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Non-pharmacological treatment of insomnia in cancer patients: a randomized, controlled, non-inferiority trial investigating mindfulness-based and cognitive-behavioral approaches.

Garland, Sheila Nadine

UNIVERSITY OF CALGARY

Non-pharmacological treatment of insomnia in cancer patients: A randomized, controlled, non-inferiority trial investigating mindfulness-based and cognitive-behavioral approaches

by

Sheila Nadine Garland

A DISSERTATION

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Abstract

Patients who are diagnosed and treated for cancer are three times more likely than the general population to experience disturbed sleep and insomnia. The presence of persistent insomnia places patients at a higher risk for psychological and physical morbidity and reduced quality of life. This dissertation examined the use of non-pharmacological interventions to address insomnia in a heterogeneous sample of cancer patients. Cognitive-Behavioral Therapy for insomnia (CBT-I) is considered a well-established intervention, however a substantial proportion of people do not experience a treatment response or complete insomnia remittance. Mindfulness-Based Stress Reduction (MBSR) is generating a considerable amount of research interest in the area of insomnia due to its demonstrated effectiveness in reducing cognitive and physiological arousal, factors associated with disturbed sleep. We employed a non-inferiority design to determine whether MBSR performs to the same standard as CBT-I for insomnia, while providing additional benefits such as improved mood and lower appraisals of stress. MBSR was non-inferior to CBT-I for improving sleep when assessed three months after treatment completion, but not immediately post-program. This result is attributed to MBSR producing slower but continual improvements over time while CBT-I generated rapid effects that were largely maintained. While both groups demonstrated the ability to reduce stress symptoms and mood disturbance, those receiving CBT-I uniquely improved sleep quality and dysfunctional sleep beliefs. Secondary analyses were performed on the full sample (N=111) to examine associations between dispositional mindfulness, sleep and psychological outcomes. Mindfulness facets of acting with awareness, non-judging and non-reacting were associated with better sleep and psychological outcomes, but

mindfulness was not predictive of fewer sleep disturbances above and beyond the influence of symptoms of stress and mood disturbance. We then focused specifically on the MBSR group (n=32) to examine whether improvements in mindfulness were associated with sleep and psychological outcomes. This sub-study suggests that one of the mechanisms by which MBSR may improve sleep outcomes is through a reduction in dysfunctional sleep-related beliefs. This body of work emphasizes the need to conduct patient-centered research and expands potential treatment options for patients with insomnia.

Preface

In the course of this dissertation, the following four manuscripts have been prepared for publication, the first of which has been published. In all cases, the first author undertook the analysis, interpreted the results, and wrote the manuscripts. This was completed under the guidance of Drs. Carlson and Campbell. All authors provided critical reviews of the manuscripts and contributed intellectual content. The published article was reproduced in its entirety and included as a chapter in this document with permission from the publisher.

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Garland, S. N., Carlson, L. E., Antle, M., Samuels, C., & Campbell, T. A Comparison of Mindfulness-Based Stress Reduction to Cognitive Behavioral Therapy for the Treatment of Insomnia Comorbid with Cancer: a Randomized, Non Inferiority Trial.

Garland, S. N., Campbell, T. S., & Carlson, L.E. Associations between Dispositional Mindfulness, Insomnia, Sleep Quality and Dysfunctional Sleep Beliefs in Post-Treatment Cancer Patients.

Garland, S. N., Campbell, T. S., & Carlson, L.E. Impact of Mindfulness-Based Stress Reduction on Mindfulness and Dysfunctional Sleep Beliefs in Cancer Patients with Insomnia.

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As I reflect on the people who have played key roles in helping me get to where I am today, I must begin by recognizing the important contribution of Dr. Linda Carlson. I am not sure why she chose me to be her undergraduate honours student, but that decision changed the direction of my life. Linda has been an incredibly positive role model. She has demonstrated that success only comes when you have passion, determination, and resilience. Linda has always encouraged me to set high standards and work hard to achieve them. I have learned many lessons from Linda, some of them difficult, but all of them necessary. Linda has provided me with a very solid foundation from which to build my career and I am forever grateful.

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To my committee members, Dr. Mike Antle, Dr. Valerie Kirk and Dr. Cynthia Gross, I appreciate the time and expertise you have volunteered to review this dissertation. I hope you have as much fun reading about this project as I have had in conducting it.

I am fortunate to have had the opportunity to train in a department that is internationally recognized for its research and clinical excellence. I would like to acknowledge the many other staff and students whom I have had the pleasure to work

with over the years. Dr. Barry Bultz was pivotal in directing the focus of my education and making me feel at home within psychosocial oncology. He has also been extremely generous in his support for me and this research. Dr. Guy Pelletier has always been available for advice and assistance. I am conscious that I may not be where I am if it were not for his behind the scenes advocacy. I am grateful to the MBSR program facilitators, Shirley McMillan, Mike Mackenzie and Doug MacLean for giving up several evenings and Saturdays. Tobi Ceh, Linette Savage, Codie Rouleau and Jillian Johnson provided much needed research support. This research would not have been possible without the financial support provided by the Canadian Cancer Society Research Institute, the Alberta Cancer Board and a Francisco J. Varela award provided by the Mind and Life Research Institute.

Lastly, I would be remiss if I did not acknowledge the efforts of the patients who participated in this research. I intend to honour these contributions by widely disseminating the results of this study with the hope that other patients may be guided towards the most appropriate intervention to treat their insomnia. I also plan to expand on this research with future studies aimed at improving our understanding of the association between cancer and sleep while evaluating how best to prevent and treat these sleep disturbances.

Dedication

I have had incredible support from my friends and family throughout this process and I dedicate this dissertation to them. I am grateful to my friends who have patiently helped me through the challenges that come with growth and enthusiastically celebrated my successes. I have been able to count on support from my stepfather and despite his suggestion that I “get a real job”; I know that he is proud of me. Of the people who have stood with me through the smooth and rough patches of life, my mother is the person who deserves the most recognition. She has provided unquantifiable emotional support and encouraged me to challenge the limits of my comfort and capability. I believe in myself now because she believed in me first!

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
ACT	Acceptance and Commitment Therapy
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CBT-I	Cognitive Behavior Therapy for Insomnia
CSOSI	Calgary Symptoms of Stress Index
DBAS	Dysfunctional Beliefs and Attitudes about Sleep Scale
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders - Fourth Edition, Text Revision
EEG	Electroencephalogram
FFMQ	Five Facet Mindfulness Questionnaire
FIRST	Ford Insomnia Response to Stress Test
ICC	Intraclass Correlation Coefficient
ICD-10	International Classification of Diseases - Tenth Edition
ICSD-2	International Classification of Sleep Disorders, 2nd Edition
ISI	Insomnia Severity Index
ITT	Intent-to-Treat
LMM	Linear Mixed Models
MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
MID	Minimally Important Difference
MMPI	Minnesota Multiphasic Personality Inventory
MSLT	Multiple Sleep Latency Test
NREM	Non Rapid Eye Movement
OR	Odds Ratio
PP	Per-Protocol
PET	Positron Emission Tomography
POMS-SF	Profile of Mood States-Short Form
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
REM	Rapid Eye Movement
SE	Sleep Efficiency
SOL	Sleep Onset Latency
TAU	Treatment as Usual
TST	Total Sleep Time
WASO	Wake After Sleep Onset

Epigraph

"Sleep (is like) a dove which has landed near one's hand and stays there as long as one does not pay attention to it; if one attempts to grab it, it quickly flies away"

Victor E. Frankl (1965). The Doctor and the Soul. 2nd ed. New York: Knopf (page 253)

CHAPTER 1: THE PREVALENCE AND IMPACT OF INSOMNIA AND CANCER

1.0 What Defines Insomnia?

Our understanding of what constitutes insomnia is influenced by three diagnostic manuals: the International Classification of Diseases - Tenth Edition (ICD-10), the Diagnostic and Statistical Manual for Mental Disorders - Fourth Edition, Text Revision (DSM-IV-TR), and the International Classification of Sleep Disorders, 2nd Edition (ICSD-2). The ICD-10 provides the most general description of insomnia as "a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final wakening" [1]. The DSM-IV-TR expands on this definition and describes primary insomnia as "a complaint of difficulty initiating or maintaining sleep or of nonrestorative sleep, for at least 1 month… (that) causes clinically significant distress or impairment… (and) does not occur exclusively during the course of another sleep disorder… mental disorder…(or as a) direct physiological effect of a substance or general medical condition" (pg. 604) [2]. The DSM-IV-TR diagnostic description further suggests that, "primary insomnia is often associated with increased physiological, cognitive or emotional arousal in combination with negative conditioning for sleep" as well as "a marked preoccupation with, and distress due to, the inability to sleep" (pg. 599).

The primary difficulty with the diagnostic criteria set out by the ICD-10 and DSM-IV-TR is the restriction that insomnia cannot be diagnosed when another psychiatric or medical disorder co-exists with and contributes to the sleep disorder. The ICSD defines psychophysiological insomnia as "a disorder of somatized tension and learned sleep-preventing associations that results in a complaint of insomnia and associated decreased functioning during wakefulness" (pg. 28) [3]. However, unlike the

ICD-10 and DSM-IV-TR, the ICSD recognizes that insomnia often occurs co-morbid to another psychological and/or medical condition and that both require recognition and treatment for optimal outcomes. A recent comparison of the reliability and validity of the DSM-IV-TR and ICSD-2 insomnia diagnoses recommended an amalgamation of the two systems and encouraged the editors of DSM-5 to specify a more inclusive insomnia disorder category to allow for an insomnia diagnosis regardless of any coincident sleep-disruptive comorbidities [4]. *The allowance for insomnia to be diagnosed at the same time as a psychological or medical condition represents an important recognition that insomnia often does not diminish with the resolution of the other disorder.*

1.1 Overall Prevalence of Insomnia

Insomnia prevalence rates vary in the general population depending on the measurement tool used. Ohayon compiled data from 45 epidemiologic studies from 16 different countries and categorized the findings according to the DSM-IV-TR diagnostic criteria for insomnia [5]. Based on the presence of insomnia symptoms, global prevalence rates ranged from 30-48%. When a frequency restriction of at least 3 nights per week was implemented, the global prevalence rate was reduced to 16-21%. When the presence of daytime consequences was added, global prevalence rate dropped again to 9-15%. When all the diagnostic criteria were present, the global prevalence rate for insomnia was 6%, not including insomnia comorbid with medical and psychological conditions. In a large epidemiologic survey of 10,094 adult members of a US health plan, 23.6% of individuals met the DSM-IV-TR, ICSD-2 or ICD-10 diagnostic criteria for insomnia [6]. In this same sample, the presence of insomnia significantly predicted decrements in perceived health,

even after controlling for comorbid physical and mental conditions [7] and was associated with 13.6% of all workplace absenteeism days [8].

On a more local scale, Morin and colleagues conducted a national telephone survey of 2,000 Canadians using a geographically stratified random digit dialing method to determine insomnia prevalence [9]. Participants were interviewed regarding their sleep difficulties during the past month, including type, severity, duration and impact. They were further asked whether they had consulted a health professional about their sleep in the past year and what treatments were provided. Of the total sample, 40.2% reported they experienced difficulty falling asleep, staying asleep or waking too early at least 3 nights per week for the past month. When the combined DSM-IV-TR and ICD-10 diagnostic criteria for insomnia was applied 13.4% had insomnia. Ten percent of the sample had used prescription medication for sleep in the past month. The demographic characteristics that predicted higher levels of insomnia were: female gender (Odds Ratio (OR)=1.50), being between ages 50-59 (OR=1.66), and being divorced/separated (OR=1.81) or widowed (OR=1.99). Among individuals meeting the diagnostic criteria for insomnia, only 23.9% reported consulting with a health professional in the last year. In addition, people with insomnia were 5.5 times more likely to report their physical health as poor and 6.5 times more likely to report their mental health as poor. These findings indicate that *insomnia is a global problem and also represents a significant concern for a substantial proportion of Canadians*.

1.2 Overall Prevalence and Cost of Cancer in Canada

Cancer is one of the leading causes of global morbidity and mortality, second only to heart disease [10]. In Canada, approximately 177,800 people were diagnosed with cancer

in 2011. It is estimated that 40% of women and 45% of men in Canada will be diagnosed with cancer during their lifetime [11]. The cost of cancer on both the economy and those affected by cancer are considerable. The estimated total economic cost of cancer in Canada, including medical, non-medical and productivity loss for the year 2009, was $6,580,751,609 [12].

A person is considered a "cancer survivor" from the time of diagnosis through the balance of his or her life, highlighting that the physical and emotional effects of cancer do not disappear when the cancer is treated or potentially cured [13]. As a result of improved detection and treatment methods, the relative survival rate for people diagnosed with cancer increased by 8% between 1994 and 2006. This translates into a 63% survival rate at 5-years post-diagnosis. [11]. *Improved survival rates mean that more Canadians will require ongoing treatment for the persistent physical and psychological side effects of a cancer diagnosis.*

1.3 Prevalence of Cancer-Related Distress

The psychological, social and spiritual costs of cancer impact not only the patient but also family members and support persons. *The distress associated with cancer can be understood to exist on a continuum ranging from "common normal feelings of vulnerability, sadness, and fears, to problems that can become disabling such as depression, anxiety, panic, social isolation and spiritual crisis"* [14]. Some studies have reported that close to 40% of individuals with cancer report high levels of cancer-related distress, however this research has been cross-sectional and does not provide information about the relative stability of distress levels [15,16]. Carlson, Waller, Groff, Giese-Davis and Bultz examined the trajectory of distress, depression, anxiety, pain and fatigue over the

course of 12 months in a sample of 877 newly diagnosed heterogeneous cancer patients [17]. Single item visual analogue scales (i.e. thermometers) were used to measure distress, fatigue and pain while anxiety and depression were assessed using part C of the Psychological Screen for Cancer at baseline, 3, 6 and 12 months. Although levels of distress, depression and anxiety decreased over time, 29% of people were still reporting clinically elevated levels of distress 12 months post-diagnosis. Pain and fatigue are important components of distress and these levels did not decline over time, with 20% and 40% of patients remaining above the recommended clinical cutoff, respectively. *High levels of distress can lead to poorer treatment outcomes and decreased overall quality of life* [16].

1.4 Prevalence of Sleep Disturbances and Insomnia in Cancer

Sleep disturbances have been identified as an important but often overlooked consequence of cancer [18]. Prevalence rates for sleep disturbances in individuals with cancer range from 30-50%, depending on the definition and measurement tool used [19-21]. The prevalence of insomnia and the persistent impact of cancer on sleep were examined in a longitudinal study of a heterogeneous sample of 962 French-Canadians [22]. Patients were contacted by phone and a semi-structured interview was used to categorize people into three groups: 1) good sleepers, no complaint of sleeping difficulties; 2) patients with insomnia symptoms, some complaint of difficulty (but not meeting criteria for an insomnia diagnosis); and 3) patients with insomnia syndrome, experiencing difficulty with sleep onset or maintenance exceeding 30 minutes, more than 3 nights per week for longer than one month. At the pre-operative stage 59% reported disturbed sleep, while 31% experienced difficulties that were significant enough to warrant an insomnia

diagnosis. When assessed 18 months post-diagnosis, 21% were still reporting problems with sleep, 15% of which had been experiencing chronic insomnia. Prevalence rates were highest among women with breast and gynecological cancer and lowest in men with prostate cancer. This research supports the notion *that sleep disturbances and insomnia are prevalent and persistent concerns for a significant portion of cancer survivors*.

The development and impact of insomnia from the perspective of the cancer patient has also been explored [23]. Twenty-one individuals with breast, prostate or colon cancer, an insomnia disorder, and a mean time since cancer diagnosis of 34 months participated in focus groups. The discussions were content-analyzed for significant themes and sub-themes. The majority of participants (n=19) reported that the onset on their sleep difficulty followed their cancer diagnosis, whereas the remaining two individuals reported that cancer had exacerbated a pre-existing sleep problem. *The 'experience of being a cancer patient' was described as a major cause of sleep difficulty* and was comprised of the following subthemes: 'suppressed stresses', 'disruption to daily routine', and 'the impact of chemotherapy, radiotherapy or hormone therapy'. One person described 'suppressed stresses' as, "It was the stress of the diagnosis catching up with me that caused my sleep problem … and I didn't recognize it at the time". *The majority of participants (n=16) reported that the effects of poor sleep were more overwhelming than the effects of cancer treatment.* The effects of poor sleep were divided into six major categories: mood (changes in temperament, 33%), physical symptoms (feeling tired/fatigued, 58%), relationships (rescheduling social activities/putting things off, 50%), sleep quality (frequent night time awakenings, 67%), behavioral modifications (daytime naps, 42%) and cognitive consequences (catastrophising, 42%).

Of note, the participants reported their sleep difficulties were most problematic in the transition from active treatment into follow up cancer care. They believed that persistent sleep difficulties were a major barrier when trying to return to normal functioning and contributed to the continuation of an 'illness role'. The participants also voiced concern that they were not provided with enough information about the potential impact of cancer on sleep and how to prevent these or where/when to seek treatment. These qualitative results suggest that *sleep disturbances can be related to the psychological and treatment-related effects of cancer, represent a significant barrier to returning to normal functioning, and are often not discussed with patients.*

1.4.1 Disturbed Sleep, Insomnia and Other Cancer Consequences

Sleep disturbances frequently co-occur with other commonly reported cancer side effects, such as pain, fatigue, psychological distress and depression [24-26]. The relationships between pain, fatigue, depressed mood and difficulty sleeping were explored with structural equation modeling in a large cross-sectional sample of 11,445 people undergoing treatment for cancer [27]. Patients were asked to rank the severity of common cancer symptoms on a Likert scale from 0 (Not a problem) to 10 (As bad as possible) using the Patient Care Monitor, an oncology specific software package [28]. The most common cancer diagnoses were breast and genitourinary, but individuals with gastrointestinal, hematological and lung cancer were also well represented. The overall prevalence of occasional trouble sleeping was 55%, with moderate to severe difficulties being endorsed by 26% of the sample. Depressed mood exerted a direct and strong influence on trouble sleeping, pain and fatigue ratings. Independent of mood, trouble sleeping also had a direct influence on pain and fatigue levels. Based on these results, *the*

use of targeted interventions to treat depressed mood and difficulty sleeping would be expected to also positively impact pain and fatigue levels.

A more recent study also investigated the relationships between sleep difficulty, self-reported pain and emotional distress in a sample of 2862 cancer outpatients participating in a symptom monitoring service [29]. Sleep difficulty was defined as difficulty falling asleep, staying asleep, or sleeping too much, more than half the nights during the previous two weeks. Of the entire sample, 30.2% reported problems with sleep with higher prevalence being related to younger age, cancer type (breast/gynecological), and active disease or treatment. Individuals reporting significant pain were 2.7 times more likely to experience sleep difficulty than those without pain, whereas people with higher levels of emotional distress were 4.5 times more likely to reports problems with sleep that those with low distress levels. The authors conclude that pain, distress and sleep difficulty frequently co-exist and that it may be important to treat more than one symptom at a time [29].

Additionally, Koopman and colleagues examined the relationships between sleep disturbance, depression, and salivary cortisol in 97 women with metastatic breast cancer [30]. Women who reported greater pain were more likely to have difficulty falling asleep, while women with higher depression scores reported more difficulty falling asleep, premature waking in the morning, frequent waking throughout the night and increased medication usage. Cortisol samples indicated that elevated evening cortisol was significantly related to sleep loss. Although it has been established that sleep disturbances and insomnia frequently co-exist with pain, fatigue and psychological distress, a cause-and-effect relationship has not yet been established. *Considering the high degree of*

overlap between sleep disturbances, emotional distress, pain and fatigue, scarce healthcare resources require that comprehensive evidence-based interventions effectively address these inter-related concerns.

1.4.2 Chemotherapy as a Contributor to Disturbed Sleep and Insomnia

Research is beginning to explore the role of chemotherapy as a contributor to the sleep disturbances among individuals with cancer [31-33].The most commonly reported sleep problem by patients undergoing chemotherapy is the inability to maintain sleep (63.3%), with disruptions being attributed to the anxiety and worry related to the cancer diagnosis/treatments and the effects of cancer treatments themselves (i.e. post-surgical pain/discomfort, overall fatigue, nausea, feeling too hot/cold, increased bathroom use and steroid-induced agitation) [33]. In a prospective study of 823 patients undergoing chemotherapy, 39.8% reported moderate or severe insomnia symptoms after their first chemotherapy treatment [34]. These sleep disturbances persisted throughout subsequent chemotherapy cycles in 60% of patients. The highest prevalence of insomnia complaints were reported in patients with breast cancer, followed by gynecologic, hematologic, and lung cancers. Younger age was a significant predictor of insomnia symptoms: each 10-year increase in age was associated with a 29% decrease in the probability of reporting insomnia. Patients reporting difficulty with sleep were also more likely to report higher levels of depression and fatigue [34].

The strength of the evidence for the impact of chemotherapy on sleep-wake patterns was explored in a systematic review of 21 articles comprising 833 women with early stage breast cancer conducted by Kotronoulas, Wengstrom and Kearney [35]. The overall incidence rate of sleep disturbances ranged from 26-50% when determined using

the Pittsburgh Sleep Quality Index [36] adjusted cutoff score of 8, which is recommended for individuals with cancer. Sleep disturbances persisted up to one-year post chemotherapy with increased nocturnal awakenings and time spent awake, frequent daytime napping and sleepiness, representing an overall disruption in circadian rhythms [35].

Research including people with cancer diagnoses other than breast cancer strengthens the evidence for the impact of chemotherapy and other cancer treatments on sleep disruption. One hundred eighty-five patients with breast, prostate, lung or brain cancer were assessed post-chemotherapy, surgery and/or hormone therapy but prior to the initiation of radiation, with self report measures of sleep and actigraphy (i.e. the continuous wrist-based measurement of movement) [37]. Based on self-report questionnaires, 40-50% of individuals experienced sleep disturbances. The prevalence of significant sleep disturbances was reduced to 30% when using an actigraphy-measured cutoff of less than 80% sleep efficiency (i.e. the percentage of time spent in bed compared to the time actually spent sleeping). The actigraphy sleep data was then compared to the normal reference range. Patients experienced significantly more time awake at night, less total sleep time and reduced sleep efficiency while also sleeping an average of 50 minutes during the day, as compared to healthy adult values. *It appears that treatment for cancer, particularly chemotherapy, may place a range of patients at a higher risk for developing clinically significant sleep disturbances and partially account for the higher than average prevalence rates demonstrated in this population.*

1.4.3 Disturbed Sleep, Insomnia and Quality of Life

Not only are cancer-related sleep disturbances widespread - representing a significant concern for people irrespective of their stage in the cancer trajectory - they can also negatively impact overall quality of life and cancer therapy outcomes. The relationship between insomnia and patient satisfaction with quality of life was explored in a cross-sectional analysis of 954 individuals with a variety of cancer diagnoses, most commonly breast (26%), colorectal (19%) and lung (16%) [38]. Regardless of age and treatment status, every 10-unit increase in self-reported insomnia symptoms was related to a 0.42 unit decline in overall quality of life, with particularly strong decreases in subjective health/physical (-0.67) and psychological/spiritual (-0.42) domains. *This supports the relationship between disturbed sleep, perceived physical functioning, and psychological well-being, which highlights sleep quality as an important contributor to overall quality of life.*

Although not conclusive, there is evidence that impaired sleep can also have a negative impact on objective health outcomes. The relationship between rest/activity rhythms, treatment response, and survival in 200 patients with metastatic colon cancer was investigated by Mormont and colleagues [39]. Patients with dysregulated sleep/wake patterns were 5 times more likely to die within 5 years than patients with a more distinguishable circadian rhythm (i.e. easily differentiated activity levels during wake and sleep). The relationship between actigraphy assessed sleep/wake pattern and overall quality of life was also assessed in this sample [40]. The researchers were interested in exploring the impact of having a dampened circadian rhythm, characterized by flat profiles with less activity during the day and more activity during the night, on overall

depression and quality of life. Compared to people with these flat profiles, those patients with marked rest/activity patterns reported less depressive symptoms and better overall quality of life.

The importance of circadian rhythm was further explored in 104 women with metastatic breast cancer [41]. Although activity levels are commonly used to assess circadian rhythm, hormones with predictable daily patterns can also be used. Cortisol is a corticosteroid produced by the adrenal glands and is characterized by higher morning levels and lower evening levels, representing a predictable linear slope. Additional cortisol is then produced in response to physical and psychological stress. In this study, cortisol was measured at 0800, 1200, 1700 and 2100 hours for 3 consecutive days and the average slope of the diurnal cortisol pattern was evaluated. Flattened or dampened circadian cortisol rhythm, represented by lower morning and higher evening cortisol levels, was significantly associated with more frequent nocturnal awakenings, fewer circulating natural killer cells and shorter survival time. Overall, these studies suggest that *the maintenance of robust circadian rhythms and consistent sleep and wake patterns has the potential to reduce depressive symptomotology, improve overall perception of quality of life and potentially translate into better physical outcomes and survival*.

