussed motivation and general compliance issues of the therapy. Stimulus control and sleep restriction procedures were continued, and participants were provided with a **sleep hygiene** handout, which was reviewed to develop a plan for behavior change if necessary. The session ended by reinforcing the importance of the sleep diary, prescribing a new time to bed/time out of bed, and confirming the next appointment for the following week.

Week Four: Session four began with reviewing the patient's sleep diary from the previous week and calculating sleep variables. Same as previous weeks, the therapist identified changes to medication use, medical problems, addressed any immediate concerns/problems with participation (e.g., adverse events, symptoms, illnesses, or new stressors) and discussed

motivation and general compliance issues of the therapy. Stimulus control and sleep restriction procedures were continued, and participants were introduced to and suggested to practice **relaxation strategies** if necessary (e.g., deep breathing, imagery, progressive muscle relaxation). The session ended by reinforcing the importance of the sleep diary, prescribing a new time to bed/time out of bed, and confirming the next appointment for the following week.

Week Five: Session five began with reviewing the patient's sleep diary from the previous week and calculating sleep variables. Same as previous weeks, the therapist identified changes to medication use, medical problems, addressed any immediate concerns/problems with participation (e.g., adverse events, symptoms, illnesses, or new stressors) and discussed motivation and general compliance issues of the therapy. Stimulus control and sleep restriction procedures were continued, and the therapist conducted **cognitive therapy** by identifying catastrophic thoughts, discuss why the worry may happen, introduced cognitive techniques and designated a worry time earlier in the evening. The session ended by reinforcing the importance of the sleep diary, prescribing a new time to bed/time out of bed, and confirming the next appointment for the following week.

Week Six: Session six began with reviewing the patient's sleep diary from the previous week and calculating sleep variables. Same as previous weeks, the therapist identified changes to medication use, medical problems, addressed any immediate concerns/problems with participation (e.g., adverse events, symptoms, illnesses, or new stressors) and discussed motivation and general compliance issues of the therapy. Stimulus control and sleep restriction procedures were continued, and the therapist reviewed any strategies that need further reinforcement. The session ended by reinforcing the importance of the sleep diary, prescribing a new time to bed/time out of bed, and confirming the next appointment for the following week.

Week Seven: The final session began with reviewing the patient's sleep diary from the previous week and calculating sleep variables. The therapist reviewed the overall process, provided the patient with a **relapse prevention** handout to remind them how to maintain gains, discussed sleep restriction guidelines for if insomnia returns, discussed prophylaxis (how insomnia develops etc.) and elaborated on how gains will continue with proper stimulus control.

Appendix B

Ethical Approval from the Health Research Ethics Board of Memorial University

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

September 26, 2018

Department of Psychology
232 Elizabeth Ave
St. John's, NL, A1B 3X9

Dear Dr. Garland:

Researcher Portal File # 20190558
Reference # 2018.168

RE: "A Pilot Trial of Cognitive Behavior Therapy For Insomnia And Cognitive Complaints in Breast Cancer Survivors "

This will acknowledge receipt of your correspondence dated September 27, 2018.

Your application was reviewed by the Health Research Ethics Board (HREB) at the meeting held on August 23, 2018. Your revised application has been reviewed by the Co-Chair under the direction of the HREB.

Ethics approval of this research study is granted for one year effective September 24, 2018. This ethics approval will be reported to the board at the next scheduled HREB meeting.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- CBT4PCI advertisement revised 29AUG18.
- Recruitment Letter revised 29AUG18
- CBT4PCI Consent Form revised 30JULY18 clean
- Recruitment Letter revised 30JULY18
- Assessment Package
- CBTI4PCI Protocol V1 July 2018
- CBT4PCI advertisement 12JULY18

MARK THE DATE

This ethics approval will lapse on September 24, 2019. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event Form.

If you do not submit the completed Ethics Renewal form prior to date of renewal:

- **You will no longer have ethics approval**
- You will be required to stop research activity immediately
- You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again
- Lapse in ethics approval ***may result in interruption or termination of funding***.

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; to **Research Grant and Contract Services** should your research depend on funding administered through that office.

Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes in the protocol/consent without HREB approval may result in your ethics approval being revoked, meaning your research must stop.** Request for modification to the protocol/consent must be outlined on an amendment form available on the Researcher Portal website as an Event Form and submitted to the HREB for review. Please refer to the attached guidance document regarding on-going reporting requirements to the HREB.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), ICH Guidance E6: Good Clinical Practice Guidelines (GCP), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,

_____

Dr. Craig Pochini (Co-Chair, Clinical Trials)
Health Research Ethics Board

Appendix C

FACT-Cog PCI Subscale:

FACT-Cognitive Function (Version 3)

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.

	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
1. I have had trouble forming thoughts	0	1	2	3	4
2. My thinking has been slow	0	1	2	3	4
3. I have had trouble concentrating	0	1	2	3	4
4. I have had trouble finding my way to a familiar place	0	1	2	3	4
5. I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
6. I have had trouble remembering new information, like phone numbers or simple instruction	0	1	2	3	4
7. I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
8. I have had trouble finding the right word(s) to express myself	0	1	2	3	4
9. I have used the wrong word when I referred to an object	0	1	2	3	4
10. I have had trouble saying what I mean in conversations with others	0	1	2	3	4
11. I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4

12. I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
13. I have forgotten names of people soon after being introduced	0	1	2	3	4
14. My reactions in everyday situations have been slow	0	1	2	3	4
15. I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
16. My thinking has been slower than usual	0	1	2	3	4
17. I have had to work harder than usual to express myself clearly	0	1	2	3	4
18. I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
19. I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
20. I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Appendix D

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