1.4.4 Pharmacological Treatment of Insomnia in Cancer Patients

The treatment for cancer patients with sleep difficulties is typically pharmacological. The most commonly prescribed drug classes for sleep are sedatives and hypnotics, but antidepressant and antipsychotic medications are increasingly being used off label to treat insomnia [42]. The distinction between sedative and hypnotic medication can be one of amount, with lower doses having a calming or sedating effect and higher

doses used to induce sleep. The most common sedative-hypnotic medications are benzodiazepines (e.g. lorazepam, diazepam, temazepam). Non-benzodiazepine hypnotic medication refers to the newer class of 'z-drugs', such as zopiclone [42]. Medical oncologists commonly prescribe sleep aids to assist patients through difficult periods in their treatment, (e.g. chemotherapy). In a sample of 124 women with breast cancer, 52.4% of patients discussed sleep with their provider during active chemotherapy and 32.3% were prescribed sleep aids [43]. However, that number may not accurately represent the proportion of cancer patients taking sleeping medication because it focused on oncologists' prescribing practices, while patients may be given sleep aids by other providers as well, such as their general physician. Moore, Berger and Dizona examined the sleep diaries of 219 women undergoing chemotherapy for breast cancer who were assigned to the control group of a behavioral intervention for sleep [44]. They assessed the use of sleep aids nightly through the 8 weeks of chemotherapy treatment and then again at 30, 60, 90 and 365 days post treatment. At some point during the study year, 46% of the sample had used prescription sleep aids. Close to half of the sample (46%) received a prescription for sleeping medication during chemotherapy and although sleep medication is only recommended for short-term use, 30% of the original sample was still using prescription sleep aids one year following treatment completion. Unfortunately, sedative medications can have dangerous side effects for cancer patients. *Long-term hypnotic use is associated with continued sleep difficulty and performance problems, memory disturbances, driving accidents and falls in the general population* [45]. There has also been suggestive research highlighting the association between hypnotic use and a greater than threefold increase in mortality, even after controlling for demographic variables and

comorbidities [46]. As such, *physicians and patients sometimes prefer non-pharmacological interventions to treat insomnia.*

Unfortunately, the research on insomnia and cancer has not been adequately incorporated into clinical care and patients are often left to cope with their sleep difficulty with minimal resources and support. A qualitative study with 26 individuals previously treated for cancer at a Canadian institution who met the DSM-IV-TR diagnostic criteria for insomnia examined their experience of sleep difficulty and generated ideas for improved care [47]. The perception that sleep was not sufficiently addressed by their medical team emerged as a primary theme. Specifically, patients reported that they were not asked about sleep, leading the patient to believe that it was not important to their doctor or other health professionals. Some patients admitted they were reluctant to bring up their sleep concerns with their provider because they viewed sleep as less important than their cancer, or because they assumed the only treatment option provided would be medication. Patients also reported that they lacked information about how cancer and treatments might impact sleep. They identified a preference to have this information early on in the treatment process in order to reduce fear and anxiety. Overall, the results indicated patients felt the assessment and treatment of insomnia needed to be a routine part of their cancer care. *Considering the prevalence, significance, and potential impact of insomnia, cancer patients require information about non-pharmacological and pharmacological treatments in order to make timely and informed treatment decisions.*

1.5 Summary

Sleep disturbances and insomnia are a prevalent concern for approximately one-third of individuals diagnosed with cancer, compared to one-fifth of the general population. The increased rate of sleep difficulty experienced by cancer patients has been attributed to the emotional consequences of being diagnosed with cancer and the effects of cancer treatment, particularly chemotherapy. Insomnia frequently coexists with pain, fatigue, depression, distress, and other common cancer side effects. Even after completion of cancer treatments, insomnia can persist and contribute to a reduced quality of life. An increased recognition of the relationship between cancer and insomnia by health professionals, and a reluctance of patients to rely on medication, has contributed to the growth, provision, and evaluation of non-pharmacological insomnia treatments.

CHAPTER 2: REVIEW OF INSOMNIA THEORY AND CONTRIBUTING FACTORS

2.0 Developmental Theories of Insomnia

In order to design non-pharmacological treatments for insomnia and evaluate their effectiveness in cancer survivors, an understanding of the conceptual models of insomnia is required. Each of the models described below contribute to explaining the multi-factorial, complex developmental pattern and persistent nature of insomnia.

2.0.1 The Behavioral Model of Insomnia (Spielman's 3P Model)

The behavioral model of insomnia, also known as Spielman's 3P model, aims to explain interactions between predisposing, precipitating and perpetuating factors in the development of insomnia. The 3P model was the first behavioral theory of insomnia to gain wide acceptance and subsequent theories of insomnia tend to draw heavily from its foundation [48]. Predisposing and precipitating factors explain insomnia development, whereas perpetuating factors explain the mechanisms by which insomnia can become chronic. Predisposing factors increase the underlying vulnerability to develop insomnia and comprise biological features such as age and sex, psychological traits such as the tendency to worry, and social factors such as work requirements to maintain a sleep schedule incompatible with their circadian preference (i.e. shift-work or night-shifts) [49]. A predisposition to sleep disturbance, however, requires a sufficiently stressful precipitant, or combination of precipitants, before it may be expressed. *Precipitating factors are thought to be acute occurrences of a stress-related trigger. Diseases that disrupt homeostasis, including cancer, can be broadly thought of as both physical and psychological stressors* [50].

Predisposing and precipitating factors are consistent with traditional diathesis-stress models of illness. Perpetuating factors refer to the behaviors that an individual

engages in while attempting to manage a sleep difficulty, which in turn might actually contribute to the persistence of insomnia. Examples include: going to bed earlier, "trying" harder to sleep, napping during the day, and engaging in activities other than sleep while in bed. When sleep related stimuli are repeatedly paired with insomnia related wakefulness, a classically conditioned cognitive and somatic arousal response is produced, which can then become a perpetuating factor. Thus, the 3P model provides one possible explanation for how acute insomnia can develop into chronic insomnia [48]. Recent adaptations and extensions of this model, considered below, have further increased the understanding of specific neurological, cognitive and physiological aspects of insomnia.

2.0.2 The Neurocognitive Model of Insomnia

The neurocognitive model extends the behavioral model of insomnia by suggesting that classical conditioning of sleep-related stimuli with insomnia-related wakefulness can also lead to exaggerated levels of cortical hyperarousal, in addition to cognitive and somatic hyperarousal, at sleep onset or during the sleep period [51]. Heightened cortical arousal, associated with stress-induced worry and/or rumination, may be assessed indirectly in the frontal and temporal brain regions and is indexed by increases in high frequency electroencephalogram (EEG) activity (> 20 Hz). Increased high frequency EEG activity might allow for greater sensory and information processing in the pre-bed hours and during sleep which is hypothesized to contribute to the disruption of sleep continuity and/or sleep state misperception [48].

2.0.3 The Cognitive Model of Insomnia

The cognitive model of insomnia suggests that *individuals with insomnia have negatively toned cognitive activity throughout the day and before bed, which leads to an overall increase in arousal and distress* [52]. This initiates an attentional bias and a monitoring of perceived internal (e.g. body sensations for signs of fatigue) and external (e.g. the alarm clock) sleep-related threats that might indicate to a person that they did (or will) not receive enough sleep. The detection of a sleep-related threat might validate the need to monitor and reinforce the need for worry and concern. This is problematic because selective attention and monitoring produces arousal, which creates additional physical sensations while also increasing the probability of detecting meaningless cues that would otherwise remain unnoticed. These processes work together to create an exaggerated perception of the deficit in sleep and its potentially negative impact on daytime performance. Adding to the daytime dysfunction is the tendency to hold erroneous beliefs about the impact of sleep disruption and the utility of worry while also engaging in counterproductive safety behaviors, such as cancelling appointments or taking a nap during the day. The cognitive model highlights the *importance of targeting specific cognitive maintaining factors (i.e. attentional bias) and eliminating the use of safety behaviors in the successful treatment of insomnia.*

2.0.4 The Psychobiological Inhibition Model

The psychobiological inhibition model suggests that difficulty with sleep initiation and maintenance is caused by the failure to inhibit wakefulness [53], as opposed to the conditioned hyperarousal suggested by Perlis [51]. Failure to inhibit wakefulness is thought to occur from an activation of a cognitive *attention-intention-effort* pathway.

When a person experiences difficulty sleeping, their *attention* shifts towards the process of sleep, something that is typically an automatic and passive event. This shift in attention prevents the normal disengagement from wakefulness and changes sleep to a purposive or *intention*al activity. When an individual experiences difficulty sleeping, they demonstrate active *effort* to sleep, which further impairs the inhibition of wakefulness. This model suggests that *successful treatment of insomnia might include attention training or acceptance-based approaches in order to address counter productive efforts to fix or force sleep* [53].

2.1 Contributing Factors to the Development and Maintenance of Insomnia

2.1.1 Evidence for the Role of Psychosocial Stress

Early retrospective research by Healy and colleagues explored the role of stressful life events on the onset of insomnia in 31 adults with insomnia and 31 self-identified good sleepers without complaints of insomnia [54]. Insomnia was defined as a self reported sleep onset latency of over 30 minutes and nocturnal awakening with difficulty falling back asleep occurring at least 4 nights per week. The frequency and intensity of 42 normal life experiences, both positive (i.e. marriage or outstanding personal achievement) and negative (i.e. loss of a job, illness, or death of family member) that are typically associated with self-reports of stress were assessed. Individuals with insomnia endorsed more stressful life experiences in the year prior to the onset of insomnia relative to good sleepers. Specifically, individuals with insomnia reported more personal losses, episodes of illness, undesirable life events and/or losses in the social domain and subjectively attributed their insomnia to one of these major events. Although this research is notable for being the first study to examine the association between stressful life events and

insomnia, the reliance on retrospective self-report measures limits the ability to draw firm conclusions.

Cartwright and Wood expanded on Healy's work and explored the prospective differential impact of a stressful event, either considered resolved or chronic, using objective indices of sleep quality [55]. Sixty-one individuals undergoing marital separation/divorce were assessed with 3 consecutive nights of polysomnography (PSG) at the time of recruitment and again 1 year later. After 1 year, individuals whose divorces were not yet finalized (n=19) tended to experience less delta sleep (deeper sleep) and more rapid eye movement (REM) sleep, suggesting a lighter overall sleep experience. Those individuals who completed their divorce tended to recover their delta sleep, demonstrating that the *adjustment to, or removal of, a stressor may have positive effects on sleep quality.*

Friedman and colleagues further questioned the role of stress in contributing to insomnia in a retrospective study of 84 older adults, who self-identified as good or poor sleepers [56]. Participants rated the frequency of life stressors such as increased responsibility or deterioration of health, as well as the perceived level of the intensity of the stressor. Sleep was assessed with validated self-report instruments, sleep diaries, and wrist actigraphy. In contrast to Healy, there were no self-reported differences in the number of prior life stressors experienced by poor and good sleepers, rather it was the tendency to appraise life events as stressful that was associated with problems with sleep onset in the poor sleepers group. The investigators hypothesized that people experiencing insomnia as a result of life-stress may have a tendency to appraise potentially stressful

events as more stressful, which could predispose or make them particularly vulnerable to this disturbance.

Following up on the hypothesis that poor sleepers may have a tendency to negatively appraise life events, Morin, Rodrigue and Ivers examined the relationship between perceived stress and coping skills in a community sample of 40 individuals with insomnia and 27 good sleepers [57]. Participants provided three weeks of daily self-reports of their sleep, stress and pre-sleep arousal levels. Retrospective assessments of the amount and impact of stressful life events experienced in the past year were provided in addition to their appraisal of their ability to cope with stress. The people in the poor sleepers group reported more frequent and intense negative life events, perceived themselves to have less control over events, used more dysfunctional emotion-focused coping strategies (i.e., avoidance), and had higher levels of pre-sleep cognitive and somatic arousal. While there were no differences between the groups in the number of reported daily minor stressors, the insomnia group tended to evaluate the same number of stressors as more stressful than good sleepers. The relationship between daily stress and disturbed sleep was fully mediated by cognitive and somatic arousal. In summary, the research does not support the notion that exposure to stressful life events produces insomnia. Rather*, the combined effect of a negative appraisal style and a reliance on emotional coping may lead to the perception that life events are more stressful, increasing the risk to develop insomnia.*

Research using objective assessments of sleep provides additional support for the relationship between negative appraisals of stress and disturbed sleep. Hall and colleagues investigated associations between psychological stress, depressive symptoms,

hyperarousal and electroencephalographic profile in 14 adults with primary insomnia [58]. Hyperarousal was defined as decreased delta power (deeper sleep) and elevated alpha and beta power (lighter sleep) throughout NREM sleep. Stress symptomotology was assessed by the combined tendency to experience stress-related intrusive thoughts and self-reports of current stress levels. Elevated levels of subjective stress and intrusive thought tendencies were associated with an attenuation of delta power and heightened alpha and beta power, supporting the hypothesis that negative appraisal of life-stress can negatively impact objective sleep quality [58].

The impact of psychological stress on subjective and PSG measured sleep was further explored in a cross sectional study of 30 individuals with chronic primary insomnia [59]. Participants completed questionnaires measuring the presence and impact of perceived stress one week prior to undergoing three consecutive nights of PSG. Despite a non-significant relationship between PSG measured sleep (e.g. sleep onset latency or sleep efficiency), higher levels of perceived stress were associated with more subtle measures of decreased EEG delta power and increased EEG beta power in NREM sleep representing more time spent in lighter stages of sleep. The tendency to avoid unpleasant emotions and/or events was also significantly associated with lower parasympathetic tone (indexed by high frequency heart rate variability), indicating more physiological arousal. Considering the association between hyperarousal, perceived stress and alterations in the time spent in light versus deeper sleep stages, the authors suggest that *stress reduction/management techniques may be a helpful supplement to traditional insomnia therapies and improve sleep via arousal pathways.*

In the context of sleep disorders, the word stress is often used to refer to a multitude of actual and perceived physical and psychological experiences that may exert differential effects on sleep. Kim and Dimsdale conducted a systematic review of 63 articles examining the effect of three categories of psychosocial stress on polysomnographic sleep: stressful life events, experimentally imposed stressors and traumatic stress [60]. Psychosocial stress caused by life events was associated with increased sleep onset latency, decreased sleep efficiency, increased awakenings and reductions in REM and slow wave sleep. In addition, stressful event-related intrusive thoughts and avoidance behaviors were associated with a longer sleep onset latency and time awake during the night. Short-term experimental stressors, such as watching an aversive film, an intellectually challenging test, or provocative questioning, were associated with increased sleep onset latency, more frequent nocturnal awakenings and decreased sleep efficiency on the night immediately after the induced stressor. The authors were not able to provide commentary on the 27 articles examining the overall effect of traumatic stress on sleep because of study variability and the potential confounding effect of the sleep disturbances associated with post-traumatic stress disorder [60].

The inability to achieve adequate sleep can itself represent a potential stressor. A review of the effects of sleep deprivation reveal a plethora of negative consequences including: increased blood pressure, decreased parasympathetic tone, increased evening cortisol and insulin levels, and increased proinflammatory cytokine levels [61]. Hall and colleagues published the first study to suggest that EEG assessed sleep disturbances are associated with immunity [62]. They investigated the association between sleep quality,

stress and immune outcomes in a cross sectional study of 29 individuals with bereavement-related depression. Participants completed questionnaires assessing intrusive thoughts, avoidance behaviors and sleep quality before undergoing three consecutive nights of PSG. Blood was drawn for immune analysis on isolated lymphocytes after day 2 of PSG. A greater time spent awake during the first NREM period was associated with lower circulating natural killer cells. An increased frequency of intrusive thoughts and avoidance was associated with longer sleep onset latencies and amount of time spent awake during the night. After adjusting for age, time spent awake accounted for 12% of the variance in natural killer cell counts, whereas intrusion/avoidance accounted for 7%. The authors suggested that disruption of the sleep onset process might represent one possible pathway whereby intrusive thoughts and emotional avoidance behaviors may impact immune function.

The inability to achieve restorative sleep may also exacerbate the stress response, defined as the physiological, affective and behavioral consequences of experiences that are deemed to be stressful. Hamilton, Catley and Karlson investigated the hypothesis that sleep quality and duration would moderate affective responses to stressful life events, including the experience of pain [63]. Individuals with fibromyalgia and rheumatoid arthritis (N=49) completed a self-report measure of sleep each morning over two consecutive days and then recorded momentary assessments of pain, affect and stress at 2.5-hour intervals. Participants who appraised their sleep quality as ‘good’, reported lower levels of stress and pain and experienced less negative affect compared to those individuals who reported poor sleep quality.

The relationship between stress and immunity has also been explored in healthy samples. Mezick and colleagues examined whether stressful life events and negative affect account for intra-individual variability of sleep duration, fragmentation and levels of nocturnal norepinephrine, a catecholamine involved in the physiological stress response, in 184 adults without a diagnosable sleep, psychological or medical disorder [64]. Actigraphy was used to assess sleep and wake activity for 9 consecutive days and 15hr samples of overnight urinary catecholamines were collected on days 2 and 4. Self-report of stressful life events included only those that the person considered to be 'still upsetting' and negative affect was defined by the presence of depressive and/or anxious symptoms. Even after adjusting for health factors and demographics, participants who reported more negative affect and life stress had greater variability in objectively measured sleep duration and fragmentation. Higher levels of norepinephrine were associated with fragmented sleep, representing a blunting of the nocturnal decline in sympathetic nervous system activity in those people with greater reported negative affect. This suggests that *individuals reporting higher levels of negative affect may be more susceptible to the influence of life stress and experience sleep disruption related to increased production of stress hormones.*

2.1.2 Evidence for the Role of Hyperarousal

One of the first and most widely cited examinations of the physiological differences between poor and good sleepers was published in 1967 by L.J. Monroe [65]. He defined good sleepers as persons who fell asleep in less than 15 minutes, did not experience nocturnal awakenings or report subjective sleep difficulty, whereas poor sleepers were defined as persons who took longer than 30 minutes to fall asleep, woke up

at least once during the night and reported subjective sleep difficulty. The total sample consisted of 16 participants (sex not specified) in each group with a mean age of 25 years. The groups were compared on EEG-recorded sleep variables, physiological measures of rectal temperature, vasoconstrictions, body movements, heart rate, pulse volume and skin resistance and psychological measures of personality pathology. Poor sleepers had significantly less stage 2, REM, and overall sleep and more nocturnal awakenings compared to good sleepers. Poor sleepers also demonstrated higher rectal temperature, more vasoconstrictions per minute, frequent body movements during the night, and increased skin resistance. Based on the Minnesota Multiphasic Personality Inventory, poor sleepers also reported more depressive and anxious symptomotology. It was further noted that the sleep poor sleepers did achieve could be characterized as more "awake-like" compared to good sleepers. Even at this early stage, the authors suggested that there might be a basic autonomic difference that distinguishes good sleepers from poor sleepers.

Perlis, Giles, Mendelson, Bootzin and Wyatt identify "four paradoxes of insomnia" that support the hyperarousal hypothesis [51]. First, when sleep is measured objectively with PSG, individuals with insomnia misidentify sleep as wakefulness 73% of the time compared to 45-50% in individuals without insomnia. Secondly, patients with insomnia have difficulty in accurately estimating the time they take to fall asleep and the amount of time spent sleeping. Specifically, sleep onset latencies are overestimated by 10-45 minutes and total sleep time is underestimated by 30-45 minutes than is evident by PSG. Thirdly, patients with insomnia report greater subjective improvement when treated with hypnotic medication than can be confirmed with PSG. The reported gains from

medication use are not congruent with the actual reduction in sleep latency (~15 minutes) and increase in total sleep time (~30 minutes). Finally, the sleep produced when individuals with insomnia are treated with hypnotics is noticeably abnormal (e.g. more delta and theta sleep wave activity), yet by subjective reports the sleep quantity and quality has improved. The noted discrepancies between the self-reported and PSG measured sleep have led researchers to further examine psychophysiological explanations.

A review of the role of hyperarousal literature suggests that *insomnia may result in part from a genetic vulnerability to wake-promoting brain activity, including a tendency to worry/ruminate, that is exacerbated by psychosocial/medical stressors and maintained by dysfunctional sleep related behavior and learned sleep preventing associations* [66]. In order to examine objective hyperarousal, Nofzinger and colleagues used Positron Emission Tomography (PET) to assess glucose metabolism during NREM sleep in 7 individuals with primary insomnia and 20 controls [67]. The authors hypothesized that individuals with insomnia would demonstrate higher whole brain metabolism over the 24-hour period than controls, suggesting that perceived sleep difficulties may be due to a failure of the wake-promoting brain structures to decline in metabolism from wake to sleep. There were no differences between the two groups on objective sleep as measured by PSG. Consistent with the hypothesis, on PET measured outcomes, individuals with insomnia showed an increased 24-hour global cerebral glucose metabolism and a smaller decline in relative metabolism from waking to NREM sleep. They also demonstrated reduced waking metabolism in the frontal cortex suggestive of inefficient sleep. Although additional studies are needed, this research provides initial support for the hypothesis that

people with insomnia may exhibit increased brain activity during sleep and while awake, suggestive of hyperarousal.

Another question yet to be definitively answered is whether cognitive and physiological arousal are predisposing risk factors for insomnia, or a consequence of the disorder. In order to address this question, Drake, Richardson, Roehrs, Scofield, and Roth set out to determine whether a vulnerability to stress-related sleep disturbance would predict increased laboratory induced sleep disturbance, elevated multiple sleep latency test (MSLT) scores, and increased heart rate [68]. Participants were assessed with two consecutive nights of PSG followed by MSLT and heart rate monitoring during the day. The MSLT is an assessment of the ability to fall asleep during the day and has been used as a measure of overall hyperarousal. The Ford Insomnia Response to Stress Test (FIRST) is a 9-item Likert-type questionnaire that measures vulnerability to sleep disruption as a reaction to stressful life events, such as having an argument, an important meeting the next day, or a bad day at work.

Based on responses to the FIRST questionnaire, 104 individuals drawn from the general population were median split into high (n=50) and low (n=54) categories. Those in the high category were more likely to be female and older. Increased vulnerability to insomnia, as indicated by relatively high FIRST scores, was associated with increased nighttime sleep latency (23 vs. 9 minutes) and decreased sleep efficiency (80% vs. 88%). Significant group differences in overall arousal, represented by a longer MSLT sleep onset, were also observed during the day but not in measured heart rate. The authors suggest that *hyperarousal, as measured by an elevated response to stress-induced sleep*

disruption, is an important contributor to transient insomnia vulnerability and may also predispose people to more chronic sleep disturbance.

The tendency to experience disturbed sleep as a response to various challenges has been coined 'sleep reactivity'. Research conducted with monozygotic and dizygotic twins is beginning to explore the heritability of sleep reactivity [69]. An online survey containing the FIRST and additional insomnia questions was completed by 1782 individual twins (including 744 twin pairs). The overall prevalence of insomnia based on the DSM-IV-TR criteria was 21%. Structural equation modeling was used to estimate heritability by examining the proportions of variance in insomnia and sleep reactivity that could be accounted for by genetic, shared and non-shared environmental influences. Heritability estimates for sleep reactivity was 43% in males and 29% in females. Heritability estimates for insomnia was 43% for males and 55% for females. The authors suggest that a genetic component to sleep reactivity may make certain individuals more vulnerable to transient insomnia following exposure to mental stress. Prospective studies that examine individuals at risk for insomnia are needed to explore how insomnia may develop in predisposed individuals.

Although arousability may have a genetic component, certain personality traits may also contribute to the risk of developing insomnia. Fernandez-Mendoza and colleagues examined whether ruminative personality traits, inadequate stress-coping strategies and cognitive-emotional hyperarousal place people at a higher risk for developing insomnia in a sample of 501 adults [70]. Individuals were excluded if they self-identified as a "poor sleeper", defined as a score greater than 5 on the PSQI, leaving a final sample of 234 participants. After adjusting for sex, depression and anxiety, the

following characteristics were associated with FIRST scores: arousability, neuroticism, pre-sleep cognitive arousal, emotion-oriented coping, perceived stress and rumination. These results support the notion that psychological characteristics contribute to the development of insomnia and are not consequences of it. *Based on the evidence for 24-hour hyperarousal in insomnia, some researchers have argued that effective treatments should also target daytime characteristics of hyperarousal* [71].

2.1.3 Evidence for the Role of Dysfunctional Sleep Beliefs

Morin and colleagues suggest that the negative beliefs individuals hold about their capacity for restful sleep can place people at risk for, and serve to maintain, insomnia symptoms [72]. Faulty beliefs, expectations, and attributions are thought to be similar to schemas in cognitive therapy (as opposed to situational automatic thoughts). Schemas are relatively stable cognitive frameworks that help a person make sense of the world, or in this case, to understand their sleep difficulty. New information that is consistent with this schema is easily remembered and incorporated, whereas information that is not in line with their belief may be ignored or forgotten (e.g. the person who believes that they are a bad sleeper may be more likely to recall the nights they perceived their sleep as poor versus those night that were good).

The main categories of dysfunctional beliefs and attitudes about sleep are: 1) unrealistic expectations about sleep needs and daytime functioning (e.g., I must get 8 hours of sleep to feel refreshed and function well the next day); 2) beliefs that sleep is unpredictable and uncontrollable (e.g., I can't ever predict whether I'll have a good or a poor night's sleep); 3) misconceptions and false attributions about the causes of insomnia (e.g., I believe insomnia is essentially a result of a chemical imbalance); 4) distorted

perceptions of the consequences of poor sleep (e.g., After a poor night's sleep, I know it that it will interfere with my daily activities on the next day); and 5) faulty beliefs about sleep promoting practices (e.g., When I don't get a proper amount of sleep on a given night, I need to catch up on the next day by napping or on the next night by sleeping longer) [73]. The prominence of these beliefs has been captured in the Dysfunctional Beliefs and Attitudes about Sleep (DBAS) scale [74].

It is not the existence of these sleep beliefs that is problematic per se, it is the strength and rigidity of the endorsement of these beliefs that is thought to be dysfunctional. The first study to examine the presence of deeply engrained underlying beliefs and attitudes toward sleep compared 74 older adults with primary or secondary insomnia to 71 good sleepers. Individuals with insomnia held significantly stronger beliefs related to the perceived consequences of insomnia to physical and mental health, the relationship of poor sleep to mood disturbance and lack of energy, and the unpredictability and controllability of sleep [72]. The authors suggested that *the presence of dysfunctional sleep beliefs may serve to exacerbate insomnia and that these should be addressed as part of a comprehensive treatment program.*

Yang, Chou, and Hsiao further investigated the association between dysfunctional beliefs and attitudes about sleep and trait vulnerability to insomnia (as measured by the FIRST) in 439 young adults [75]. Participants were characterized as good sleepers (n=132) or poor sleepers (n=307) based on a PSQI cutoff score of 5. Even in participants not currently reporting sleep difficulty, positive correlations between dysfunctional sleep beliefs and trait vulnerability to stress-related sleep disturbance were present. This suggests that *dysfunctional beliefs about sleep may not only perpetuate existing sleep*

difficulty but also contribute to the risk for developing insomnia in predisposed individuals.

Cross-sectional research has established that dysfunctional sleep beliefs are related to the development of insomnia, but it is also important to investigate the role of these beliefs in the maintenance of insomnia. Jansson and Linton examined the prospective relationship between somatic arousal, anxiety/depression, sleep related beliefs and sleep status in 1,986 adults over the course of one year [76]. Participants were divided into categories of insomnia (n=210, 11%), poor sleep (n=526, 27%), normal sleep (n=821, 42%) and good sleep (n=379, 20%) based on their self-report of their sleep quality during the past 3 months. Although all the predictors contributed significantly to the maintenance of insomnia, the most prominent mechanism was beliefs about the long-term negative consequences of insomnia. Ninety-one percent of the participants in the insomnia category were characterized by strong beliefs about the negative long-term consequences of insomnia, anxiety, depression and arousal. The authors recommend a variety of techniques to address these dysfunctional sleep-related beliefs including: cognitive restructuring, behavioral experiments, interoceptive exposure, directed attention and relaxation training [76].

Harvey suggests that there are 5 key cognitive processes that influence sleep, the first being *worry* [77]. Worrying about the negative impact of poor sleep (e.g. If I don't get to sleep, I won't be able to function tomorrow) serves to create a state of psychological arousal and anxiety. When an individual is anxious they tend to then *selectively attend to and monitor for internal or external threats* to their ability to fall asleep (e.g. I'll never get to sleep with that traffic noise). This in turn, increases the individual's worry and

anxiety. These distorted cognitions lead to a *misperception of their sleep disturbance*, whereby individuals often underestimate the actual amount of time spent sleeping and overestimate both the amount of time it takes them to fall asleep and the negative consequences of poor sleep on next day functioning. *Negative beliefs* about sleep serve to exacerbate this process. For example, the belief that one requires 8 hours of uninterrupted sleep may be unrealistic. Lastly, as an attempt to deal with sleep disturbance, individuals will engage in *safety or maintaining behaviors* (like consuming alcohol before bed to help them relax) that only prevent their fears from being disconfirmed and further exacerbates the sleep disturbance.

Several researchers have replicated the association between dysfunctional sleep beliefs and insomnia in other patient populations, established that these beliefs are modifiable with Cognitive-Behavior Therapy, and demonstrated that reductions in the extent to which an individual endorses such beliefs are related to improved sleep [78-82]. The durability of these changes has also been established with reductions in DBAS scores being related to improved sleep 12 and 24 months post-treatment [79].

2.1.4 Evidence for the Role of Pre-Sleep Cognitions

Not only do people with insomnia report more specific dysfunctional sleep beliefs, they also report increased overall pre-sleep cognitive activity. Wicklow and Espie examined the nature, content, and effect of pre-sleep cognitions in 21 individuals with insomnia using voice activated audio recording equipment over 3 consecutive nights [83]. Objective sleep was measured with wrist actigraphy. Participants were instructed to set the recorders at their bedside while they attempted to fall asleep. They were told to express themselves freely and say aloud any thoughts they had during this time. Content

analysis was used to categorize the qualitative data into the following categories: 1) rehearsing/planning, problem solving (43% of total thoughts, n=465); 2) sleep and its consequences (20%, n=217); 3) reflections on quality of thoughts, e.g. mind-racing (12%, n=129); 4) arousal status, e.g. thinking about feeling exhausted (9%, n=93); 5) external noise (6%, n=69); 6) autonomic experiences, e.g. heart rate, feeling cold (6%, n=67); 7) procedural factors, e.g. thinking about what to say aloud (3%, n=35); and 8) rising from bed, e.g. thinking about getting up (1%, n=15). The thought categories of 'sleep and its consequences' and 'rehearsing, planning and problem solving' explained 16% of the variance in objectively measured sleep onset latency. Patients often describe being 'unable to turn their mind off'. This research applied novel methodology to capture the pre-sleep mental arousal or 'cognitive load' and validates the subjective report of increased pre-sleep cognitions.

2.1.5 Evidence for the Role of Attentional Bias

Attentional biases are described as discrete changes in the direction of attention in the response to a "threat" [84]. This line of research suggests that people with insomnia may be more sensitive to threat-related stimuli and tend to unknowingly direct their attention toward threatening information. Attentional bias has been demonstrated to maintain a wide range of anxiety-related psychological conditions [85] and substance use disorders [86]. Espie and colleagues have conducted much of the research on the role of attention and insomnia and have employed novel experimental paradigms to evaluate the attention-intention-effort pathway of the Psychobiological Inhibition Model. The tendency to preferentially attend to objects related to the bedroom environment was investigated using a flicker paradigm, in which sequences of visual images are presented to the

participant [84]. The original stimulus was an image of seven sleep-related and seven neutral objects, equally arranged in the scene. The sleep-related changed stimulus had one sleep related cue removed (e.g. a bedroom slipper) and the neutral changed stimulus had one neutral cue removed (e.g. a glove). The original and changed visual images were presented in continuous succession until the participant detected the change. A mask was employed in between the original stimulus and the changed image to suppress transient visual memory.

One-hundred ninety-two volunteers were recruited and categorized into three groups self-identifying as good, moderate and poor sleepers [84]. These categories were distinguished by the following PSQI cutoffs: good sleepers (0-2), moderate sleepers (4-5) and poor sleepers (6 or greater). Both the poor and moderate sleepers detected the sleep-related change significantly faster than the good sleepers. Further, the poor sleepers detected the sleep-related change faster than the neutral change, which suggests the presence of a sleep-related attentional bias. The effect size for this difference was 0.60 (Cohen's d), suggesting a medium effect. In contrast, the good sleepers showed a large effect and an opposite bias to attend to the neutral images (-0.91). Follow up regression analyses showed that as sleep problems increased, the latency to detect the sleep related change significantly decreased. The presence of an attentional bias in insomnia has also been demonstrated towards the bedroom clock as a salient cue for wakefulness and sleep difficulty [87].

There is also evidence for the contribution of attentional bias in the development and maintenance of insomnia in individuals with cancer. Taylor, Espie and White used an experimental emotional Stroop task to investigate whether people with persistent

insomnia (n=15) had a greater attentional bias for sleep related cues than people with acute insomnia (n=18) [88]. Participants were mainly middle-aged women with breast cancer (52%). Individuals in the acute and persistent insomnia groups had been diagnosed approximately 2 months and 14 months prior. The emotional Stroop task presented 20 sleep-related words (i.e. tired, pillow), 20 cancer-related words (i.e. tumor, illness), and 40 neutral words (i.e. sandwich, window) to participants in random order in one of four colors. The participant was told to focus on the color of the word and not the meaning. They were instructed to press the color-coded button that corresponded to the color of the word while their response latency was recorded.

There was no significant between-group difference for individuals with persistent or chronic insomnia on the cancer interference index, indicating that both groups responded in a similar time frame to cancer-related words. The response latency to cancer-related words was significantly longer than to neutral words, suggesting that these words are still emotionally salient. However, individuals with cancer and persistent insomnia took significantly longer to respond to sleep-related words, confirming the hypothesis that *individuals with persistent insomnia may have an attentional bias towards sleep-related cues and that this may be one pathway to the development of chronic insomnia* [88].

2.2 Summary

Theories to explain the development and maintenance of insomnia have become more complex as research has identified specific behaviors, personality factors, cognitive styles, and neurological features that characterize people with insomnia. Stressful life events are often cited as the trigger for the onset of insomnia but research suggests that

individuals with disturbed sleep do not experience more stressful life events than those individuals with no sleep difficulty. What sets people apart who are at risk for insomnia is an appraisal that these stressors are of greater magnitude and a belief that they will be unable to cope. There is also initial evidence that people with insomnia may have a genetic predisposition to experience sleep disturbance in response to stress. People with insomnia also tend to demonstrate: 1) greater negative affect; 2) higher levels of daytime and nighttime physiological and cognitive arousal; 3) more dysfunctional sleep beliefs; 4) increased pre-sleep cognitive activity; and 5) an attentional bias towards sleep-related cues and perceived threats, all of which contribute to sleep difficulty. As a whole, this research suggests that the *biological, behavioral, cognitive aspects of insomnia are tightly interwoven and that successful treatment may need to, as much as possible, address these multiple contributing factors.*

CHAPTER 3: NON-PHARMACOLOGICAL TREATMENTS FOR INSOMNIA

3.0 Cognitive Behavioral Therapy for Insomnia (CBT-I)

3.0.1 CBT-I Program Description

The recognition that individuals with insomnia exhibit cognitive, physiological and cortical hyperarousal, demonstrate particular cognitive patterns and attentional biases, and strongly endorse problematic sleep-related beliefs has led to the development of a treatment designed to address these inter-related components. *Cognitive behavioral therapy for insomnia (CBT-I) combines principles from stimulus control therapy and sleep restriction therapy (+/- relaxation therapy) with formal cognitive restructuring in order to target overarousal, dysfunctional behaviors and maladaptive thoughts, beliefs, and attitudes.*

Dr. Richard Bootzin introduced stimulus control, the first behavioral intervention for insomnia, in 1972. *Stimulus control targets the conditioned arousal associated with insomnia that is caused by the failure to establish discriminative stimuli for sleep or the presence of sleep incompatible stimuli*, such as reading, and watching television in bed. Lying awake in bed while trying to sleep further strengthens the association between the bed and wakefulness, while falling asleep in places other than your bed, such as the couch, strengthens the association between sleep and non-sleeping environments. Stimulus control recommendations are as follows: 1) lie down to sleep only when sleepy, 2) avoid using the bed for activities other than sleep or intimacy, 3) get out of bed if unable to sleep within 15-20 minutes and return to bed only when sleepy, 4) repeat this pattern throughout the night as necessary, 5) get up at the same time every day and 5) avoid napping throughout the day [89].

When Dr. Arthur Spielman described sleep restriction in 1987, he challenged the typical goal of individuals with insomnia to spend more time in bed in order to sleep longer [90]. Sleep restriction does not in fact 'restrict' sleep, it limits the time a person spends in bed to the time that they are actually sleeping and is highly compatible with stimulus control. The first objective in sleep restriction is to determine a morning wake-up time that can be closely adhered to on a daily basis. The individual then determines their 'sleep window' based on their current sleep ability as recorded in their sleep diary. Their current sleep ability is then subtracted from their wake up time to determine their bedtime. An extra 30 minutes is typically added to the estimated sleep ability to allow for potential underestimation of sleep ability, unproblematic nocturnal awakenings and the normal time it takes to transition from wakefulness to sleep. For example, a patient with 5.5-hour sleep ability might decide they want to get up at 7:00 am every morning. This would bring their designated bedtime to 1:00 am. *Sleep restriction has the following important objectives: 1) it reduces the increased arousal caused by an individuals effort to force sleep by keeping them out of bed until they are really sleepy, and 2) it reduces the time to fall asleep and time spent awake during the night by consolidating sleep into longer and more restorative sections.* Once the individual is able to maintain a sleep efficiency of 85% or greater, the sleep window is expanded in 15-30 minute intervals until no further gains are produced.

Given the research on the influence of negative sleep beliefs, attentional biases and pre-sleep cognitions, cognitive therapy is increasingly being recognized as an important component of a comprehensive insomnia treatment [91]. According to the principles behind cognitive therapy, it is not the events that are inherently good or bad it

is our appraisals or interpretations of these events that make them so. *The primary goal of cognitive therapy in insomnia treatment is to identify problematic thoughts that may contribute to the development of, or reinforce, behaviors that produce pre-sleep arousal, examine these thoughts for accuracy and if necessary, modify them to be more rational and/or realistic.* The therapist initially helps the patient identify their dysfunctional sleep cognitions and the resulting emotional reactions using thought records. The patient is instructed to describe the situation that produced the thought, the content of the thought, the emotional reaction and its intensity in detail. These beliefs are then evaluated with cognitive restructuring techniques including, but not limited to, reappraisal, reattribution, decatastrophizing, attention shifting and hypothesis testing [73]. The patient is then able to apply their revised or alternate thought to the situation and note the impact on the intensity of the emotion. Although psychoeducation may serve the goal of delivering information, the use of these cognitive therapy techniques allows the person to realize that their beliefs may not be wholly accurate through a process of guided discovery. Once learned, the patient can continue to use cognitive therapy techniques to better manage their problematic sleep beliefs and cognitive responses.

The rationale for including relaxation therapy in a comprehensive non-pharmacological treatment program follows logically from research demonstrating that individuals with insomnia report higher levels of both daytime and nighttime cognitive and physiological arousal. *Relaxation therapy is thought to improve sleep by reducing sympathetic nervous system activity and facilitating physiological and mental de-arousal* [73]. Progressive muscle relaxation and imagery are among the most commonly included

therapies but there is little evidence to suggest differential effectiveness between those and a range of other techniques [92].

3.0.2 Evidence for the Overall Efficacy of CBT-I

CBT-I, with or without relaxation therapy, is recommended by the American Association of Sleep Medicine, and is considered well established by the American Psychiatric Association [93]. CBT-I has demonstrated efficacy for treating primary insomnia in several randomized controlled trials when compared to treatment as usual [94], waitlist control groups [95,96], pharmacotherapy +/- medication placebo [97-101], relaxation therapy and behavioral placebo [102,103], and sleep hygiene education [104]. Insomnia comorbid with psychiatric or medical disorders, such as anxiety, major depression, or chronic pain has also been effectively addressed with CBT-I [104,105]. Research has further established that CBT-I can be successfully delivered to groups of individuals [106,107], by telephone [108], over the Internet [109], or with self-help manuals [110,111].

Okajima, Komada and Inoue conducted the most recent meta-analysis of subjective and objective outcomes from 14 randomized, controlled trials of CBT-I published between 1990 and 2009 with a combined total of 959 participants [112]. For sleep outcomes measured by sleep diaries, large effect sizes were reported for total time spent awake (0.83) and sleep efficiency (0.82). Medium effect sizes were reported for early morning awakenings (0.66), sleep onset latency (0.57), wake after sleep onset (0.59), and total sleep time (0.58). When outcomes were measured by actigraphy or PSG, effects sizes were attenuated with a medium effect size for sleep onset latency (0.58), and small effect sizes for total sleep time (0.28) and sleep efficiency (0.43). It was further established that the changes produced by CBT-I are more durable than what is seen with

pharmacological treatment, and effect sizes continued to increase 12 months post-treatment for total sleep time (0.95), wake after sleep onset (0.91) and sleep efficiency (1.14). The superior durability of CBT-I over prescribed medication for insomnia was further demonstrated in a systematic review of randomized controlled trails comparing CBT-I to any prescription or non-prescription pharmaceutical agent for sleep [113].

The strongest evidence for the efficacy of CBT-I versus medication comes from a study evaluating the short and long-term effects of CBT-I, on its own or combined with medication, for persistent insomnia [101]. One hundred and sixty individuals who met the combined DSM-IV-TR and ICSD criteria for insomnia were randomly assigned to CBT-I alone or CBT-I + 10 mg of nightly zolpidem. After completing the 6-week group treatment program, those in the CBT-I alone treatment were randomized a second time to extended individual CBT-I for 6 months or no additional treatment, whereas those who were in the combined treatment group were randomized to extended individual CBT-I alone or extended CBT-I with zolpidem on an 'as needed' basis. Participants were assessed with sleep diaries, PSG and questionnaires assessing sleep. CBT-I, singly or combined with medication, was effective for treating insomnia in the short-term with over 60% demonstrating a treatment response after the 6 week trial and 42% were considered to be 'in remission'. Based on sleep diary data, patients in the CBT-I group reported greater mean reductions than the combined group in sleep onset latency (20 vs. 12 minutes) and wake after sleep onset (69 vs. 83 minutes). The combined group reported greater mean improvements than the CBT-I alone group in sleep efficiency (16% vs. 14%) and an additional 16 minutes of total sleep time. The best long-term outcomes however, were demonstrated by patients initially treated with the combined approach

followed by maintenance CBT-I with a discontinuation of medication. The skills learned in CBT-I are thought to empower the individual and allow for self-implementation should sleep difficulty recur as opposed to medication, which requires continued use for persistent benefit. As demonstrated, *there is strong empirical evidence that CBT-I is effective in treating primary insomnia, as well as insomnia comorbid with psychiatric and medical disorders and that CBT-I produces benefit that are more durable than what is typically seen with medication*.

3.0.3 The Efficacy of CBT-I in Individuals with Cancer

CBT-I has demonstrated efficacy for treating insomnia comorbid with medical disorders, including cancer [105]. Davidson, Waisberg, Brundage and MacLean published the first report of a 6-week non-pharmacological sleep therapy program using CBT-I components (stimulus control, relaxation, 'worry time' and sleep hygiene) to improve sleep quality of a heterogeneous group of 12 cancer patients with insomnia [114]. Post treatment effect sizes ranged from 0.58 for total sleep time to 2.0 for sleep efficiency, indicating a statistically and clinically significant improvement in patient functioning. Similarly, Quesnel, Savard, Simard, Ivers and Morin [115] investigated a multimodal CBT intervention in a sample of 10 women with non-metastatic breast cancer in a multiple-baseline design. Participants attended 8 manualized weekly group sessions targeting behaviors, cognitions, and providing education about sleep. Objective (PSG) and subjective (sleep diaries and questionnaires) measures were collected pre and post-treatment and then again 3 and 6 months after treatment completion. At the end of the study, half of the participants met the classification cutoff for "good sleepers", designated as 85% sleep efficiency. This percentage increased to 71% at the 6-month follow up.

Although both of these studies were limited by small sample sizes, they provided the foundation for larger trials of efficacy.

Savard, Simard, Ivers, and Morin investigated the efficacy of CBT-I in a randomized waitlist-controlled trial of 57 women with breast cancer. Patients were assessed before and after treatment and again at 3, 6, and 12-month follow-ups. Outcomes included sleep quantity/quality (assessed with sleep diaries and PSG), psychological functioning [116] and immune functioning [117]. Pre-to-post program sleep diaries revealed significant reductions in the sleep onset latency and time spent awake at night and improvements in sleep efficiency. These improvements were mirrored on the PSG assessment of sleep. Total sleep time steadily increased over the 12-month study period with participants averaging an additional 38 minutes of sleep by study completion. The proportion of individuals experiencing clinically significant change was 70% at the 12-month follow up period. Study participation was also related to immune enhancement as demonstrated by increases in cytokine secretion (IFN-γ and IL-1β), however the clinical relevance of these changes is unclear [117].

The largest trial to date of CBT-I for insomnia in cancer was conducted by Espie and colleagues [118]. This study assigned 100 heterogeneous post-treatment cancer patients to 5-week CBT-I intervention or treatment as usual (TAU) using a 2:1 randomization allocation. The TAU group was intended to represent normal clinical practice whereby physicians were free to offer appointments, prescribe and manage medications. Statistical and clinically significant improvements in subjective measures of sleep were demonstrated for sleep onset latency, wake after sleep onset and sleep efficiency in the CBT-I group with effect sizes of -0.86, -0.97 and 1.09 respectively. The actigraphy

results replicated these findings but effects sizes were slightly lower, ranging between -0.13 for sleep efficiency and 0.51 for wake after sleep onset. These results translated into a reduction of approximately 1 hour in sleep onset latency and time spent awake during the night compared to no change in the TAU group. These improvements in sleep outcomes were significantly related to increased quality of life and reduced daytime fatigue. CBT-I has also been shown effective when delivered individually to women with breast cancer [25], over the Internet to a heterogeneous sample of cancer survivors [119] and in a self-help format [111].

3.0.4 Limitations of CBT-I

Despite the evidence that CBT-I is a safe, effective and durable intervention, there is still a significant amount of people whose insomnia does not respond, or remit after treatment. In Morin et al.'s study comparing CBT-I alone or combined with medication (reviewed above), patients were considered to be treatment responders if they experienced a 7 point or greater reduction in their insomnia severity score, and a treatment remitter if their insomnia severity score was less than 8 points [101]. For the CBT-I only group, 40% did not experience a treatment response and 61% still experienced a varying degree of insomnia symptoms. Harvey and Tang have voiced similar concerns that although CBT-I produces clinically significant change, the effect sizes are lower than what is produced with CBT-I for other psychological disorders [120]. Based on the literature reviewed in Chapter 2, perhaps CBT-I does not adequately, or comprehensively, address the multitude of factors that contribute to the development and maintenance of insomnia. Also, there is an increasing awareness that not all effective treatments are effective for every person [121]. Cancer patients also typically experience a range of other symptoms

comorbidly with sleep disturbance, which CBT-I may not target, such as distress, depression, anxiety about the illness and difficulty coping. Clearly, *there is a need to improve and/or expand the available insomnia treatment options.*

3.1 Mindfulness-Based Stress Reduction (MBSR)

3.1.1 MBSR Program Description

Mindfulness Based Stress Reduction (MBSR) is a program originally created to help patients cope with stress, pain and illness. The intention of the MBSR program is to develop skills in *mindfulness, described as non-judgmental awareness of the present moment, in order to self-regulate emotions and reactions to stress* [122]. Through practicing mindfulness meditation, participants learn to observe their thoughts and feelings, with an attitude of acceptance, acknowledging each of them without evaluation or an attempt to change them, even if they are unpleasant or unwanted. Mindfulness can be contrasted with states of mind or behavior that occurs automatically with attention being focused elsewhere [123]. *Mindfulness is hypothesized to help prevent becoming caught up in negative thinking patterns, allowing the individual to behave in more flexible and adaptive ways and minimize automatic, habitual or impulsive reactions that may contribute to physiological stress reactivity or increase emotional distress* [124].

There are some differences in how MBSR is taught depending on the population being served. Program length ranges from 6 to 10 weeks, class time varies from 1 to 3 hours and a full or half day silent retreat may or may not be included. There is typically a daily home practice requirement but this can also range from 20-45 minutes [125]. An examination of class contact hours and reported benefit did not find evidence that shortened versions of MBSR are less effective than the standard 8 week treatment model

[125]. This is particularly important when offering MBSR to people with medical conditions or other limitations who may experience challenges with a more intensive treatment program. Regardless of the necessary modifications, there are 3 standard MBSR components: psychoeducation and didactic instruction about mindfulness, stress and the mind-body connection; formal and informal mindfulness meditation practice, including hatha yoga; and group discussion and support.

The didactic component of the MBSR program provides the rationale for how stress can be created and maintained with particular ways of thinking (i.e. rumination and worry) and how this might be reflected and experienced by the physical body. Participants are introduced to mindful attitudes (i.e. nonjudgment, patience, beginner's mind, trust, nonstriving, acceptance, and letting go) and these are framed as an alternate way of responding to daily experiences, as opposed to automatically reacting to them [126]. To highlight how people often go through life on autopilot, depriving themselves of the opportunity to notice the details of their experience, participants are led through a beginner's mind exercise designed to introduce them to the experience and the richness of present moment awareness. The beginner's mind exercise is typically performed with a raisin or pretzel, but any food object that can appeal to all the senses can be utilized. Participants are encouraged to view this object as if they have never encountered it before: What are the qualities of its appearance? What does it smell like? Does it make any sounds? What does it feel like in your hand or on your lips and tongue? What does it taste like? While completing the exercise, participants are also encouraged to notice their cognitive, emotional and physical responses in order to capture the full range of their present moment experience. Mindful attitudes are infused throughout the program and are

continually re-visited to help participants cope with current stressors, difficulties in their meditation practice, and develop a larger context for their concerns [126].

The MBSR program employs a variety of meditation techniques designed to enhance mindfulness including: body scan; sitting meditation; walking meditation, imagery, loving-kindness meditation and gentle hatha yoga as a form of mindful movement. Breath awareness and diaphragmatic breathing are introduced first in order to anchor attention and deepen the relaxation response. *Using the breath as the focus of the meditation in the initial stages has the advantage of being readily transportable and encouraging translation of meditation practice into daily activities.* The body scan is the first formal meditation technique that participants practice. This exercise begins with breath awareness but then attention is moved to the physical body, usually beginning with the toes and feet and moving up to the face and top of the head. Each component of the body is attended to, noting the particular sensations in that area (or lack thereof) without judgment, and then letting that area of the body dissolve from awareness.

The body scan is followed by the practice of sitting mediation. The participant begins with breath awareness and gradually opens their awareness to other thoughts and sensations, practicing nonjudging, acceptance and letting go of experience, then returning to focusing on the breath. Imagery meditation is often included to remind individuals of the qualities of the image (i.e. the calmness of a lake) which helps to encourage the development of those qualities in themselves [126]. Walking meditation and gentle hatha yoga allow the participant to practice awareness of the experience of movement and promote a deeper connection to their physical self. The yoga component is introduced as a method of coordinating breath and movement and not as a form of physical exercise,

although it can help develop muscle tone and flexibility. Modifications are readily available for people who have physical limitations. Walking meditation allows the individual to build a deeper connection to their experience of the external environment. These formal meditations are complimented by informal meditations that can be practiced as one goes through their day and mini breathing exercises that help promote a sense of calm and help manage difficult emotions as they occur. *Participants are provided with a variety of mindfulness options, for formal and informal practice, in order to meet the preferences and unique circumstances of each individual and promote the development of mindfulness as an approach to life and not just a situational technique* [126].

The support provided by the group members and facilitators is an important component of the MBSR program. Like learning any other skill, mindfulness meditation can have its challenges. Having a group of individuals who are all interested in achieving the same goal can provide a sense of community and understanding, assist participants to problem-solve through difficult periods, and ultimately persevere in their practice. There is also something to be gained from learning from other people who have shared similar experiences and broadening our experience to include different perspectives.

3.1.2 Evidence for the Overall Efficacy of MBSR

Mindfulness-Based Stress Reduction is increasingly being offered to help people reduce perceived stress, manage negative mood states, and cope with physical illness. Several randomized controlled trials have investigated the impact of MBSR in non-clinical samples, as well as for a variety of psychological and medical conditions. Controlled MBSR trials in non-clinical samples have been conducted with undergraduate

university students [127], medical students [128] and community adults [129,130]. The efficacy of MBSR has been tested in individuals with anxiety disorders [131,132] while an intervention that combines mindfulness meditation with cognitive therapy (MBCT) has been used to prevent depressive relapse [133]. The utility of MBSR to improve psychological and physical outcomes has been investigated in a wide array of medical disorders including cancer [134-137], fibromyalgia [138,139], multiple sclerosis [140], asthma [141], type 2 diabetes [142], obesity [143], HIV [144,145], chronic pain [146], and among organ transplant patients [147]. Randomized controlled trials of MBSR are only one part of an expansive research base, with additional support added by numerous quasi-experimental and qualitative studies of MBSR. As a testament to the interest in improving dissemination and availability of MBSR, studies are beginning to explore the feasibility of Internet delivered mindfulness interventions [148].

The strength of the evidence of MBSR has been the focus of a number of systematic reviews and meta-analyses [125,140,149-152]. Hofmann, Sawyer, Witt and Oh conducted the most recent, comprehensive meta-analysis of 39 studies evaluating the effect of mindfulness-based interventions on anxiety and depressive symptoms comprising 1,140 individuals with a diagnosed psychological or medical disorder [153]. The mindfulness-based interventions included were restricted to those adhering to (or closely resembling) MBSR or MBCT. The most frequent medical disorder studied was cancer (9), followed by chronic fatigue (3) and fibromyalgia (3). The most common psychological disorder represented was generalized anxiety disorder (5), followed by depression (4) and panic disorder (3). The overall effect size (Hedges' *g*) was 0.63 for reducing anxiety and 0.59 for reducing depression. This meta-analysis was unique in that

it considered baseline symptom severity in order to determine whether elevated symptoms of anxiety or depression were in fact present, to control for ceiling and floor effects. The effect sizes for anxiety and depression were 0.97 and 0.95 in studies that included patients with elevated levels at baseline. When only those studies employing a control group were examined, the effects sizes for symptoms of anxiety and depression dropped to 0.41 and 0.33, comparing treatment to control conditions. However, a controlled effect size calculation was only possible for 16 of the 39 trials, and these were primarily waitlist control groups. This highlights the need to conduct randomized trials with well-defined symptom profiles and active treatment controls. These results suggest that *mindfulness-based interventions can be beneficial for improving symptoms of anxiety and depression, including those that are associated with a medical disorder such as cancer*.

MacCoon and colleagues published preliminary validation research with a non-clinical sample of 63 healthy individuals randomly assigned to MBSR or an active control group in order to isolate and test the active ingredients of MBSR [154]. The Health Enhancement Program control group was designed to match the nonspecific treatment factors of MBSR and provide a credible treatment rationale while not including any mindfulness training. The Health Enhancement Program had the following components: music therapy, nutrition education, functional movement and physical activity, group discussion and exercises. Mindfulness was assessed with a thermal pain test to reduce the transparency and demand characteristics associated with self-report questionnaires. Depending on the assigned treatment group, the instructions for the thermal pain task were to “notice the music” or “notice your emotions, sensations and thoughts”. The

thermal pain test required the participant to judge their internal mental processes by rating the intensity and unpleasantness of the pain. Both groups reported significant improvement in psychological functioning but only the MBSR group demonstrated moderated pain ratings, leading the authors to conclude that mindfulness was an active ingredient and worked to selectively alter the appraisal of unpleasant stimuli. The results from this study suggest that trials comparing MBSR to other matched treatment programs are needed to move the field of MBSR research forward.

3.1.3 Evidence for the Efficacy of MBSR in Cancer Patients

MBSR is increasingly being recommended to reduce the psychological distress associated with a cancer diagnosis [155]. From 2000-2009, MBSR was one of the most frequently researched clinical interventions for cancer patients [156]. Ledesma and Kumano performed a meta-analysis of 4 controlled and 6 uncontrolled studies of MBSR in cancer patients published prior to 2007 [157]. The sample (N=583) was comprised primarily of women who completed treatment for early stage breast cancer. The results were separated into: 1) mental health - defined as anxiety, depression, stress and the psychological components of quality of life, and 2) physical health - defined as self-reported and objectively measured physical parameters and symptoms. The physical health category was quite diverse and included outcomes such as dietary fat intake, sleep quality, and hormonal measures (cortisol, prostate specific antigen). The overall effect size reported for mental health outcomes was moderate ($d = 0.48$). The effect size in controlled studies ($d = 0.37$) was slightly lower than for uncontrolled studies ($d = 0.50$). For physical health, the overall effect size was 0.18, with similar effects in controlled and uncontrolled

studies, but this may be attributable to the wide variety of outcomes included in the analysis.

A more recent meta-analysis including published literature up to and including January 2011 identified 19 studies (5 RCTs, 4, non-randomized trials, and 10 observational studies) [158]. The authors analyzed the results separately for overall quality of life (n=248), mood disturbance (n=411) and psychological distress (n=587). A small and nonsignificant effect was reported for overall quality of life (d = 0.29,) whereas significant moderate effects were demonstrated for mood disturbance (d = 0.42,) and psychological distress (d = 0.58). Much of the research included in both of these meta-analyses were criticized for having small sample sizes, lack of follow up data, failure to apply intention to treat analyses, and reliance on waitlist or usual care control groups.

Several additional randomized controlled trials of MBSR in cancer have been published since the release of the review described above [134,135,159,160]. The largest trial of MBSR to date included 214 women with early stage breast cancer randomly assigned to MBSR or a usual care control group [134]. The primary outcome was mood disturbance, as measured by the Profile of Mood States, but assessments of quality of life and endocrine symptoms (i.e. hot flashes) were also completed at weeks 0, 8 and 12. *The MBSR group reported statistically significant improvements in overall mood disturbance, breast and endocrine related quality of life and general wellbeing compared to the usual care group, which were maintained at the one-month follow up assessment. More notably the treated group also reported clinically relevant improvements in quality of life and well being*, as measured by minimally important change values on the Functional Assessment of Cancer Therapy-Breast and World Health Organization well being questionnaires.

Another large trial of MBSR included 172 women with early stage breast cancer randomly assigned to one of three treatment arms: MBSR, nutrition education (active control) or a usual care group [135]. Assessments were completed at baseline and again at 4, 12 and 24 months post participation. Relative to the active and/or usual care conditions, MBSR reduced psychological distress, enhanced acceptance of emotional states, improved active coping strategies and facilitated a sense of meaning and spirituality. The most enduring changes observed at the 24-month follow up assessment was demonstrated for spirituality and acceptance of emotional states.

In addition to patient reported outcomes, there is some evidence that MBSR participation may also impact immune and endocrine functioning in cancer patients [161-165]. The only randomized controlled trial to assess the ability of MBSR to impact biological outcomes was conducted by Lengacher and colleagues [156]. Eighty-two women who had received a lumpectomy and completed adjuvant radiation with or without chemotherapy for stage 0-III breast cancer were randomized to a 6-week MBSR or a usual care control group. Immune measures included Th1, Th2, T cell activation and percentage of lymphocyte subsets in peripheral blood samples. Although both groups experienced a recovery in B and natural killer cells after completion of active cancer treatment, patients in the MBSR group uniquely experienced a more rapid recovery of functional T cells. Although the clinical relevance of these changes has not been determined and the results have not yet been replicated, the authors suggest that these improvements may provide some immune protection benefit for the women in the MBSR group. Despite room to improve the design and reporting of MBSR research, *the bulk of*

controlled and uncontrolled research support the use of MBSR as an effective treatment for improving psychological and physical well-being in individuals with cancer.

3.2 The Theoretical Rationale for using MBSR for Insomnia

Lundh provides a rationale for using mindfulness and acceptance-based interventions in the treatment of insomnia [166]. He suggests that there are diurnal fluctuations in cognitive, as well as physiological, activity. During the day, people tend to engage in goal directed and controlled information processing, (e.g. problem solving and decision-making). At night, sleep is facilitated by cognitive deactivation and a reduction in the amount of controlled and strategic information processing, paralleling physiologic deactivation characterized by a decrease in muscle tone and a slowing of the cardiovascular and respiratory systems. In this way, *mindfulness may facilitate cognitive deactivation and physiological dearousal by allowing the individual to disengage from their daily concerns and strivings.* The mindfulness principles of letting go, acceptance and non-striving are theoretically congruent to the passive nature of sleep and encourages a shifting of one's relationship to sleep-related thoughts, as opposed to actively challenging and changing the thoughts, as would be practiced in CBT-I [167].

Repetitive thought patterns are defined as prolonged and recurrent thoughts about one's self, and one's concerns or experiences [168]. Repetitive thinking can be constructive (i.e. mental simulation, reflection, and problem solving) or unconstructive (i.e. worry, rumination and perseverative cognition). Unconstructive repetitive thought patterns are thought to be at the core of a variety of depressive and anxiety disorders [168]. Repetitive thinking has also been associated with increased cortisol secretion [169], reduced immune responses [170], and dysregulated cardiovascular function [171]. Of all the repetitive thought

patterns, *the tendency to ruminate has been identified as an important contributing factor to the development and maintenance of insomnia.* Carney, Edinger, Meyer, Lindman and Istre used a cross-sectional design to explore rumination in a sample of 243 university students [172]. The sample was categorized according to sleep quality and depressive symptomatology. Based on a PSQI cutoff score of greater than 5, 104 participants were identified as poor sleepers with the remaining 139 as good sleepers. Using a Beck Depression Inventory-II cutoff score of 14 or greater, 155 participants reported at least mild depressive symptoms, with the remaining 88 not endorsing significant depression. Compared to good sleepers, participants reporting poor sleep were more likely to respond to depressed mood by ruminating. The ruminative thoughts of poor sleepers were somatic in nature and focused on daytime symptoms of fatigue, poor concentration and low mood. State and trait rumination have also been linked to increased objective and subjectively measured sleep onset latency after an experimentally induced acute psychosocial stressor [173].

The relationship of rumination and worry to disturbed sleep was further explored in a sample of 210 people with insomnia recruited from sleep medicine clinics [174]. Those people with higher rumination scores had significantly lower sleep efficiency, worse sleep quality, and spent more time awake after sleep onset. Rumination independently contributed to insomnia and was not dependent on the presence of depression. The tendency to worry was not significantly related to sleep diary outcomes or depression. The authors suggest that *mindfulness-based programs that target rumination may provide an additional treatment option for insomnia* [174].

The association between mindfulness, depressive symptoms and rumination has been explored in sample of 77 women with cancer after MBSR program participation [175]. The women in the treatment group reported higher levels of mindfulness and lower levels of rumination after program participation, compared to a waitlist comparison group. The authors found that changes in rumination, but not mindfulness, mediated the impact of the MBSR program on depressive symptoms. This raises the possibility that increased mindfulness may not act directly to improve psychological outcomes, but rather through a series of other cognitive and affective changes. A recent unpublished dissertation by Labelle details the results of a longitudinal, waitlist-controlled study assessing the relationship between mindfulness and emotional regulation, characterized as rumination, worry and experiential avoidance, in a heterogeneous sample of 211 cancer patients after participating in an MBSR program [176]. As predicted, the participants in the MBSR group reported improvement on several measures of psychological functioning not seen in the control group. Mediation analyses demonstrated that increased mindfulness through MBSR participation lead to enhanced emotional regulation, which then led to improved mood and reduced stress symptomotology. Specifically, the tendency to refrain from judging inner experience was the strongest mediator of the effect of MBSR on rumination. Unfortunately, this study did not include an assessment of sleep, preventing the determination of the relationship between mindfulness, rumination and sleep outcomes.

Mindfulness meditation may allow participants to disengage from ruminative processing. Increasing the objectivity through which internal experience is viewed is intended to change one's relationship to the thoughts, as opposed to changing the

thoughts themselves and has been referred to as *reperceiving* [177]. Shapiro, Carlson, Astin and Freedman suggest that *reperceiving may account for the salutary effects of MBSR by increasing self-regulation, clarifying values, promoting cognitive, emotional and behavioral flexibility and allowing for the development of tolerance for, or a desensitization to, difficult emotional states through exposure* [177].

It is unclear whether the effects of MBSR are stronger for physiological or cognitive arousal reduction or whether these mechanisms are addressed simultaneously. Although relaxation is not the goal of mindfulness practice, Jain and colleagues [178] investigated whether the benefits of mindfulness meditation are a result of the relaxation response by comparing it directly to a relaxation training intervention. They compared 81 university students randomized to four, 90-minute mindfulness meditation sessions (n=27), somatic relaxation (n=24) or a waitlist control (n=30) on measures of overall distress, positive states of mind, rumination and distraction. The mindfulness meditation group used formal MBSR techniques, such as the body scan, hatha yoga, walking meditation and loving kindness meditations. The somatic relaxation group used progressive muscle relaxation, simple breathing techniques and guided imagery. The intervention participants received manuals and audio recordings for home practice and were matched in terms of contact time. Both groups reported significant improvements on overall psychological distress and positive states of mind as compared to the control group. Notably, only the mindfulness meditation group reported significant improvements in rumination and distraction and the improvements in psychological distress were partially mediated by reductions in rumination. These results suggest that *while the practice of mindfulness meditation may produce effects comparable to formal*

relaxation techniques, it has the additional ability to reduce cognitive arousal by reducing rumination and distraction.

3.2.1 Preliminary Evidence for the Role of Mindfulness in Insomnia

A systematic review of articles published on or before 2006 evaluating the effects of mindfulness meditation on sleep disturbance identified 7 eligible articles [179]. Six articles evaluated MBSR interventions, while one article reported on MBCT. Four of the studies did not include a control group and the remaining 3 employed a nonrandomized comparison group. Only one of the studies used a sample with clearly assessed and defined insomnia [180]. The majority of studies (5/7) were conducted in patients with chronic illness for which disturbed sleep is a frequent co-occurrence, such as cancer (3), fibromyalgia (1) and solid organ transplantation (1). The remaining 2 studies included patients with anxiety disorders and people recruited from an inner city medical clinic. Four uncontrolled studies reported statistically significant improvements in sleep whereas 3 controlled studies did not. Recommendations for further research included: 1) the application of adequately powered, randomized designs with active control groups; 2) the selection of individuals with clearly defined sleep difficulty or an insomnia disorder; and 3) the use of validated subjective and objective assessments of sleep. The authors concluded that the *value of MBSR for resolving sleep difficulties remains theoretically interesting but clinically and statistically unresolved.*

Since Winbush, Gross, and Kreitzer published the above review, research has continued to explore the sleep benefits of mindfulness [179]. Yook and colleagues investigated the utility of MBCT for treating insomnia symptoms in 19 patients with a generalized anxiety disorder or panic disorder without agoraphobia [181]. The authors noted

that insomnia shares some of the same characteristics as anxiety disorders such as safety behaviors and dysfunctional thought control strategies. Assessments of anxiety and depression were completed using clinicians rating scales. Participants completed sleep diaries and validated measures of sleep quality, worry, and rumination. Although participants were not required to have clinically significant insomnia for study inclusion, 47% scored over the recommended PSQI cutoff of 5 at baseline. After completing the 8-week program, only 1 person continued to report significant sleep disturbance. Using nonparametric statistics, significant improvements were demonstrated for overall sleep disturbance, anxiety, depression, worry and rumination. Of all the outcomes measures, worry was significantly associated with sleep disturbance, independent of rumination, anxiety and depression.

Considering that excessive pre-sleep arousal has been identified as a characteristic of individuals with insomnia, the effect of MBSR on levels of pre-sleep arousal was explored by Cincotta, Gehrman, Gooneratne and Baime [182]. Using a one-group, pre-post experimental design, a sample of 56 people were recruited from the community with a wide range of problems including anxiety, depression and chronic pain, although having a psychological or medical condition was not a formal inclusion criteria. Participants completed self-report assessments of cognitive and somatic pre-sleep arousal, insomnia severity, meditation practice, subjective (sleep diary) and objective (actigraphy) measures of sleep prior to, and after, program participation. Despite not being recruited based on the presence of insomnia, the mean insomnia severity score was in the range warranting further investigation. An intent-to-treat analysis was used to account for a 46% attrition rate but reasons for drop out were not provided. A significant reduction in overall arousal

levels was reported but it was only the reduction in cognitive pre-sleep arousal that accounted for 36% of the variance in insomnia severity. The authors call for future trials to measure arousal levels, specific cognitive distortions, and ruminative processed in populations with carefully defined insomnia diagnoses.

The only study to target individuals with insomnia and offer a standardized MBSR program was conducted by Gross and colleagues [183]. They randomly assigned 30 individuals (22 women and 8 men) with chronic insomnia in a 2:1 randomization allocation to MBSR or pharmacotherapy (3mg eszopliclone). In addition to subjective and actigraphic evaluation of sleep, quality of life, anxiety and depression were assessed at baseline, post program/2 months, and at 5 months. At 2 months, the pharmacotherapy group was significantly better than the MBSR group for improving sleep diary assessed total sleep time (d = 0.74 vs. d = 0.25), wake after sleep onset (d = - 1.24 vs. d = -0.46), and sleep efficiency (d = 1.11 vs. d = 0.61) but not sleep onset latency (d = 0.36 vs. d = 0.57). When sleep was assessed with actigraphy, the pharmacotherapy group demonstrated significant moderate effects for total sleep time (d = 0.63) and sleep efficiency (d = 0.52) whereas the MBSR group demonstrated a small effect on sleep onset latency (d = 0.31). Significant effects for both groups were reported on subjective measures of insomnia severity and sleep quality, but only the MBSR group reported improvements in sleep self-efficacy and dysfunctional sleep beliefs. No improvement was demonstrated for anxiety, depression and quality of life in either group. Additionally, one-fifth of the people in the MBSR condition were also reported to be using sleeping medication, which does not allow for a clean comparison of the two treatments. Despite several strengths including the use of a randomized design, an active control group,

objective measures of sleep, and a power calculation, the results need to be replicated with a larger sample size.

3.2.2 The Use of MBSR for Treating Insomnia in Individuals with Cancer

Preliminary evidence suggests that *MBSR may have a positively impact on sleep quality and quantity in individuals with cancer*. Carlson, Speca, Patel and Goodey published the results of study conducted with 59 breast and prostate cancer patients [165]. Patients were asked to indicate how many hours they slept at night (on average) and whether they perceived their sleep to be poor, adequate or good. The number of people reporting poor sleep prior to and after participating in an MBSR program was 40% and 20% respectively and the average number of hours slept per night increased from 7.1 to 7.6. Despite some encouraging findings, the results of this study are hampered by the absence of a formal assessment of sleep or a comparison group.

Another exploratory study with 63 women with stage II breast cancer examined the specific impact that MBSR may have on sleep disturbances secondary to cancer [184]. Participants in this study completed sleep diaries and psychological questionnaires prior to and after the 6-week intervention and then again at 1, 3 and 9 months post program. Patients in the MBSR program were compared to a "free choice" control group who were encouraged to engage in one of several stress management techniques when needed (e.g. talking to a friend, taking a warm bath, and exercise). The control group was also provided with a workbook including community resources, poetry and space for journaling. There were no significant differences over time or between the groups, however participants who engaged in more mindfulness practice and applications reported feeling more refreshed after sleep. The lack of findings may be explained by the

presence of relatively low levels of sleep disturbance at baseline. Participants were reporting a mean sleep efficiency of 88% (above the recommended cut off of 85%) and an average of close to 7 hours of sleep per night. As such, this study did not allow for an adequate assessment of the ability of MBSR to improve sleep.

Our research group investigated the impact of MBSR on sleep disturbance in a nonrandomized sample of 63 heterogeneous cancer patients using a validated sleep questionnaire [185]. Despite not being recruited on the basis of reporting significant sleep disturbance, 90% of patients scored 5 or greater on the PSQI at baseline. After program completion, a significant reduction in total sleep disturbance was reported, as well as an improved perception of their sleep quality. It was unclear whether the improvements demonstrated were related more to an activation of the physiological relaxation response, whether the practice of mindfulness reduced the amount of negative and ruminative thoughts, or if it was just a historical process of healing from cancer treatment. At that time, we suggested that *MBSR could improve sleep quality by the dual action of reducing stress induced arousal and maladaptive cognitions* but that adequately powered and controlled trials are necessary before conclusive statements of efficacy are possible [185].

3.3 Summary

Cognitive-behavior therapy is an effective treatment for insomnia co-morbid with psychological and medical conditions, including cancer. Yet a substantial proportion of insomnia patients do not respond or fully recover after CBI-I treatment. Research has yet to clarify who is best treated with CBT-I. Until then, preliminary studies suggest that MBSR may have a beneficial impact on sleep quantity and quality in people diagnosed with cancer. The mechanisms for the salutary effects of MBSR on sleep may include

reduced physiological arousal, decreased rumination and worry, less experiential avoidance, improved mood and stress appraisals. Adequately powered research is required to evaluate the impact of MBSR for insomnia and determine its comparative efficacy to CBT-I.

CHAPTER 4: I-CAN SLEEP: RATIONALE AND DESIGN OF A NON-INFERIORITY RCT OF MINDFULNESS-BASED STRESS REDUCTION AND COGNITIVE BEHAVIORAL THERAPY FOR THE TREATMENT OF INSOMNIA IN CANCER SURVIVORS

4.0 Abstract

Individuals with cancer are disproportionately affected by sleep disturbances, relative to the general population. These problems can be a consequence of the psychological, behavioral and physical effects of a cancer diagnosis and treatment. Sleep disturbances often persist for years and, when combined with already high levels of cancer-related distress, may place cancer survivors at a higher risk of future psychopathology, health problems and poorer quality of life. It is important to develop and evaluate treatments that comprehensively address the common symptom profiles experienced by cancer survivors

Methods: This study is a randomized controlled non-inferiority trial comparing Cognitive Behavior Therapy for Insomnia (CBT-I; a known efficacious treatment) to Mindfulness-Based Stress Reduction (MBSR; a treatment with demonstrated potential). This design can efficiently compare the two treatments directly and determine whether MBSR performs to the same standard as CBT-I for the treatment of insomnia with additional benefits of reducing cancer-related distress. Participants are randomly assigned to an 8-week CBT-I or MBSR group. Sleep indices are measured using subjective (sleep diaries) and objective (actigraphy) assessment tools. The primary outcome is insomnia severity. Secondary outcomes include sleep quality, symptoms of stress, mood disturbance, mindfulness, and dysfunctional beliefs and attitudes toward sleep. Assessments are completed at three time periods: pre-treatment, post-treatment and at 3 month follow up.

Conclusions: Considering the high prevalence of distress and sleep disturbances in the cancer population, should MBSR produce sleep effects comparable to CBT-I, it may be

more comprehensive - making it the treatment of choice for addressing cancer-related psychological sequelae.

4.1 Background

Thirty to 50% of cancer patients experience sleep disturbance, a prevalence rate twice that of the general population [18,34,186]. Sleep disturbance has been associated with a myriad of negative psychological symptoms including depression [187], reduced quality of life [38], increased health care utilization [188] and decreased work productivity and quality [189]. Close to 40% of individuals with cancer report high levels of distress [15,16] defined as "an unpleasant emotional experience of a psychological, social and/or spiritual nature… such as depression, anxiety, panic, social isolation and spiritual crisis" [14]. High levels of distress can lead to poorer treatment outcomes, increased health care costs and decreased overall quality of life [16]. Combined, the effects of sleep disturbance and psychological distress can place a significant burden on cancer recovery.

The identification and treatment of 'symptom clusters' has the potential to improve treatment efficacy. Symptom clusters are thought to have a more complicated and detrimental impact on patient functioning than single, unrelated symptoms because of the potential for collective and synergetic effects [190]. Sleep problems are known to frequently co-exist with symptoms of depression and anxiety [191,192] which can negatively impact treatment outcomes [187]. The delivery of interventions that target symptom clusters has the potential to be a more effective and efficient way of addressing common co-existing patient concerns and improving overall quality of life. This project investigates the potential of Mindfulness-Based Stress Reduction (MBSR) as an efficient and comprehensive treatment for insomnia in addition to psychological distress in individuals with cancer, compared to Cognitive Behavioural Therapy for Insomnia (CBT-I), a disorder specific intervention.

Cognitive Behavioral Therapy for Insomnia is the gold-standard non-pharmacological treatment for insomnia and has demonstrated efficacy for treating insomnia in cancer patients [105,116,118]. However, the CBT-I program does not directly target the high levels of psychological distress that often co-occur with cancer. In contrast, MBSR has demonstrated efficacy for improving symptoms of stress, mood disturbance and overall distress in cancer patients [136,137,157,162,163,165]. In addition to distress, preliminary evidence suggests that MBSR may also improve overall sleep quality, thereby possibly addressing an important and common symptom cluster [179,185]. The determination that MBSR produces improvements in sleep, in addition to cancer-related distress, may allow for more effective, efficient and comprehensive treatment provision.

MBSR is intended to teach the development of mindfulness, defined as moment-to-moment, present-centered, purposive and non-judgmental awareness [122]. It is proposed that the practice of mindfulness may allow people to detach themselves from the cycle of dysfunctional thoughts that serve to maintain disturbed sleep and prevent generating further physiological and cognitive arousal. Research using a standardized definition of insomnia and an adequately powered randomized controlled design is needed to evaluate hypotheses based on these preliminary findings. Such research would clarify the combined impact of MBSR on the sleep disturbance and distress symptom cluster in cancer patients.

4.2 Methods

Study Design

This project is a randomized controlled non-inferiority trial comparing a known efficacious treatment for insomnia (CBT-I) to a treatment of interest with demonstrated potential (MBSR). Using a non-inferiority design allows for an efficient comparison of the two treatments directly and determination of whether the investigative treatment performs to the same standard as the established treatment while providing additional benefits. The research design complies with the recommendations suggested by an expert panel of 25 sleep experts for assessment and reporting in insomnia research studies [193]. Participants are blind to treatment condition and randomly assigned to participate in either CBT-I or MBSR. Both treatments are delivered to groups (CBT-I: 2 groups of 8-10; MBSR: 1 group of 16-20, per cohort). Assessments (sleep diary, actigraphy and questionnaires) are completed at three time periods: pre-treatment, post-treatment and at 3 month follow-up. All study procedures have been reviewed and approved by the Conjoint Health Research Ethics Board of the University of Calgary/Alberta Health Services and participants are required to provide written informed consent before engaging in any research-related activity.

Participants

All interested English-speaking individuals over the age of 18 years with non-metastatic cancers are eligible to participate, with no restrictions being placed on tumor location. To minimize the effect of active treatment on results, participants are required to have completed treatment at least 1 month prior to program initiation (patients on continued hormone treatment are not excluded). Participants must meet the criteria for primary or secondary insomnia as defined by the Diagnostic and Statistical Manual of Mental disorders, 4th Edition, Text Revision (DSM-IV-TR) [2] and the International

Classification of Sleep Disorders [3]. The diagnostic criteria specifies that the individual must have experienced difficulty initiating or maintaining or non-restorative sleep for at least 1 month (DSM-IV-TR) and that the sleep disturbance causes clinically significant impairment or distress in important areas of functioning. Participants are required to meet additional criteria commonly used in insomnia research [73]. These include: sleep latency or time awake after sleep onset greater than 30 min, sleep efficiency of less than 85%, and disturbances that occur three or more days per week.

Patients are screened for the following exclusionary conditions: being on active chemotherapy or radiotherapy, the presence of another sleep disorder other than insomnia (e.g. sleep apnea), the presence of another Axis I disorder not in remission (e.g. major depressive disorder, alcohol or drug dependence), the inability to attend at least 5 out of the 8 treatment sessions, the refusal to be randomized, previous participation in an MBSR or CBT-I program, and employment in a job requiring shift work that would impair the ability to establish a regular sleep schedule. Participants are not excluded for using psychotropic medication (e.g. antidepressants) provided that the dose was not recently altered (stable over the previous 6-weeks). The use of hypnotics or sedatives also does not exclude individuals from participation. Considering the high use of benzodiazepines within the oncology population, past research has included participants who met diagnostic criteria for insomnia, despite the use of benzodiazepines, and included monitoring of medication use [116].

Recruitment and Retention

The Tom Baker Cancer Centre (TBCC) is located in Calgary, Alberta (a city of approximately 1 million people), and services all of southern Alberta, representing a

catchment area of more than 1.5 million people. This large tertiary academic cancer centre receives approximately 32,500 patient visits annually. The study is advertised as the ***I-CAN*** *SLEEP Research Program: A study for individuals with* ***I****nsomnia and* ***CAN****cer*. Participants are able to self refer and are made aware of the study through posted announcements and pamphlets available in main areas of the cancer center and its satellite locations. New patients of the TBCC are informed of opportunities to participate in research studies at patient orientations. Physicians and nurses at the TBCC and individual counsellors in the Department of Psychosocial Resources are able to refer patients. Advertising to date has also included notifying community support groups, posting study information on websites frequented by patients, media releases in local newspapers and television programs, paid radio advertisement spots, outdoor billboard advertising and invitation letters mailed through the provincial cancer registry.

In addition to these avenues of referral, patients with sleep difficulties are identified through a distress screening questionnaire that all TBCC patients complete during their first centre visit. Patients who indicate sleep as a concern are contacted by phone by a research assistant or mailed a study invitation. Patients who respond directly to the invitation, advertisements or who are referred by a health professional undergo an initial telephone screening by one of the research team and the study goals and procedures are explained.

Potentially eligible participants complete the Sleep Disorders Questionnaire (SDQ) [194] over the phone with the assistance of a research assistant. The SDQ is based on the DSM-IV-TR and ICSD-R criteria for insomnia and includes 18 questions designed to differentiate between those individuals who: 1. Meet criteria for a sleep disorder, 2.

Report problems with sleep but do not meet criteria, and 3. Do not report problems with sleep. The SDQ has demonstrated satisfactory convergent validity with another well-validated sleep instrument as well as sensitivity of 95% and specificity of 87% for distinguishing insomnia patients from controls [194]. Participants who fall into the first and second categories are scheduled for a clinical interview.

Clinical Interview

Patients are scheduled to meet with one of the primary researchers who administers the Structured Clinical Interview for the DSM-IV (SCID) [195] to confirm the presence of insomnia and rule out the presence of a comorbid sleep disorder or Axis I disorder (not in remission). The study procedures are explained in detail and written consent is obtained for study participation and to access medical records to confirm tumor location, stage and treatments received.

Information Session

Eligible participants are scheduled to meet with one of the research team a month to two weeks prior to program initiation to allow time for week-long ambulatory sleep monitoring using actigraphy and sleep diaries. At this appointment, actigrapy monitoring is explained, participants are instructed on how to record their sleep using a sleep diary and baseline questionnaires of sleep, mood, stress, mindfulness, and beliefs about sleep are completed. This process takes approximately 60 minutes. Participants are provided with a contact number of one of the research team should they have any questions about the sleep diary or require assistance with the actigraphy equipment at any time during the week. Upon completion and return of the baseline sleep diary and actigraphy assessments, participants receive the details of their treatment group allocation.

Measures

The primary outcome measure is the Insomnia Severity Index [196]. Secondary outcomes include: Actigraphy [197], Sleep Diaries [73], the Pittsburgh Sleep Quality Index [198], the Dysfunctional Beliefs and Attitudes about Sleep scale [74], the Calgary Symptoms of Stress Inventory [199], the Profile of Mood States-Short Form [200] and the Five Facet Mindfulness Questionnaire [201]. A description of the measures can be found in Table 4.1.

Protection against Bias and Allocation to Groups

Participants are randomly allocated to one of two conditions using a computer-based random number generation program on a cohort-by-cohort basis with a 1:1 allocation ratio. The primary investigators are kept blind to participant allocation, except for SG who is involved with recruitment, testing and program delivery. Prior to program assignment, the treatment programs are referred to in a general manner that does not reveal the program content. Specifically, participants are told they will be assigned to one of two programs, the content of which may include modifying their sleep pattern, talking about how to manage stress, discussing how thoughts and habits may make it difficult to fall asleep at night, as well as practicing relaxation, meditation, gentle stretching exercises and completing some work at home. Following completion of the baseline assessments, each participant is sent an email indicating to which group they have been allocated (CBT-I or MBSR) and an explanation/rationale for the particular approach. They are not provided with information about what the other treatment program consists of. Participants do not have the opportunity to discuss their program assignment with attendees of the other program.

Treatment Arms

Mindfulness-based Stress Reduction (MBSR): The intervention is provided over the course of eight, weekly, 90-minute sessions, plus one 6-hour weekend intensive silent retreat. The program is intended to facilitate an increased awareness of one's typical internal and external reactions to stress and to introduce meditation techniques as a way of promoting healthy responses to stress [137]. The group stress reduction program was modeled on the work of Jon Kabat-Zinn [122] and has been adapted and standardized for use in individuals with cancer [126]. The MBSR program consists of three primary components: 1) didactic instruction, 2) experiential practice, and 3) group process. Group facilitators model attitudes of mindfulness including nonjudging, acceptance, patience, non-striving, and letting go. Participants are provided with information on the effect of stress on health and options for mindful versus reactive responses to stress.

Various types of mindfulness meditation techniques, such as the body scan, sitting meditation and walking meditation, are introduced and practiced in class, with daily home practice being highly encouraged. Mindful movement is introduced with the inclusion of gentle Hatha yoga postures. Group members are encouraged to discuss their experience in class allowing for supportive problem solving [137]. In addition a booklet is produced and distributed containing information pertinent to each week's instruction, including a bibliography for those wishing to pursue relevant themes in greater depth. Additionally, two compact discs with a variety of guided meditation and yoga tracks are provided to help with home practice.

Cognitive Behavioral Therapy-Insomnia (CBT-I): This program is based on the work of Morin and Espie [73]. It is designed to be delivered to groups of 6-10 individuals over the course of 8 weeks, with classes of 90 minutes duration. CBT-I is comprised of 4

individually validated therapies: Stimulus Control Therapy (SCT), Sleep Restriction Therapy (SRT), Cognitive-Behavioral Therapy (CBT) and Relaxation Therapies (RT). SCT is based on the theory that the body eventually becomes conditioned to associate the sleep time and setting with arousal (e.g. only go to bed when sleepy and refrain from lying awake in bed). SCT is designed to break the perpetuating behaviors and re-associate the bed with positive sleep experiences. SRT is designed to restrict time spent in bed to closely match the time actually spent sleeping. A sleep efficiency percentage is calculated and when the individual is able to achieve 85% sleep efficiency their sleep time is increased. This process continues until the person can achieve a restful night's sleep with few or no disturbances. CBT addresses the dysfunctional thoughts and beliefs that serve to maintain and exacerbate insomnia. Individuals are taught to monitor these thoughts and beliefs, challenge their validity and replace them with adaptive cognitions conducive to the sleep process. RT targets the physiological and cognitive arousal that accompanies insomnia. Proper sleep hygiene is also a program component, involving the promotion of healthy sleep behaviors and altering interfering environmental conditions.

Each session begins with a review of the previous weeks sleep diary and any adherence issues. Then the new treatment component and rationale is introduced and participants are provided with didactic material for home reference. Lastly, homework assignments for the upcoming week are reviewed.

Power Analysis and Sample Size

To deem that MBSR produces results that are not inferior to CBT-I, an acceptable margin of non-inferiority on our primary outcome of subjective insomnia severity was established to be 50% of the minimum clinically significant difference produced by CBT-

I on the Insomnia Severity Index. Based on research and clinical experience, the minimum clinically important difference is 8 points on the ISI [202]. Hence, the treatment groups will be considered equivalent if their average ISI total scores do not differ by more than 4 points. Using the figures provided in a RCT of CBT-I in women with breast cancer [116] and in individuals with chronic insomnia [101], the standard deviation for ISI in this population was estimated to be 6. Sample size determination followed the recommendations outlined in Hwang and Morikawa [203]. Using a one-tailed test and a 5% significance level, 35 participants in each group would provide adequate power (80%) to reject the null hypothesis that the ISI changes produced by MBSR are not similar to those produced by CBT-I. Please refer to the sample size calculations provided in Figure 4.1.

Based on clinical experience of randomized controlled trials of clinical programs conducted through the TBCC, a conservative attrition rate of 40% over the full course of the study was factored in, increasing the necessary sample size to 55 individuals per group. To obtain an adequately large final sample size for the present study (CBT-I: n = 35; MBSR: n=35), approximately 380 patients presenting with self-identified sleep difficulties will need to be screened for eligibility, based on the following assumptions: approximately 40% of the patients screened (n=152) will be eligible to participate; 80% of these (n=122) are expected to consent to participate; 90% who consent will likely complete the baseline assessment and begin the programs (n=110); 80% who begin the programs (CBT-I: n=44; MBSR: n=44) will remain to complete post-treatment assessments, and 80% who complete the programs are expected to complete the 3-month follow-up assessment. This results in a sample size of 35 per group (N=70). Refer to Figure 2 for flowchart.

4.3 Analytic Approach

Intent-to-treat analyses have been criticized for being anticonservative in non-inferiority trials because they typically decrease the differences between groups and favor the null hypothesis, which in the case of a non-inferiority trial would increase the chance of concluding that the two treatments are similar [204]. Conversely, per-protocol analyses do not consider the impact that dropouts may have on outcome and downplay the influence of patients remaining in the study who are more likely to be those who respond. Therefore a hybrid analysis of intent-to-treat and per-protocol will be performed on the data as recommended by Sanchez and Chen [205]. This technique will exclude non-adherent participants as per-protocol and use the maximum likelihood estimation method to account for missing data as per intent-to-treat.

Patients will be compared using t-tests or chi-square analyses (as appropriate) on primary demographic variables (e.g. age, gender, length of disease) and study variables (e.g. sleep efficiency, symptoms of stress) at baseline to verify randomization success. Attendance and homework completion will be tracked and reported. The primary outcome for analysis is subjective insomnia severity on the ISI. The percentage of patients no longer meeting the clinical cutoff for insomnia on the ISI will be determined. A one-tailed analysis of variance (ANOVA) will be performed to compare groups and determine non-inferiority. Compliance with the assumptions of normal distribution and homoscedasticity will be assessed. Cluster effects as a consequence of group randomization will be evaluated using the intraclass correlation coefficient (ICC). Considering the planned ANOVA analysis, if the ICC value is significant, the F statistic will be corrected as recommended by Hedges and Rhoads [206]. Follow up scores at post-

program and three months will be compared using repeated-measures ANCOVA, adjusting for baseline values. This will be repeated on secondary outcome measures and bonferonni corrections will be used to account for multiple comparisons.

Treatment Fidelity

Sessions will be videotaped and two from each cohort will be randomly selected for review by an independent assessor familiar with the delivery of each of the interventions. The sessions will be evaluated using a predetermined criteria for treatment fidelity developed specifically for this trial. The checklist consists of items related to the specific treatment instructions and the absence of elements from the comparison group. Each of the therapists has received specialized training in their modality and is not trained in the other.

4.4 Discussion

Cancer survivors are at increased risk for insomnia by virtue of the emotional consequences of a cancer diagnosis [23], the effects of the cancer treatments (e.g. chemotherapy [32], hormone therapy [207,208]) and the disruption it can cause to daily routines which work as circadian anchors to promote regular sleep pattern. The burden of elevated psychosocial distress combined with significant difficulty achieving restful and restorative sleep, can hamper cancer recovery. There is some evidence that sleep disturbance is related to increased mortality in individuals with cancer. Mormont et al. [39] investigated the relationship between rest/activity rhythms, quality of life, treatment response, and survival in 200 patients with metastatic colon cancer. Patients with dysregulated circadian rhythmicity (i.e. poorly differentiated activity levels during wake and sleep) were 5 times more likely to die within 5 years than patients with a more

distinguishable circadian rhythm. Those patients with marked rest/activity patterns also reported better overall quality of life [40]. Despite evidence that sleep disturbances are common and potentially harmful conditions and the negative influence that psychological distress has on sleep, comprehensive treatments that address the co-morbid symptoms of psychological distress and sleep disturbances have not yet been evaluated.

The potential of mindfulness to improve outcomes for the treatment of psychological disorders is increasingly recognized and efforts have been made to incorporate mindfulness into traditional nonphamacological treatments. The addition of mindfulness to traditional cognitive therapy (Mindfulness-Based Cognitive Therapy) for the treatment of depression has been demonstrated to lower risk of depressive relapse, reduce antidepressant usage and is cost-effective, advantages offered beyond traditional pharmacological interventions [209]. The application of mindfulness to the treatment of insomnia is based on evidence that individuals experience circadian rhythms in physiological and cognitive arousal (or mental activity), meaning that arousal is high during the day and low at night, and where a dearousal of mental processes is a necessary precursor to successful sleep experiences [166]. The practice of mindfulness teaches the practitioner to self-regulate their own arousal by focusing in the present reality instead of ruminating about impending stress and future consequences. Breathing regulation is also taught as part of the program so that practitioners may be able to self-modulate arousal via this mechanism as well. This has the potential effect of reducing pre-bed cognitive and physiological arousal, setting the stage for improved sleep quality and quantity.

The combination of cognitive-behavioral treatments with mindfulness-based techniques for improving sleep in non-medical populations is beginning to be

investigated [210,211]. Preliminary results from an uncontrolled study of 27 individuals suggest that increased mindfulness may be related to sleep improvements [167]. Significant changes were seen in total wake time, time in bed and number of awakenings but not in total sleep time or subjective sleep quality. To date, there have been no attempts to apply combination treatments for insomnia in cancer survivors.

The absence of a no-treatment group or placebo/sham treatment is the most obvious limitation of the current research, although the comparison with CBT-I, an empirically supported intervention considered to be the gold standard treatment of insomnia, reduces the utility of a control group. However, the current design does prevent an exploration of change due to the passage of time alone (maturation) or statistical regression towards the mean, which may make their insomnia symptoms less severe at follow up assessments. However, Savard et al (2009) evaluated the persistence of insomnia in a sample of 939 patients with a non-metastatic cancer diagnosis at the time of diagnosis and again 2 months later [212]. Of the patients that had an insomnia syndrome or insomnia symptoms at diagnosis (59.5%), this persisted in 68% of the sample, suggesting that without treatment insomnia is relatively stable once developed. Additionally, although patients undergo a thorough sleep history interview intended to identify sleep disorders, patients are not screened with PSG to rule out the possibility of sleep apnea or periodic limb movement disorder. Relying on self-report of these conditions may not successfully screen out all possible cases, which may reduce treatment effects. Finally, the follow up in this study is limited to three months following treatment, preventing conclusions about the efficacy of the treatment to maintain effects after this specified time frame. Nevertheless, non-pharmacological interventions for insomnia, including

those included in CBT-I, have been shown to produce durable effects for at least 6 months [213].

This study has several strengths and addresses many of the gaps in current literature. First of all, the non-inferiority study design is a novel and efficient way of determining whether an investigative treatment is as good as a standard treatment in addition to offering other benefits. This allows for a quicker translation of knowledge into clinical practice and improves patient access to effective treatments. Secondly, participants are not being limited by tumor location, which will increase the generalizability of the results. Finally, establishing the ability of a comprehensive treatment such as MBSR to positively impact cancer-related distress and sleep disturbance in individuals with cancer would increase available treatment options.

Conclusions

While CBT-I is recommended as a first-line treatment for insomnia, it may not address the psychological distress that can accompany a cancer diagnosis. In contrast, MBSR has demonstrated efficacy for reducing cancer-related distress, but has not been properly investigated to determine its impact on sleep disturbances. The demonstration that MBSR can address distress AND insomnia, two of the most common cancer-related side effects, has the potential to increase the efficiency of service delivery, reduce treatment cost, and improve the lives of cancer survivors.

Table 4.1 Primary and Secondary Outcomes

Measure	Description
Primary Outcome	
Insomnia Severity Index (ISI)	The ISI is a brief measure designed to assess subjective sleep complaints and the amount of associated distress. It is comprised of seven items designed to measure severity of sleep-onset and sleep maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, impairment attributed to the sleep problem, and degree of distress elicited. Items are scored on a five-point scale ranging from 0 to 4 with higher scores representing more severe insomnia symptoms. When validated in a sample of cancer patients, the optimal cutoff scores were 0-7 (no clinically significant sleep difficulties, 7-14 (sleep difficulties warrant further investigation) and 15+ (presence of clinically significant insomnia) [214].
Secondary Outcomes	
Actigraphy	Actigraphy monitoring provides objective information on our primary outcome measure of sleep efficiency as well as indices of sleep latency, total sleep time, and frequency and duration of awakenings. Patients will wear the GT1M Actigraph manufactured by Actigraph, LLC. Data will be analyzed using the Actilife software program, version 5, provided by Actigraph using the Sadeh algorithm [215] for distinguishing sleep and wake activity. Actigraphy is a relatively non-invasive way to monitor wakefulness and sleep based on the presence or absence of movement. The GT1M Actigraph is electrode-free, has dimensions of 3.8x3.7x1.8 centimeters, weighs 27 grams and is worn similar to a watch with the inclusion of a movement detector and memory storage. Individuals are able to comfortably wear the device for the prescribed assessment period of one-week pre and post treatment and again at 3 month follow up.
Sleep Diary	The sleep diary provides a night-by-night, self report of sleep pattern and quality and will be completed by participants in both treatment conditions. The sleep diary will be used to calculate a subjective report of our primary outcome measure of sleep efficiency, as well as sleep-onset latency, wake after sleep onset, total sleep time, time in bed, number of awakenings, sleep quality, and terminal wakefulness. Sleep diaries are considered a reliable and valid measure of insomnia symptoms [193].
Pittsburgh Sleep Quality Index (PSQI)	The PSQI instrument was specifically designed for use in clinical populations to assess seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) and a global score. It consists of 19 self-rated questions that are scored on a 0 to 3 scale over a period of one month. It has sensitivity and specificity in distinguishing good and poor sleepers. Acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity have been demonstrated [198].
Dysfunctional Beliefs and attitudes about Sleep Scale (DBAS-16)	The DBAS-16 is an abbreviated version of the original 30-item scale designed to assess the disrupted cognition often associated with sleep disturbance [216]. Instructions ask the participant to indicate the extent to which he/she agrees with the statement on a Likert scale ranging from 0 (strongly disagree) to 10 (strongly agree). The 4 factors of the DBAS-16 are: perceived consequences of insomnia, worry/helplessness about insomnia, sleep expectations and medication use. The DBAS-16 has acceptable internal consistency ($\alpha = .77$ for clinical and $\alpha = .79$ for research). Furthermore, the DBAS-16 is able to accurately distinguish

	normal sleepers from those with insomnia and those individuals who have received CBT-I from those treated with other behavioral insomnia treatments [74].
Calgary Symptoms of Stress Inventory (C-SOSI)	The C-SOSI is a shortened version of the original 95 item Symptoms of Stress Inventory [217]. The C-SOSI has 56 items and is designed to measure physical, psychological, and behavioral responses to stressful situations. The items are rated on a 5-point scale from "never" to "frequently". A total stress score is obtained in addition to 8 subscale scores: Depression, Anger, Muscle Tension, Cardiopulmonary Arousal, Sympathetic Arousal, Neurological/GI, Cognitive Disorganization and Upper Respiratory Symptoms. Chronbach's alpha for the C-SOSI total score was 0.95, with subscale coefficients ranging from .80 (Upper Respiratory Symptoms) to .92 (Anger). The C-SOSI demonstrated appropriate convergent and discriminant validity with other thoroughly validated measures [199].
Profile of Mood States-Short Form (POMS-SF)	The POMS-SF is a 37-item scale that assesses six affective dimensions (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia and confusion-bewilderment) and provides a total mood disturbance score. The original 65 item POMS has been widely used to study the psychological aspects of cancer and as an outcome of psychosocial interventions [218]. The measure has demonstrated good internal consistency for the six subscales and the total score (Chronbach's alphas ranging from .80 to .91). The POMS-SF has been validated in a cancer patient population and has demonstrated convergent and discriminant validity [200].
Five Facet Mindfulness Questionnaire (FFMQ)	The FFMQ was included to investigate possible relationships between mindfulness and sleep, a research area that has garnered significant interest [179]. The FFMQ was developed from a factor analysis of five independently developed mindfulness questionnaires. The analysis yielded five factors that accounted for 33% of the variance. The five facets included in the FFMQ are: attending to sensations, perceptions, thoughts and feelings; describing experience with words; acting with awareness; non-judging of experience; and non-reactivity to inner experience.

Figure 4.1: Sample Size Calculations

α - Significance Level (5%)
β -Type II Error (20%)
δ - Non-inferiority Margin (4)
σ - Pooled Standard Deviation (6)

$$N = 2 [(Z_{(1-\alpha)} + Z_{(1-\beta)}) (\sigma / \delta)]^2$$

$$N = 2 [(1.645 + 0.84) (6 / 4)]^2$$

$$N = 2 [(2.49) (1.5)]^2$$

$$N = 2 [3.735]^2$$

$$N = 2 [13.95]$$

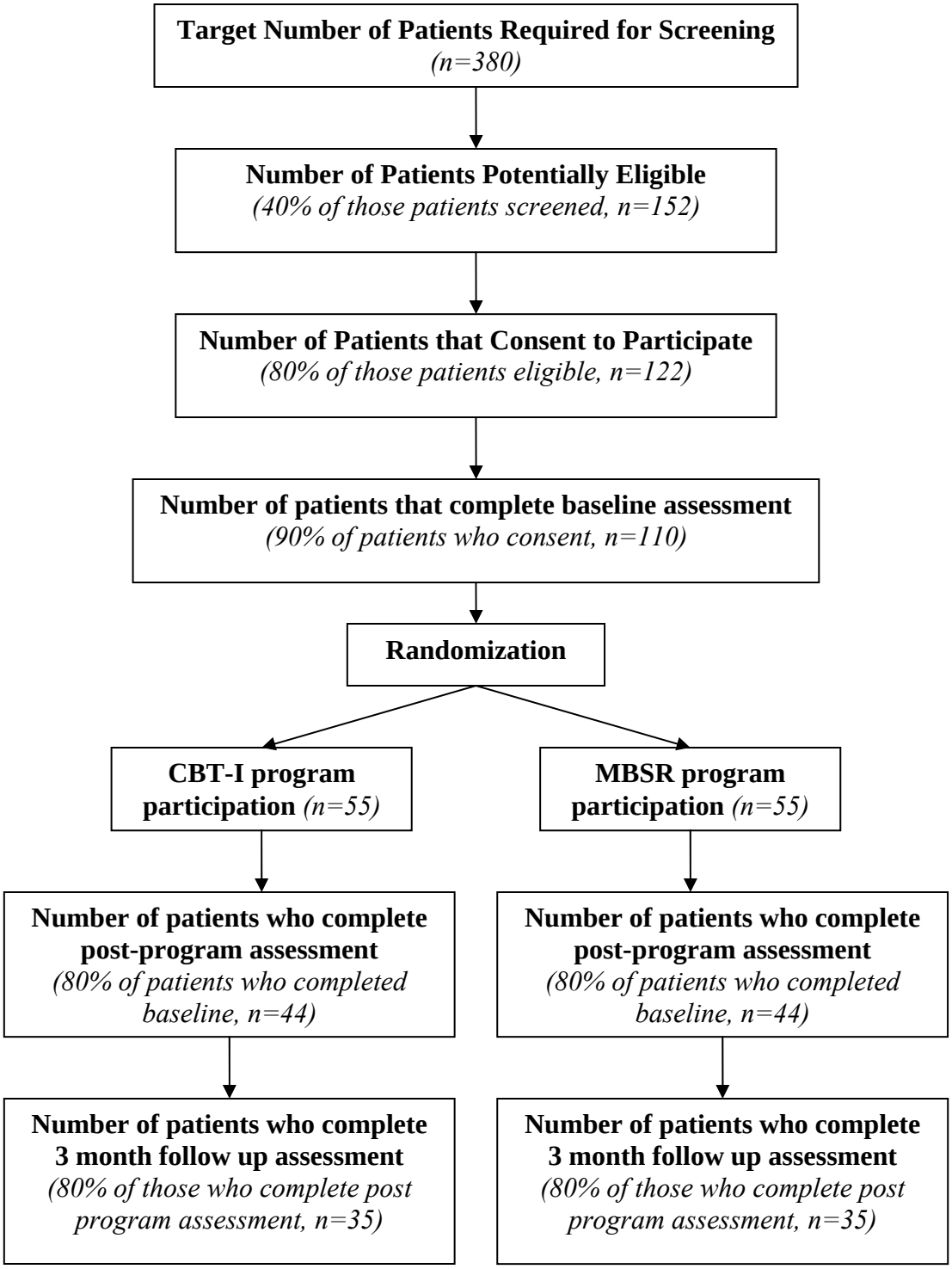
$$N = 27.90$$

Adjusting for attrition of 20%,

$$N = \frac{28}{1-0.20} = 35$$

Effective sample size per treatment arm is 35.

Figure 4.2. Proposed Recruitment Flow Chart



CHAPTER 5: A COMPARISON OF MINDFULNESS-BASED STRESS REDUCTION TO COGNITIVE BEHAVIORAL THERAPY FOR THE TREATMENT OF INSOMNIA COMORBID WITH CANCER: A RANDOMIZED, NON INFERIORITY TRIAL

5.0 Preface

After publishing the trial protocol manuscript while the study was underway, we decided to modify the proposed statistical analysis to utilize more sophisticated and appropriate techniques. Originally we planned to use a one-tailed Analysis of Variance (ANOVA) for the non-inferiority analysis and Analysis of Covariance (ANCOVA) for the secondary outcomes, adjusting for baseline values. Instead, we chose to employ linear mixed models (LMMs) for repeated measures to analyze all the data. LMMs are recommended over ANOVA for longitudinal studies because LMMs are able to fully accommodate unbalanced allotment and data sets that result from missing data by using modeling to estimate missing follow up data, whereas a single missing data point in ANOVA causes all of that participants data to be dropped [219]. We wanted to ensure that all the data collected was used, regardless of attrition.

Olsen and colleagues recently advocated for the use of LMMs over 'complete-case analysis' or 'last observation carried forward' for analyzing their trial of CBT-I and sleep hygiene in a primary care setting with missing follow up data [220]. LMMs have also been used to analyze a trial of CBT versus pharmacotherapy that was published in JAMA [101]. Furthermore, in repeated measures designs, LMMs account for the inter-dependence of observations, whereas ANOVAs assume independence of observations and ignores the relationship between observations. For these reasons, we believe that LMMs provide a stronger statistical test.

5.1 Abstract

Context. Insomnia is a prevalent and persistent disorder that frequently co-occurs with psychological distress in cancer patients.

Objective. To determine whether effects produced by Mindfulness-Based Stress Reduction (MBSR) are not significantly worse than, or inferior to, Cognitive Behavioral Therapy (CBT-I) for the treatment of insomnia in cancer patients

Design, Setting, and Patients. The I-CAN SLEEP trial was a randomized, partially blinded, non-inferiority trial involving cancer patients with diagnosed insomnia recruited from a tertiary cancer center in Calgary, Alberta from September 2008-March 2011. Assessments were conducted at baseline, post-intervention (2 months) and three months post-program (5 months).

Interventions. CBT-I incorporates sleep restriction, stimulus control, cognitive therapy and relaxation training to re-establish a restorative sleep pattern. MBSR provides education and training in mindfulness meditation and gentle yoga in order to modify stress appraisals and physiological arousal. Both treatments were professionally delivered to small groups in weekly, 90-minute sessions over 8 consecutive weeks.

Main Outcome Measures. The primary endpoint was insomnia severity with a non-inferiority margin of 4 points. Secondary outcomes include self-reported sleep quality, dysfunctional sleep beliefs, mood and stress. Sleep diaries and wrist actigraphy were used to collect data on sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST) and sleep efficiency.

Results. Of 327 patients screened, 111 were eligible and randomized (CBT-I = 47; MBSR = 64). Participants were primarily female (72%) with a mean age of 59 and 16

years of education. The most frequent tumor location was breast (49%). For insomnia severity, MBSR was non-inferior to CBT-I when assessed at 5 months (diff = 1.10; upper 95% CI = 2.87) but not immediately post program (diff = 2.61; upper 95% CI = 4.29). On the sleep diaries, SOL reduced by 22 min in CBT-I and 14 min in MBSR. Similar reductions in WASO were observed for both groups. TST increased by 36 min in CBT-I and 44 min in MBSR. CBT-I uniquely improved sleep quality and dysfunctional sleep beliefs while both groups demonstrated the ability to reduce stress symptoms and mood disturbance.

Conclusions. For insomnia severity, MBSR produces results that are not significantly worse than CBT-I when assessed at 5 months but not immediately post-program.

Trial Registration: clinicaltrials.gov Identifier: NCT01335776

5.2 Background

Sleep disturbance is one of the most frequent problems reported by cancer patients after the completion of cancer treatment. In a prospective study of 962 cancer patients with a variety of diagnoses and stages, 21% reported problems with sleep 18 months post-diagnosis, with 15% suffering chronic insomnia. [22]. Additional studies have echoed that approximately 1/3 of cancer patients will experience sleep difficulty at some point during or after treatment [21,29,34].

Sleep disturbance frequently co-occurs with distress - another common consequence of cancer. The distress associated with cancer encompasses "common normal feelings of vulnerability, sadness, and fears, to problems that can become disabling such as depression, anxiety, panic, social isolation and spiritual crisis" [14]. Of 877 patients screened for distress within one month of their first oncology appointment, 51% reported significant levels of distress [17]. When re-assessed 12 months after their diagnosis, 29% of patients still indicated elevated distress levels. The experience of distress can place cancer patients at a greater risk for sleep disturbances [29]. The relationship between distress and sleep disturbance is likely bidirectional, suggesting that interventions to treat insomnia in cancer patients may be more beneficial if they are also effective at reducing cancer-related distress.

Although there are a variety of medications available to aid sleep, long-term use is associated with continued sleep difficulty and performance problems, memory disturbances, driving accidents and falls in the general population [45]. An effective treatment for insomnia in both medical and non-medical populations is Cognitive Behavioral Therapy for Insomnia (CBT-I), a manualized, non-pharmacological

intervention that is recommended by the American Academy of Sleep Medicine [105,221]. The efficacy of CBT-I to treat insomnia in individuals with cancer is well established and produces durable improvements in sleep onset latency and time spent awake during the night [114-116,118,222].

Mindfulness-Based Stress Reduction (MBSR) was developed to target overall distress in patients with chronic medical conditions and is a standardized, professionally delivered group intervention. Within the MBSR program, participants are guided in the development of mindfulness, defined as non-judgmental awareness of the present moment, in order to modify appraisals of potentially stressful situation and reduce overall levels of psychophysiological arousal. In individuals with cancer, MBSR has demonstrated the ability to produce statistically significant *and* clinically relevant improvements in overall mood disturbance, health-related quality of life, and general well being [134,135,159,160].

The ability of MBSR to train patients to reduce psychophysiological arousal is one potential mechanism by which MBSR may positively impact insomnia, a disorder of hyperarousal [66]. Preliminary evidence suggests that MBSR may have a positive impact on sleep quality and quantity in cancer patients [165,184,185]. Adequately powered and controlled trials are necessary before conclusive statements of efficacy are possible. The present study is a randomized, non-inferiority trial assessing the ability of MBSR to produce effects comparable to CBT for insomnia with the additional benefit of reducing cancer-related distress.

5.3 Methods

The trial design for this study has been described elsewhere and will be briefly reviewed [223]. Ethical approval was obtained from the Conjoint Health Research Ethics Board of the University of Calgary/Alberta Health Services. The reporting of this trial follows the extended CONSORT guidelines for reporting non-inferiority and equivalence randomized controlled trials [224], and is registered with ClinicalTrials.gov, number NCT01335776.

Participants

Patients were recruited from a tertiary cancer center in Calgary, Alberta. All English-speaking adults with a non-metastatic cancer diagnosis were eligible for inclusion in the trial if they had completed chemotherapy and radiation treatments at least one month prior to study participation. Participants were required to meet the combined clinical and research diagnostic criteria of insomnia [2,3,225]. Those patients using psychotropic medication were eligible for inclusion as long as their dosage was stable in the previous 6 weeks. Patients were ineligible if they screened positive for the presence of another sleep or psychiatric disorder (e.g. sleep apnea, or alcohol dependency) or had previous treatment with MBSR or CBT-I.

Interventions

Cognitive Behavioral Therapy for Insomnia: The CBT-I program is delivered to groups of 6-10 individuals over the course of eight, weekly, 90-minute sessions, for a total of 12 contact hours. CBT-I contains 4 individually validated therapies: stimulus control, sleep restriction, cognitive therapy and relaxation training. Combined, these therapies work to target and reduce sleep-related physiological and cognitive arousal to

re-establish restorative sleep function. Proper sleep hygiene is also reviewed. Each session, sleep diaries are reviewed and participants are given handouts detailing the rationale for the therapy introduced that week.

Mindfulness-Based Stress Reduction: The MBSR program is delivered to groups of 15-20 people over the course of eight, weekly, 90-minute sessions, plus one 6-hour weekend intensive silent retreat for a total of 18 contact hours. The program provides patients with psychoeducation on the relationship between stress and health, while meditation techniques including the body scan, sitting meditation, walking meditation and loving-kindness meditation are introduced to practice the development of mindful versus reactive responses to stress. Group process allows for problem solving and the incorporation of mindful attitudes (i.e. nonjudging, acceptance, patience, non-striving, and letting go). Participants also receive a program booklet and two compact discs with recorded guided meditation tracks to help with home practice [126].

Objectives

Primary Aim - (1) To establish whether MBSR produces effects that are not inferior to CBT-I for reducing insomnia severity in individuals with cancer immediately post-intervention (2 months) and three months post-program (5 months).

Secondary Aims - (2) To compare MBSR to CBT-I on measures of subjective and objective sleep quality. (3) To compare MBSR to CBT-I on self-report measures of stress symptomatology and mood disturbance.

Primary Outcome

Insomnia Severity

The Insomnia Severity Index (ISI) is a 7-item measure designed to measure severity of sleep-onset and sleep maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, impairment attributed to the sleep problem, and degree of distress elicited [196]. The recommended cutoffs are: 0-7 no clinically significant insomnia; 8-14 subthreshold insomnia; 15-21 moderate clinical insomnia, and; 22-28 severe clinical insomnia.

Secondary Outcomes

Subjective Sleep Quality

The nightly Sleep Diary [73] is used to calculate a subjective report of sleep efficiency (SE), sleep-onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), time in bed, number of awakenings, sleep quality, and terminal wakefulness. The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of subjective sleep quality in the previous month and is designed for clinical populations [198].

Objective Sleep Quality

The GT1M actigraph manufactured by Actigraph, LLC provides objective information on SE, SOL, TST, and WASO. Data were analyzed using the software program provided by Actigraph and the Sadeh algorithm [215] for distinguishing sleep and wake activity.

Psychological Outcomes

The Calgary Symptoms of Stress Inventory (C-SOSI) is a 56-item measure of physical, psychological, and behavioral responses to stressful situations [199].The Profile of Mood States- Short Form (POMS-SF) is a 37-item scale assessing distinct, transient mood states and overall mood disturbance [226].

Sample Size

Sample size determination followed the recommendations outlined by Hwang and Morikawa [203]. The minimally important difference (MID) in insomnia severity has been established to be a reduction of 8 points on the ISI [202]. Non-inferiority will be demonstrated should MBSR produce results within 50% of that demonstrated by CBT-I. The non-inferiority margin for calculating sample size was established to be 4 points on the ISI and the standard deviation to be 6 using the figures provided in a randomized controlled trial of CBT-I in women with breast cancer by Savard et al [116] and individuals with chronic insomnia [101]. Using a one-tailed test, a 5% significance level and accounting for 20% attrition, 35 participants in each group would provide adequate power (80%) to reject the null hypothesis that the ISI changes produced by MBSR are inferior to those produced by CBT-I.

Randomization and Blinding

Participants were randomly allocated to one of the two conditions using a computer-based random number generation program on a cohort-by-cohort basis and were kept blind to both treatments until baseline assessments were conducted. At that point, participants were informed only about the program they were assigned to. This was accomplished by advertising the study generally as I-CAN SLEEP: A Research Program for Individuals with Insomnia and CANcer. Interested participants were told that they would be randomly assigned to one of two programs and selected components of both the CBT-I and MBSR programs were described (e.g. “The treatment may include any, or all, of the following: modifying your sleep pattern, stress management techniques, modifying thoughts and habits that contribute to sleep difficulty, practicing relaxation, meditation, or

gentle stretching exercises and completing some work at home"). Following the completion of the baseline assessments, each participant was notified via email to which group they were allocated. Patients remained blind to the study hypotheses and the content of the other treatment group through the duration of their participation.

Statistical Methods

Analyses were conducted on both the per-protocol (PP) and intent-to-treat (ITT) samples. The PP population included all randomly allocated patients who completed baseline assessments and attended at least 5 of the 8 classes. The ITT sample included all randomly allocated participants who completed baseline assessments regardless of attendance.

Descriptive statistics and frequency distributions were generated on the sample characteristics. Independent samples t-test, chi-square or Fisher's exact tests with a Bonferonni correction were used to compare the groups on demographic and treatment variables. Linear mixed models (LMMs) for repeated measures were used to analyze the data. Effect sizes were calculated for both groups to quantify the impact of the treatment from baseline to 5-month follow up.

Non-inferiority was assessed using an *F* test statistic generated from the LMM and confidence intervals, as recommended by Mascha and Sessler [227]. This tests whether the difference between the group means is statistically larger than the non-inferiority margin (clinically significant difference) and if the upper limit of the one-sided confidence interval of the difference between the group means is less than the pre-specified margin of non-inferiority. Separate models were conducted for the primary outcome of insomnia severity and each of the secondary outcomes. An intraclass

correlation coefficient (ICC) was calculated to test whether the within group effect of cohort accounted for significant variance in the primary outcome.

For each of the models, the random effect was ID number and the fixed effects were group (MBSR or CBT-I), time, and the time by group interaction. Time was also set as a repeated measure. The restricted maximum likelihood estimate method was used to estimate the model parameters and standard errors of missing parameters with a compound symmetry covariance structure to account for the correlation between measurements. We used Type III fixed effects (F and t) and set statistical significance of p values as $< .05$. Pairwise comparisons were used to follow up any significant effects and the least significant difference method was used to control for multiple comparisons in the LMMs. IBM SPSS v. 20 was used for all analyses.

5.4 Results

Between September 2008 and March 2011, 327 patients were assessed and 111 were randomized (47 to CBT-I and 64 to MBSR). Figure 5.1 shows reasons for ineligibility, refusal, non-randomization and withdrawals. Midpoint in the trial, the randomization allocation ratio was changed from 1:1 to 2:1 favoring the MBSR group to adjust for differential drop out and ensure an adequate final sample for analysis.

Baseline demographic and symptom characteristics are presented in Table 5.1. Across treatment groups, dropouts were less educated and had higher levels of insomnia severity than completers but these differences were not statistically significant once a correction for multiple comparisons was applied.

Tables 5.2 and 5.3 summarize the baseline demographic, treatment, insomnia and symptom characteristics of the 72 patients included in the analysis. Despite differential

drop out, randomization successfully produced group equivalence at baseline. Patients were primarily female (72%), married (64%), with a mean age of 59 and 16 years of education. Close to half of the sample had been treated for breast cancer (49%) an average of 3 years prior to study participation, although several other diagnoses were represented. Patients reported that their insomnia began on average 6 years prior and thought that their cancer treatments made their difficulties with sleep worse. The majority of patients (57%) had difficulties with both sleep onset and maintenance. Several individuals were regularly taking prescription medication for sleep (31%), depression (21%) and anxiety (15%).

Non-Inferiority Analysis of Insomnia Severity

The ICC for cohort and baseline insomnia severity equaled -.017 (non-significant $p = .56$), indicating that approximately 2% of the proportion of total variance was attributable to between cohort differences, leaving 98% attributable to differences within individuals. As such, cohort was not included as a random effect in the model. In the PP analysis, the post-treatment ISI scores in the MBSR group were significantly higher than the CBT-I group and the one-sided upper confidence interval of the difference exceeded the non-inferiority margin of 4, suggesting that MBSR produced inferior results to CBT-I when assessed immediately post-program.

Insomnia severity between the MBSR and CBT-I groups was no longer different when assessed with a significance test and confidence interval at 5 month follow up, establishing non-inferiority at this time point only. Refer to Figure 5.2 for a graphical representation of the non-inferiority results and Table 5.4 for mean exact values. The ITT analysis confirms the PP results, albeit with smaller (yet still significant) *p*-values.

Sleep Dairies

The results of the LMM analysis for sleep diary outcomes are reported in Table 5.5. There were significant interactions on sleep diary measures of SOL and SE with the change produced by the CBT-I group exceeding that produced by MBSR. The groups were significantly different from each other on SOL values at post program (diff = 12.82, $p = .010$). For the CBT-I group, the greatest change was observed between baseline and post program ($\Delta = 20.63$, $p < .001$). The MBSR group reported significant improvements occurring between post-program and follow up ($\Delta = 11.34$, $p = .009$). Overall, the CBT-I group demonstrated a 22-minute decrease in SOL while the MBSR group reported a 14-minute decrease. For SE, the MBSR and CBT-I groups were significantly different at post program (diff = -8.02, $p < .001$) and follow up (diff = -4.99, $p = .043$). The greatest amount of change occurred between baseline and post program for both groups (MBSR Δ = -4.70, $p < .006$; CBT-I Δ = -11.90, $p < .001$).

There were significant time effects demonstrated for WASO and TST, with both groups reporting significant improvements over time. The greatest amount of change in WASO occurred between baseline and post program for both groups (MBSR $\Delta = 29.51$, $p < .001$; CBT-I $\Delta = 36.24$, $p < .001$). The reduction in WASO from baseline to follow up was 37 minutes for the CBT-I group and 35 minutes for the MBSR group. For TST, both groups reported significant improvement from post-program to follow up (MBSR Δ = -.61, $p = .002$; CBT-I Δ = -.38, $p = .017$) but not from baseline to post program. The increase in TST from baseline to follow up was 36 minutes for the CBT-I group and 44 minutes for the MBSR group. The ITT results are presented in Table 5.6

Actigraphy

There were no significant interactions observed for the actigraphy measured sleep outcomes (Table 5.5). A significant group effect was demonstrated for SOL with the CBT-I group having lower values than the MBSR group at each assessment point. Significant time effects were observed for WASO. The MBSR group demonstrated significant improvement from baseline to follow up (diff = 17.71, $p = .034$) where as the CBT-I group demonstrated the greatest improvement from baseline to post-program (diff = 24.72, $p < .001$). On actigraphy measured SE, the largest improvements were demonstrated from baseline to post-program (diff = -3.44, $p = .006$) for the CBT-I group. The SE values observed for the MBSR group were not significantly different from each other at any of the time points. Significant time and group effects were observed for actigraphy measured TST. The largest improvements for the MBSR group were demonstrated between post program and follow up (diff = -32.72, $p = .002$) whereas the CBT-I group reported a significant but smaller reduction in sleep between baseline and post-program (diff = -23.53, $p = .005$). The increase in TST detected by actigraphy from baseline to follow up was 6 minutes for the CBT-I group and 17 minutes for the MBSR group. The results of the ITT analysis are presented in Table 5.6. The main differences observed in the ITT analysis are the attenuation of the significance of some of the interactions and the presence of differential group effects.

Sleep Quality and Psychological Outcomes

The results of the LMM analysis for psychological outcomes are reported in Table 5.7. There were significant interactions between the MBSR and CBT-I groups on measures of sleep quality and dysfunctional sleep beliefs with the change produced by the CBT-I group exceeding that produced by MBSR at both time points. For the CBT-I

group, the largest change in sleep quality occurred between baseline and post program ($\Delta = 5.53$, $p < .001$). In contrast, the MBSR group demonstrated significant changes from both baseline to post-program ($\Delta = 1.44$, $p = .005$) and post program to follow up ($\Delta = 1.19$, $p = .029$). On measures of dysfunctional sleep beliefs, differences emerged at post program (diff = -1.31, $p < .001$) and follow up (diff = 1.07, $p = .003$) with the CBT-I group reporting less dysfunctional sleep beliefs at both time points. The greatest amount of change occurred between baseline and post program for both groups (MBSR $\Delta = 0.68$, $p = .010$; CBT-I $\Delta = 2.45$, $p < .001$).

There were significant main effects of time for symptoms of stress and mood disturbance indicating that both groups experienced similar significant improvements over time. For symptoms of stress, the greatest amount of change occurred between baseline and post program (MBSR $\Delta = 12.00$, $p < .001$; CBT-I $\Delta = 17.53$, $p < .001$). On measures of mood disturbance, the greatest amount of change also occurred between baseline and post program (MBSR $\Delta = 10.11$, $p = .007$; CBT-I $\Delta = 15.93$, $p < .001$). The results of the ITT analysis are presented in Table 5.8. The main differences observed between the two techniques are the presence of group effects in the ITT analysis with the CBT-I group being associated with greater improvements in insomnia severity, sleep quality and dysfunctional sleep beliefs.

Clinical Significance of Treatment Effects

Participants were grouped into their respective clinical categories based on their ISI scores (Figure 5.3). At the 5-month follow up 47.5% of the CBT-I group no longer met the cutoff for insomnia compared to 21.9% in the MBSR group. It appears that insomnia severity in the MBSR participants continued to improve over time with 4 fewer

participants remaining in the moderate insomnia category at the 5 month follow up (5 people, compared to 9 at 2 months). In contrast, the CBT-I participants may have experienced a weakening of treatment effect with 1 person having moved into the severe insomnia range and 5 additional people in the moderate insomnia category (1 and 9, respectively, compared to 0 and 4 at post-program).

5.5 Discussion

Mindfulness-Based Stress Reduction was one of the most frequently researched clinical interventions for cancer patients between 2000 and 2009 [156]. Previous research suggests that MBSR might also have applications to the treatment of insomnia [165,184,185], a condition that frequently co-occurs with distress in cancer patients [29]. The goal of this study was to determine whether MBSR produces results that are not significantly worse than CBT-I, an already established intervention, for the treatment of insomnia in cancer patients. When insomnia severity was assessed immediately after completing the treatments, CBT-I produced significantly better results than MBSR. The improvements observed in the CBT-I group were largely maintained, whereas the MBSR group continued to improve. This trend led to non-significant group differences at follow up.

A possible explanation for this result may reside in the nature of the treatments themselves. The techniques included in CBT-I are specific to sleep, relatively straightforward, reasonably easy to implement and produce effects quickly. Some of the recommendations (e.g. waking up at the same time every day), however, may be difficult for patients to maintain, resulting in a slight decay of treatment effect over time. Other CBT-I trials, including trials conducted with cancer patients, have reported similar

declines, [98,104,228]. As in our study, these declines tend to be small and final outcomes remain clinically improved over baseline.

In contrast to CBT-I, the MBSR program teaches participants how to reduce overall arousal and reactivity to stress without recommending specific modifications to sleep behaviors or beliefs. It focuses on awareness and acceptance, rather than change, which may potentially decrease sleep anxiety over time. Several possibilities exist to explain the salutary effect of MBSR on sleep including: reduced physiological arousal, decreased rumination and worry, less experiential avoidance, improved mood and perceived stress levels. Future research is required to elucidate the precise mechanisms by which mindfulness may positively impact sleep.

The CBT-I group maintained greater overall improvement in SOL, SE, subjective sleep quality, and dysfunctional sleep beliefs than the MBSR group. Progressive improvement over time was demonstrated in both groups on subjectively measured WASO and TST as well as symptoms of stress and mood disturbance. When effects were broken down across outcomes by assessment time, the CBT-I group frequently demonstrated the largest change between baseline and post program, whereas the MBSR produced continued or delayed effects.

This study is characterized by several strengths. An active comparison group was employed, patients were randomly assigned, both interventions are manualized, and only patients with clinical levels of insomnia were recruited. Despite solid study design and methodology, this study has limitations that must be considered. Firstly, when compared to PSG, actigraphy tends to underestimate time spent awake because people with insomnia may lie motionless awake in bed, which the actigraph scores as sleep [229,230]. So

not unexpectedly, there were notable discrepancies between the objective (actigraphy) and subjective (diaries) sleep outcomes, particularly for SOL and WASO. Patients reported an additional 15-30 minutes of sleep onset and 20-50 minutes more time awake on sleep diaries than what was recorded by actigraphy. However, subjective report of improvements in WASO, TST and SE were confirmed by the inclusion of actigraphy in both the PP and ITT analyses. This strengthens the confidence with which we can conclude that both interventions are able to produce beneficial sleep effects. Secondly, the majority of the final sample was women with breast cancer (49%), despite an attempt to recruit a generalizable sample of all cancer types. We know that women with breast cancer are particularly vulnerable to treatment related sleep disturbance [19]. As such, this may represent the provision of service to a particularly vulnerable population.

Lastly, this study employed a modified blind-to-treatment protocol, intended to reduce the selection bias that is frequently associated with trials of behavioral interventions. Patients were introduced to the study generally and then told only about the treatment they were assigned to. This design may have contributed to the significant attrition observed in the MBSR group. One of the criteria for inclusion was inexperience with MBSR. Because the MBSR program is readily available free of charge to all cancer patients at the TBCC, a number of potential participants were excluded as they had already taken the program (n=27). As such it may be less obvious to participants not already inclined to choose this intervention (those eligible for this study) how learning meditation and yoga could contribute to sleep improvements. Sidani and colleagues demonstrated that willingness to comply with treatment was the strongest predictor of treatment preference for different behavioral interventions in persons with chronic

insomnia [121]. Measurement of treatment preference or credibility was not included in our study, preventing the determination of whether this contributed to patient attrition. This does raise the question of whether it is desirable to blind participants to behavioral interventions, where personal preference for treatment is likely to play a significant role in treatment adherence and outcome.

Non-inferiority trials typically assess a new treatment to determine if it produces similar effects as an already established treatment with additional benefits, such as reducing cost or side effects. We hypothesized that MBSR may effectively address insomnia with the additional benefit of reducing cancer-related distress. While the results suggest that the insomnia benefits provided by MBSR are comparable to CBT-I at 5-month follow up, the two groups were not significantly different in terms of their ability to improve stress and mood outcomes. Future research might evaluate the impact of patient preference on outcomes and employ dismantling designs to isolate active treatment components.

Figure 5.1: Consort Diagram and Recruitment Flow Chart

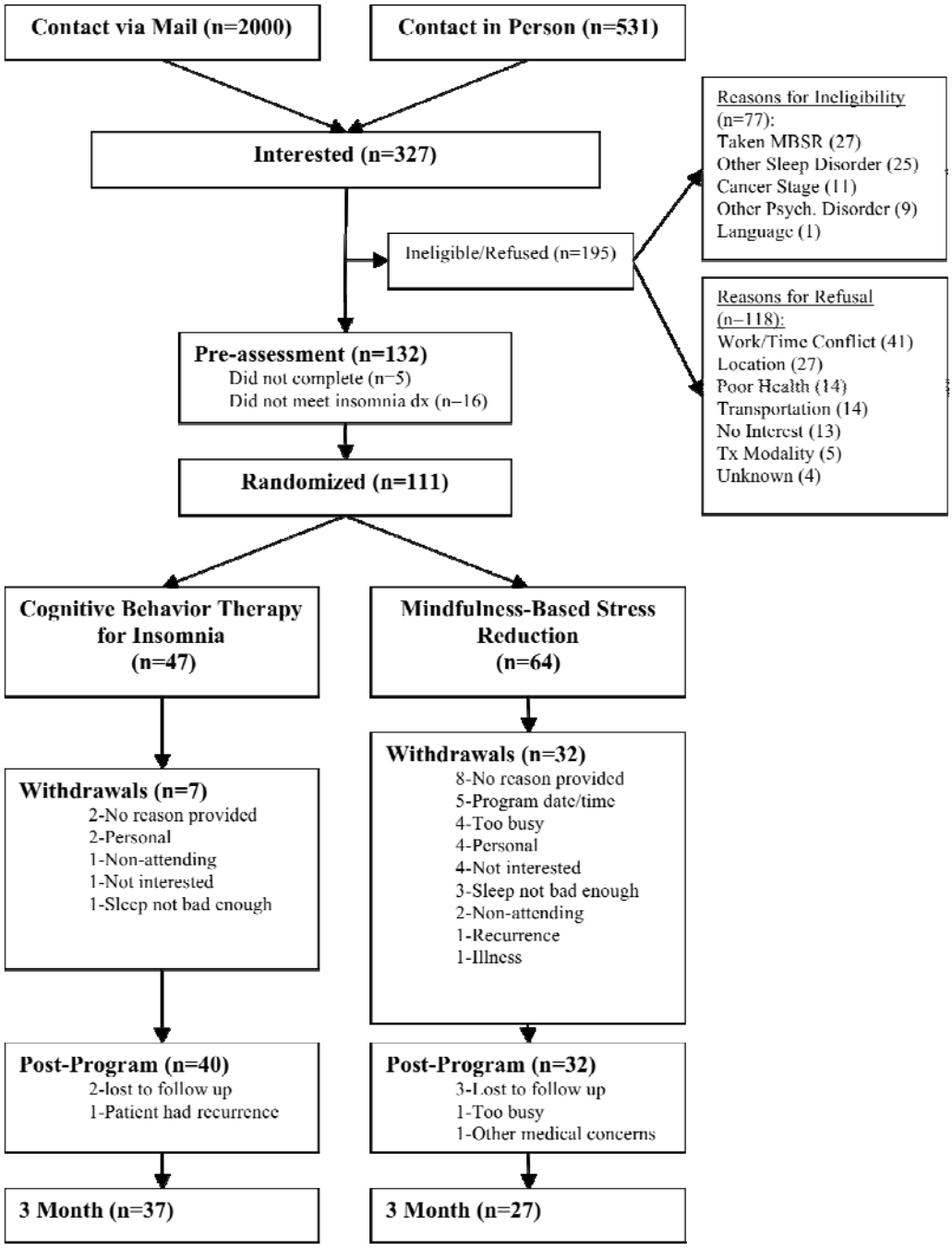


Figure 5.2: Non-inferiority Results at Post-Program and 3 Month Follow up

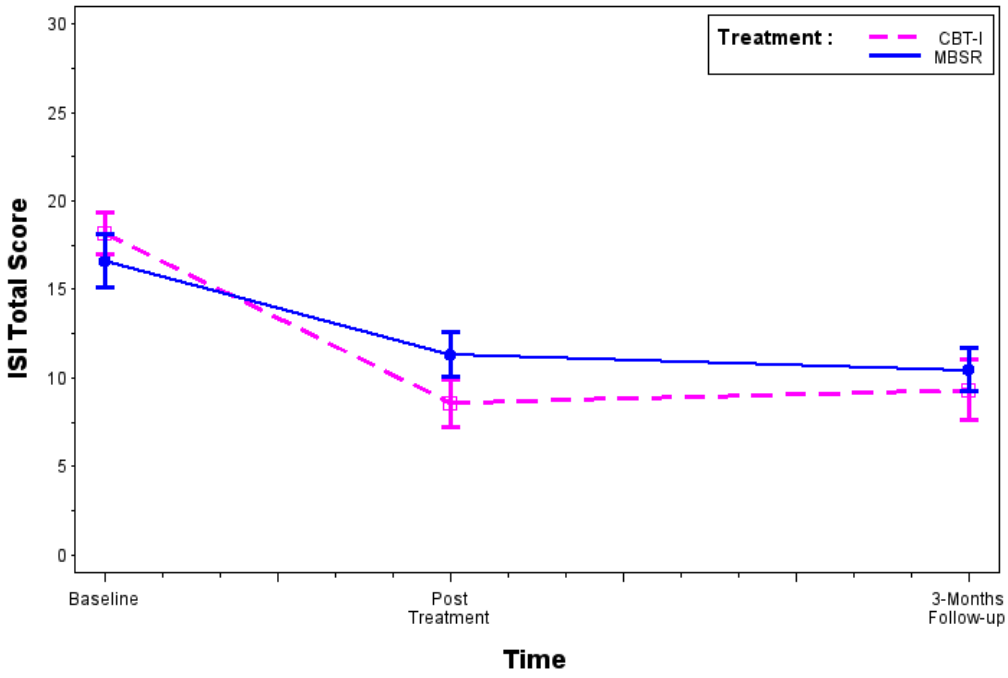
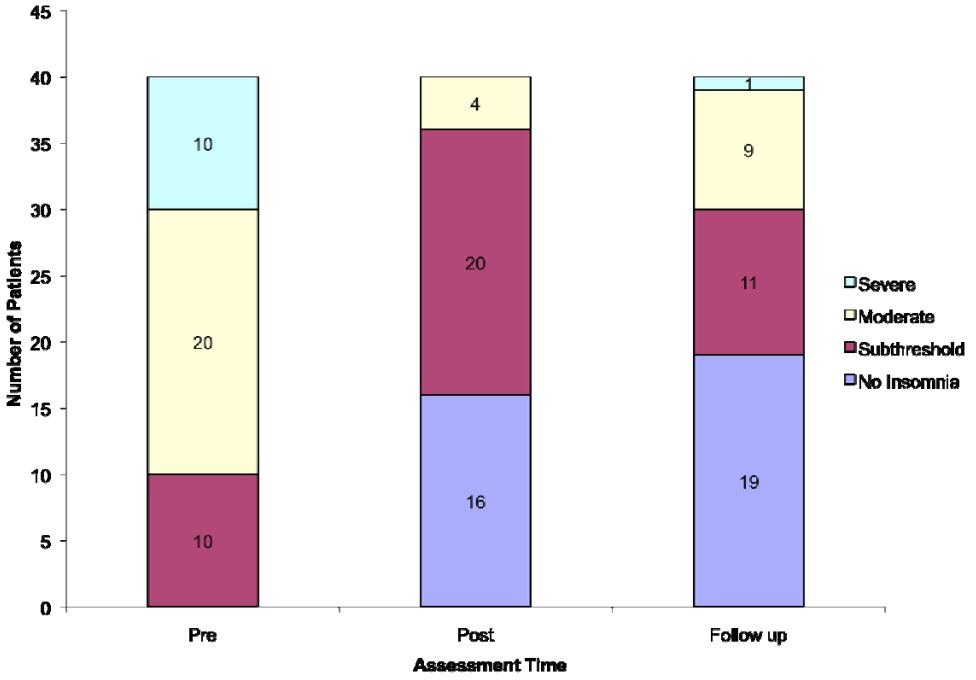


Figure 5.3: Clinical Significance of Insomnia Severity Changes in Per-Protocol Sample

A) CBT-I (n=40)



B) MBSR (n=32)

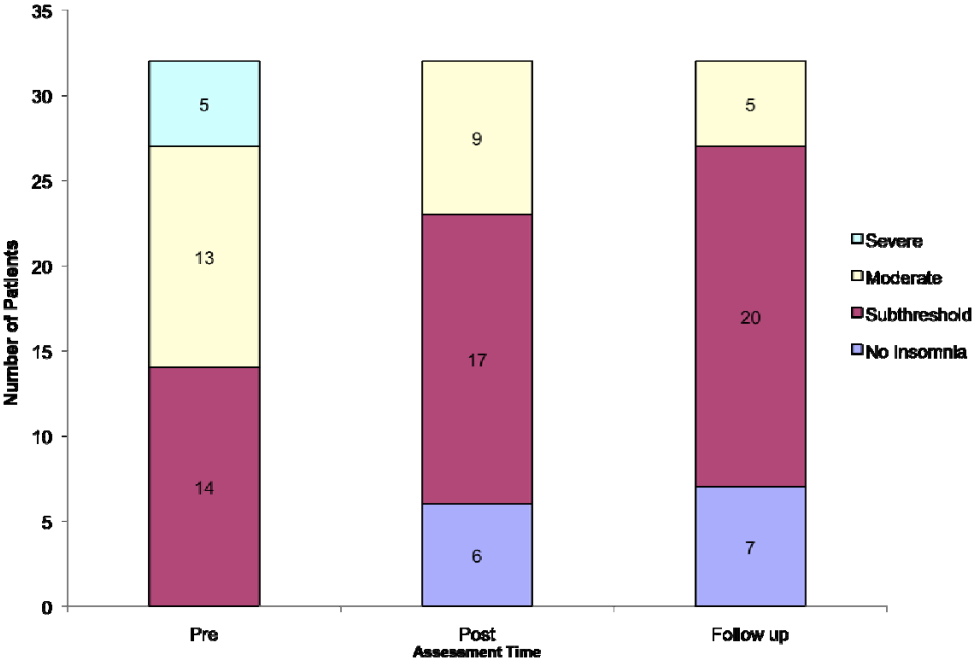


Table 5.1: Details of t-tests Comparing Completers (n=72) and Dropouts (n=39) in Overall Sample

		Completer (n=72) M (SD)	**Dropout (n=39)** M (SD)	***t* (*df*)**	**Sig**
Age		59.44 (11.44)	57.88 (10.89)	-.710 (2, 109)	.480
Sex	**Male**	20	11	.002	.962[a]
	Female	52	28	(1, 111)	
Education (yrs)		15.78 (3.56)	13.95 (3.19)	-2.681 (2, 109)	.008
Disease Duration (yrs)		3.21 (4.39)	3.14 (3.32)	-.087 (2, 109)	.931
Insomnia Duration (yrs)		6.71 (6.54)	7.75 (7.31)	.452 (2, 60)	.653
ISI Total		17.40 (4.10)	19.33 (3.94)	2.399 (2, 109)	.018
CSOSI Total		65.58 (27.04)	74.44 (38.50)	1.413 (2, 109)	.161
POMS Total		27.06 (22.59)	32.87 (29.46)	1.157 (2, 108)	.250
DBAS Total		5.34 (1.42)	5.70 (1.49)	1.291 (2, 109)	.200
PSQI Total		12.50 (3.41)	13.00 (3.86)	.703 (2, 109)	.483

[a] Chi Square test was performed.
Bonferonni correction p value = 0.005

Table 5.2: Demographic Characteristics of Per-Protocol Sample

	MBSR (n=32) Mean (SD) or n (%)	**CBT (n=40)** Mean (SD) or n (%)	***p value***	**Total (N=72)** Mean (SD) or n (%)
Age	60.33	58.73		59.44
SD	(12.21)	(10.46)		(11.21)
Range	36-87	36-88	.553	36-88
Education	15.77	15.75		15.78
SD	(2.91)	(4.02)		(3.56)
Range	11-25	11-33	.942	11-33
Sex				
Male	12 (38%)	8 (21%)		20 (28%)
Female	20 (62%)	32 (79%)	.099	52 (72%)
Employment				
Homemaker	2 (6%)	3 (8%)		5 (7%)
Full-time	11 (34%)	13 (33%)		24 (33%)
Part-time	3 (9%)	10 (25%)		13 (18%)
Retired	13 (41%)	12 (30%)		25 (35%)
Disabled	3 (9%)	2 (5%)	.477	5 (7%)
Ethnicity				
White/European	29 (91%)	38 (96%)		67 (93%)
Native/Aboriginal		1 (2%)		1 (1%)
Asian	3 (9%)			1 (1%)
Black		1 (2%)	.083	3 (4%)

* Percentages may not equal 100% because of rounding

Table 5.3: Disease, Treatment, and Insomnia Characteristics of Per-Protocol Sample

	MBSR (n=32) Mean (SD) or n (%)	**CBT (n=40)** Mean (SD) or n (%)	***p value***	**Total (N=72)** Mean (SD) or n (%)
Disease Duration (yrs)	3.19 (3.81)	3.23 (4.85)		3.21 (4.39)
Range	.17-19.90	.22-29.76	.970	.17-29.76
Insomnia Duration (yrs)	6.67 (6.72)	6.74 (6.52)		6.71 (6.54)
Range	.22-28.90	.39-24.82	.972	.22-.28.90
Cancer Location				
Breast	12 (38%)	23 (58%)		35 (49%)
Prostate	5 (16%)	3 (8%)		8 (11%)
Blood/Lymph	5 (15%)	3 (8%)		8 (11%)
Female Genitourinary	2 (6%)	4 (10%)		6 (8%)
Colon/Gastrointestinal	3 (9%)	2 (5%)		5 (7%)
Other	5 (15%)	5 (13%)	.479	10 (14%)
Previous Treatments				
Surgery	24 (75%)	35 (88%)		59 (82%)
Chemotherapy	15 (47%)	20 (50%)		35 (49%)
Radiation	13 (41%)	17 (43%)		30 (42%)
Hormonal	4 (13%)	6 (15%)	.993	10 (14%)
Current Treatments				
Hormonal	6 (19%)	9 (23%)		15 (21%)
Sedatives/Hypnotics	10 (31%)	12 (30%)		22 (31%)
Anxiolytics	2 (6%)	9 (23%)		11 (15%)
Antidepressants	4 (13%)	11 (28%)	.422	15 (21%)
Insomnia Trajectory				
Before cancer-same	7 (22%)	3 (8%)		10 (14%)
Before cancer-worse	15 (47%)	19 (48%)		34 (47%)
Began with treatment	2 (6%)	9 (23%)		11 (15%)
Began after treatment	2 (6%)	1 (3%)		3 (4%)
Missing	6 (19%)	8 (20%)	.169	14 (19%)
Insomnia Subtype				
Sleep Onset	1 (3%)	5 (13%)		6 (8%)
Sleep Maintenance	16 (50%)	9 (23%)		25 (34%)
Mixed	15 (47%)	26 (65%)	.036	41 (57%)

* Percentages may not equal 100% because of rounding

Table 5.4: Non-Inferiority Analysis of ISI Total Scores

	MBSR (n=32) EMMean (SE)	**CBT (n=40)** EMMean (SE)	**Difference** [a] (upper 95% CI) [Two-sided 95% CI]	**df**	**p value**
Per-Protocol					
Pre-Program (Baseline)	16.34 (0.754)	18.25 (0.674)	-1.91 (3.579) [-.091, 3.904]	1, 159.582	0.061
Post-Program (2 months)	11.31 (0.754)	8.70 (0.674)	2.61 (4.286) [.615, 4.610]	1, 159.582	0.011
Follow Up (5 months)	10.20 (0.808)	9.10 (0.704)	1.10 (2.870) [-1.017, 3.213]	1, 172.094	0.307
	MBSR (n=64) EMMean (SE)	**CBT (n=47)** EMMean (SE)	**Difference** [a] (upper 95% CI) [Two-sided 95% CI]	**df**	**p value**
Intent-to-Treat					
Pre-Program (Baseline)	18.23 (0.534)	17.87 (0.623)	0.36 (1.718) [-1.256, 1.980]	1, 205.610	0.660
Post-Program (2 months)	11.90 (0.722)	8.49 (0.655)	3.41 (5.020) [1.489, 5.331]	1, 231.337	0.001
Follow Up (5 months)	10.83 (0.789)	9.16 (0.683)	1.67 (3.388) [-0.391, 3.721]	1, 239.633	0.112

[a] Difference = Mean MBSR minus mean CBT.

[b] Non-inferiority is concluded if the upper 95% confidence limit is below margin of 4 and the p-value is greater than the given Bonferonni significance criterion.

Table 5.5: Statistical details of the linear mixed model analyses assessing the effect of group and time on sleep outcomes for the per-protocol sample (CBT-I n = 40; MBSR n=32)

		Estimated Marginal Group Mean (SE)			Effect Size	LMM statistical tests: F (df) [p]		
		Assessment Time			Cohen's d	(Type III tests of fixed effects)		
Outcome	Group	Baseline	Post Program (2 mo)	Follow up (5 mo)	Baseline-5mo	Group Effect	Time effect	Group*Time Interaction
Sleep Diary								
SOL (min)	CBT-I	45.02 (3.256)	24.39 (3.287)	22.70 (3.354)	-1.08	.910 (1, 67.578) [.343]	22.906 (2,129.009) [.001]*	5.663 (2,129.009) [.004]*
	MBSR	40.15 (3.641)	37.21 (3.641)	25.87 (4.004)	-0.65			
WASO (min)	CBT-I	70.51 (5.847)	34.28 (5.892)	33.77 (5.990)	-0.99	4.913 (1, 70.992) [.030]*	42.993 (2, 131.684) [.001]*	.335 (2, 131.684) [.716]
	MBSR	83.97 (6.537)	54.46 (6.537)	49.31 (7.076)	-0.91			
TST (hrs)	CBT-I	6.29 (.166)	6.51 (.167)	6.89 (.169)	0.57	.500 (1, 70.677) [.482]	15.433 (2, 131.261) [.001]*	.412 (2, 131.261) [.663]
	MBSR	6.43 (.185)	6.55 (.185)	7.16 (.200)	0.68			
SE (%)	CBT-I	73.49 (1.536)	85.39 (1.549)	85.31 (1.576)	1.22	5.809 (1, 71.635) [.019]*	40.191 (2, 132.499) [.001]*	4.998 (2, 132.499) [.008]*
	MBSR	72.67 (1.717)	77.37 (1.717)	80.32 (1.868)	0.77			
Actigraphy								
SOL (min)	CBT-I	11.88 (1.811)	7.12 (1.811)	7.34 (1.846)	-0.40	4.919 (1, 69.158) [.030]*	1.732 (2, 137.698) [.181]	2.271 (2, 137.698) [.107]
	MBSR	13.30 (2.024)	14.78 (2.024)	12.37 (2.024)	-0.08			
WASO (min)	CBT-I	110.46 (7.165)	85.74 (7.165)	82.30 (7.397)	-0.62	.056 (1, 70,435) [.814]	10.237 (2, 130.045) [.001]*	1.294 (2, 130.045) [.278]
	MBSR	103.84 (8.011)	95.02 (8.011)	86.13 (8.765)	-0.38			
TST (min)	CBT-I	393.31 (9.68)	369.79 (9.68)	399.23 (9.948)	0.10	9.525 (1, 69.393) [.003]*	11.405 (2, 128.667) [.001]*	.410 (2, 128.667) [.665]
	MBSR	426.09 (10.82)	410.73 (10.82)	443.45 (11.70)	0.28			
SE (%)	CBT-I	77.56 (1.366)	81.00 (1.366)	82.38 (1.407)	0.56	.113 (1, 70.594) [.738]	6.608 (2, 132.843) [.002]*	1.836 (2, 132.843) [.164]
	MBSR	80.15 (1.527)	80.20 (1.527)	82.37 (1.604)	0.26			

Table 5.6: Statistical details of the linear mixed model analyses assessing the effect of group and time on sleep outcomes for the intent to treat sample (CBT-I n=47; MBSR n=64)

		Estimated Marginal Group Mean (SE)			Effect Size	LMM statistical tests: F (df) [p]		
		Assessment Time			Cohen's d	(type III tests of fixed effects)		
Outcome	Group	Baseline	Post Program (2 mo)	Follow up (5 mo)	Baseline-5mo	Group Effect	Time effect	Group*Time Interaction
Sleep Diary								
SOL (min)	CBT-I	45.14 (4.251)	24.40 (4.403)	22.71 (4.454)	-0.76	4.855 (1, 89.514) [.030]*	27.624 (2, 120.766) [.001]*	4.158 (2, 120.766) [.018]*
	MBSR	49.93 (3.642)	44.03 (4.436)	33.18 (4.816)	-0.49			
WASO (min)	CBT-I	66.07 (6.328)	30.22 (6.583)	30.57 (6.670)	-0.81	2.906 (1, 98.805) [.091]	39.596 (2, 132.689) [.001]*	.724 (2, 132.689) [.487]
	MBSR	74.68 (5.423)	48.73 (6.738)	43.13 (7.371)	-0.61			
TST (hrs)	CBT-I	6.34 (.162)	6.55 (.169)	6.91 (.171)	0.51	.925 (1, 107.251) [.338]	18.501 (2, 147.782) [.001]*	.834 (2, 147.782) [.436]
	MBSR	6.05 (.175)	6.28 (.175)	6.90 (.192)	0.58			
SE (%)	CBT-I	74.13 (1.551)	86.02 (1.623)	85.90 (1.648)	1.09	13.544 (1, 102.637) [.001]*	47.990 (2, 140.990) [.001]*	4.197 (2, 140.990) [.017]*
	MBSR	70.45 (1.329)	75.97 (1.694)	79.03 (1.872)	0.67			
Actigraphy								
SOL (min)	CBT-I	11.85 (1.706)	7.10 (1.787)	7.20 (1.820)	-0.39	6.244 (1, 157.181) [.014]*	2.205 (2, 157.181) [.114]	2.318 (2, 157.181) [.102]
	MBSR	13.53 (1.474)	14.67 (1.944)	12.41 (1.969)	-0.08			
WASO (min)	CBT-I	109.29 (7.077)	85.03 (7.330)	80.74 (7.538)	-0.58	.319 (1, 103.524) [.573]	12.213 (2, 138.263) [.001]*	1.129 (2, 138.263) [.326]
	MBSR	106.35 (6.112)	96.06 (7.628)	87.31 (8.495)	-0.32			
TST (min)	CBT-I	393.53 (10.24)	368.42 (10.53)	397.54 (10.03)	0.06	3.360 (1, 103.118) [.070]	11.317 (2, 133.592) [.001]*	1.239 (2, 133.592) [.293]
	MBSR	406.02 (8.847)	395.67 (10.60)	428.42 (11.59)	0.27			
SE (%)	CBT-I	77.79 (1.306)	81.07 (1.353)	82.57 (1.391)	0.52	.071 (1, 105.446) [.071]	8.369 (2, 143.794) [.001]*	1.237 (2, 143.794) [.293]
	MBSR	78.92 (1.128)	79.58 (1.406)	81.66 (1.502)	0.26			

Table 5.7: Statistical details of the linear mixed model analyses assessing the effect of group and time on psychological outcomes for the per-protocol sample (CBT-I n = 40; MBSR n=32)

		Estimated Marginal Group Mean (SE) Assessment Time			Effect Size Cohen's d	LMM statistical tests: F (df) [p] (type III tests of fixed effects)		
Outcome	Group	Baseline	Post Program (2 mo)	Follow up (5 mo)	Baseline-5mo	Group Effect	Time effect	Group*Time Interaction
Insomnia Severity (ISI Total)	CBT-I	18.25 (.674)	8.70 (.674)	9.10 (.704)	-2.13	.599 (1, 68.992) [.441]	111.043 (2, 132.406) [.001]*	8.113 (2, 132.406) [.001]*
	MBSR	16.34 (.754)	11.31 (.754)	10.20 (.808)	-1.41			
Sleep Quality (PSQI Total)	CBT-I	13.35 (.505)	7.83 (.505)	7.77 (.516)	-1.75	.445 (1, 70.056) [.507]	80.602 (2, 133.187) [.001]*	19.040 (2, 133.187) [.001]*
	MBSR	11.44 (.565)	10.00 (.593)	8.81 (.593)	-0.82			
Stress Symptoms (C-SOSI Total)	CBT-I	69.70 (3.84)	52.18 (3.84)	49.76 (3.899)	-0.83	1.110 (1, 69.578) [.296]	35.451 (2, 132.289) [.001]*	1.117 (2, 132.289) [.330]
	MBSR	60.44 (4.29)	48.44 (4.29)	46.29 (4.445)	-0.58			
Mood Disturbance (POMS-SF Total)	CBT-I	29.48 (3.21)	13.55 (3.21)	13.21 (3.356)	-0.79	.097 (1, 69.164) [.756]	18.364 (2, 130.525) [.001]*	1.023 (2, 130.525) [.362]
	MBSR	24.14 (3.63)	14.03 (3.58)	14.36 (3.805)	-0.47			
Dysfunctional Sleep Beliefs (DBAS-16 Total)	CBT-I	5.54 (.229)	3.09 (.229)	3.36 (.235)	-1.51	5.209 (1, 70.695) [.025]	48.373 (2, 133.529) [.001]*	14.926 (2, 133.529) [.001]*
	MBSR	5.08 (.256)	4.40 (.259)	4.43 (.272)	-0.44			

Table 5.8: Statistical details of the linear mixed model analyses assessing the effect of group and time on psychological outcomes for the intent to treat sample (CBT-I n=47; MBSR n=64)

		Estimated Marginal Group Mean (SE)			Effect Size	LMM statistical tests: F (df) [p]		
		Assessment Time			Cohen's d	(type III tests of fixed effects)		
Outcome	Group	Baseline	Post Program (2 mo)	Follow up (5 mo)	Baseline-5mo	Group Effect	Time effect	Group*Time Interaction
Insomnia Severity (ISI Total)	CBT-I	17.87 (.623)	8.49 (.655)	9.16 (.683)	-1.96	6.953 (1, 103.422) [.010]*	145.915 (2, 158.269) [.001]*	4.010 (2, 158.269) [.020]*
	MBSR	18.23 (.534)	11.90 (.722)	10.83 (.789)	-1.38			
Sleep Quality (PSQI Total)	CBT-I	12.83 (.497)	7.53 (.497)	7.46 (.525)	-1.55	7.906 (1, 104.001) [.006]*	89.450 (2, 142.435) [.001]*	14.885 (2, 142.435) [.001]*
	MBSR	12.56 (.426)	10.80 (.533)	9.56 (.570)	-0.75			
Stress Symptoms (C-SOSI Total)	CBT-I	66.85 (4.303)	49.51 (4.392)	47.83 (4.44)	-0.64	.941 (1, 103.854) [.334]	40.295 (2, 135.290) [.001]*	.372 (2, 135.290) [.690]
	MBSR	70.05 (3.687)	56.01 (4.252)	54.04 (4.44)	-0.49			
Mood Disturbance (POMS-SF Total)	CBT-I	28.85 (3.332)	13.34 (3.464)	14.07 (3.60)	-0.63	.386 (1, 94.785) [.536]	21.746 (2, 134.077) [.001]*	.242 (2, 134.077) [.785]
	MBSR	29.41 (2.871)	16.92 (3.654)	17.36 (3.92)	-0.44			
Dysfunctional Sleep Beliefs (DBAS-16 Total)	CBT-I	5.59 (.214)	3.09 (.223)	3.32 (.229)	-1.51	10.804 (1, 107.014) [.001]*	65.290 (2, 151.170) [.001]*	15.129 (2, 151.170) [.001]*
	MBSR	5.38 (.183)	4.52 (.242)	4.57 (.258)	-0.46			

CHAPTER 6: ASSOCIATIONS BETWEEN DISPOSITIONAL MINDFULNESS, INSOMNIA, SLEEP QUALITY AND DYSFUNCTIONAL SLEEP BELIEFS IN POST-TREATMENT CANCER PATIENTS

6.0 Abstract

Objectives. A cancer diagnosis can be stressful regardless of diagnosis, resulting in disproportionate rates of sleep and mood disorders. Dispositional mindfulness, or the tendency to be more mindful in daily life, has been associated with better psychological functioning and reduced overall distress. This study investigated the degree to which dispositional mindfulness was associated with sleep disturbances in cancer patients with insomnia, adjusting for the influence of stress levels and mood disturbance.

Design. This cross-sectional study examined the associations between facets of mindfulness, insomnia severity, sleep quality, dysfunctional beliefs and attitudes about sleep, symptoms of stress and mood disturbance.

Methods. Participants (N = 111) were adults who had been previously treated for cancer and currently met diagnostic criteria for insomnia. Separate hierarchical regressions were performed to explore the impact of mindfulness facets (acting with awareness, non-judging and non-reacting) on levels of insomnia severity, sleep quality and dysfunctional beliefs and attitudes about sleep. Symptoms of stress and mood disturbance were considered covariates in all of the regression equations.

Results. Higher levels of acting with awareness, non-judging and non-reacting were associated with better sleep and psychological outcomes. However, mindfulness was not predictive of fewer sleep disturbances above and beyond the contribution of symptoms of stress and mood disturbance.

Conclusions. It is important to address mood symptoms and symptoms of stress as predictors of sleep disturbance in cancer patients. Individuals with higher levels of dispositional mindfulness may be less likely to experience sleeping difficulty.

6.1 Background

Definition and Cultivation of Mindfulness

Mindfulness has been defined in a variety of ways, and the definition of the concept is a topic of active discussion [124,231,232]. One of the most commonly cited definitions describes mindfulness as "awareness that arises through paying attention on purpose, in the present moment, non-judgmentally" [122]. Some theories of mindfulness suggest that it represents a dispositional characteristic (trait) that exists naturally and varies within the population, as well as an attribute of consciousness (state) that can be developed with practice and mental training [233-235]. Shapiro and Carlson suggest that mindfulness can be broken down into "big M" and "little m" categories [236]. "Big M" mindfulness refers to mindful awareness, described as a way of being and relating to experiences. "Little m" mindfulness refers to the practice of consciously developing skills in mindfulness. The "big M' and "little m" designations roughly parallel the state and trait dichotomy, but recognize that mindfulness may be better described to exist on a continuum rather than an all or nothing quality

Several elements have been proposed as constituents of the construct of mindfulness including: noticing one's internal and external experience; describing one's internal experience with words; being aware of one's actions in the present moment; taking a non evaluative stance toward one's feelings and thoughts; and allowing these thoughts and feelings to come and go without attachment to them [201]. Increasing the objectivity through which internal experience is viewed is intended to change one's relationship to the thoughts, as opposed to changing the thoughts themselves [177]. Shapiro, Carlson, Astin and Freedman suggest that mindfulness may encourage self-regulation,

values clarification, cognitive, emotional and behavioral flexibility and tolerance for difficult emotional states [177].

The tendency to be more mindful in daily life has been associated with better psychological functioning and reduced overall distress [235,237-241]. Mindfulness can be developed through formal and informal mindfulness mediation practice and has been integrated into several structured interventions including Mindfulness-Based Stress Reduction (MBSR) [122], Mindfulness-Based Cognitive Therapy [242], Dialectical Behavior Therapy [243], Acceptance and Commitment Therapy [244] and Mindfulness-Based Relapse Prevention [245]. Cultivating mindfulness has been described as a potentially effective antidote to many common forms of mental stress that involve tendencies to react to distressing internal experience by avoiding, suppressing or over-engaging in emotions [152]. Decreases in ineffectual emotion regulation strategies such as rumination [175,178], worry [176], and experiential avoidance [130,176] have been identified as potential mechanisms for how improved mindfulness leads to better overall psychological functioning.

In a sample of 268 cancer patients participating in a MBSR program, improvements in overall mindfulness accounted for 21% and 14% of the variance in improved mood and symptoms of stress [246]. When specific components of mindfulness were examined, the facets of non-judging of inner experience and acting with awareness were significantly related to improved psychological functioning. However, it has yet to be established what impact dispositional mindfulness may have on initial symptom severity in cancer patients, prior to any type of mindfulness training.

Insomnia, cancer and mindfulness

Stressful life events are well established to coincide with the onset of insomnia [56,58,59,64], and cancer is one of the most stressful life events a person can encounter, regardless of prognosis. Not surprisingly, the prevalence of insomnia in individuals with cancer is three times that of the general population [22]. Individuals with cancer are also disproportionately affected by mood disorders such as depression and anxiety [247], placing them at additional risk for sleep disturbances [248]. Preliminary research has suggested that MBSR may have a positive impact on sleep quality in individuals with cancer [165,184,185]. In a nonrandomized sample of 63 heterogeneous cancer patients, MBSR participation was related to a significant reduction in total sleep disturbance and improved sleep quality. However, it is unknown whether the observed sleep benefits were related to an increase in mindfulness or the ability of the MBSR program to reduce stress and improve mood.

The primary objective of the present study was to investigate the degree to which dispositional mindfulness was associated with insomnia severity, sleep quality, dysfunctional beliefs and attitudes about sleep, symptoms of stress and mood disturbance in cancer patients with insomnia. Secondly, considering the established relationships between perceived stress, mood disorders and insomnia, we examined whether dispositional mindfulness accounted for variance in insomnia severity, sleep quality, and dysfunctional beliefs and attitudes about sleep above and beyond the influence of levels of stress and mood disturbance.

6.2 Methods

Participants and Procedures

This study included baseline data from 111 participants recruited for a separate study comparing the effect of MBSR to Cognitive-Behavioral Therapy for insomnia [223]. Ethical approval was obtained from the Conjoint Health Research Ethics Board of the University of Calgary/Alberta Health Services. Patients were eligible for study inclusion if they met the following criteria: over the age of 18; able to speak and read English; diagnosed with non-metastatic cancer and finished chemotherapy or radiation at least one-month prior to study participation. They were required to meet a diagnosis of insomnia defined as: 1) Problems initiating or maintaining sleep with a sleep onset of greater than 30 minutes or nocturnal awakenings exceeding 30 minutes and a sleep efficiency of less than 85%; 2) The difficulty must cause clinically significant impairment in one or more areas (i.e. occupational, social, physical); and 3) The frequency of this disturbance must exceed 3 days per week and have been present for at least 1 month.

Patients were ineligible if they had another sleep or psychological disorder requiring alternate treatment or had previous experience with the practice of mindfulness. Patients were primarily recruited from outpatient oncology departments by self or physician referral, although the study was advertised through several other methods including: the distribution of posters and pamphlets throughout areas frequented by individuals diagnosed with cancer; television, radio, visual and print media advertising; and mailed invitations to eligible patients through the provincial cancer registry. Individuals were recruited to participate in a study investigating non-medication based treatments for insomnia and had not received specific details about the treatment programs at the time of their baseline assessment.

Measures

Each participant completed a form collecting information on demographic, disease and insomnia characteristics. Permission was obtained to access medical records to verify disease and treatment details.

The Insomnia Severity Index (ISI) is a 7 item screening measure of subjective insomnia symptoms, the consequences of insomnia, and the degree of distress elicited. Each item is rated on a 0-4 scale, with higher scores indicating more severe insomnia. The total score ranges from 0 to 28. The recommended cutoffs are: 0-7 no clinically significant insomnia; 8-14 subthreshold insomnia; 15-21 moderate clinical insomnia, and; 22-28 severe clinical insomnia. The ISI has established adequate concurrent and predictive validity with sleep diaries and PSG, and is sensitive to changes. Cronbach's alpha coefficients ranged from 0.76-0.78. The ISI has been validated for use in cancer patients [214]. Further evaluation has established a cutoff score of 10 to be optimal for sensitivity and specificity to detect cases [202].

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of sleep disturbance in the previous month [198]. Higher scores indicate the presence of sleep disturbances. A clinical cutoff of 5 was recommended to distinguish good sleepers from those with significant sleep disturbance. However, a cutoff of 8 has been recommended to distinguish poor sleep in clinical populations [36]. Construct validity was established and Cronbach's alpha values ranged from 0.70 to 0.78. The PSQI has been validated for use in individuals with cancer [249].

The Five Facet Mindfulness Questionnaire (FFMQ) is a 39 item self-report measure of the tendency to mindful in daily life [201]. Items are rated on a 5-point Likert scale with higher scores indicating more mindfulness. The FFMQ summarizes five

elements, or facets, important to the experience and development of mindfulness. These include: observing, describing, acting with awareness, non-judging and non-reacting. The five facets have demonstrated acceptable internal consistency, with alpha coefficients ranging from 0.75 to 0.91 [201]. There appears to be a differential response between individuals with or without meditation experience to the observe facet, which has been positively associated with psychological symptoms in non-meditators [201,250]. The sensitivity of the FFMQ to measure changes in mindfulness resulting from MBSR participation has been demonstrated in individuals with and without cancer [130,246,251].

The Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) scale is a 16-item self-report measure of the extent to which individuals endorse unhelpful sleep beliefs in the following areas: consequences of insomnia, worry about sleep, sleep expectations and medication. [74]. The DBAS-16 is an abbreviated version of the original 30-item questionnaire [216]. Items are rated on a 0-10 Likert type scale, with higher scores indicating a stronger endorsement of the dysfunctional belief. Cronbach alpha values of 0.77 and 0.79 demonstrate acceptable internal consistency for clinical and research samples. Adequate convergent and discriminant validity has been established [74]. A recommended clinical cutoff of >3.8 on the DBAS-16 has been shown to provide maximum sensitivity and specificity [252].

The Profile of Mood States-Short Form (POMS-SF) is a 37-item measure of distinct mood states [226] that was shortened from the original 65-item version [218]. The POMS has been validated for use in individuals with cancer [200]. Response items range from ‘not at all’ to ‘extremely’ with higher scores indicating greater mood disturbance. A total score is produced, measuring overall levels of tension-anxiety, depression-dejection,

anger-hostility, fatigue-inertia, and confusion-bewilderment. Cronbach's alphas ranged from 0.78 to 0.91. Convergent and discriminant validity has been established.

The Calgary Symptoms of Stress Inventory (C-SOSI) is a 56-item questionnaire assessing psychological and physiological responses to stress [199]. It is an abbreviated version of the original 94-item measure [217]. Items are rated on 5-point Likert rating scale from 0-4 with higher scores indicating greater stress symptomotology. It produces a total score, which measures the combined impact of depression, anger, muscle tension, cardiopulmonary arousal, sympathetic arousal, neurological/GI, cognitive disorganization and upper respiratory symptoms. Convergent and discriminant validity has been established with Cronbach's alpha coefficients ranging from 0.80 to 0.95. It has been validated for use in individuals with cancer [199].

Analysis

Previous research has established that the mindfulness facets of acting with awareness, non-judging and non-reacting have stronger associations to psychological variables than the facets of observing and describing [237,241]. As such, it was decided *a priori* to include acting with awareness, non-judging and non-reacting in the regression models. Separate hierarchical regressions were performed to explore the impact of these facets on levels of insomnia severity, sleep quality and dysfunctional beliefs and attitudes about sleep. To adjust for variables with well-established associations with insomnia, symptoms of stress and mood disturbance were considered covariates in all of the equations.

6.3 Results

Demographics are presented in Table 6.1. The sample was comprised of 31 men and 80 women, totaling 111 individuals. The mean age for the group was 59, with an age range of 35-88. Two-thirds of the participants were married (65%) and the sample had a mean of 15 years education. The sample consisted primarily of individuals with breast (48%) and prostate (11%) cancer, but a variety of other diagnoses were also well represented. Patients had been diagnosed with cancer approximately 3 years prior to study participation. Most of the patients had difficulty both with initiating and maintaining sleep, with the difficulty beginning an average of 6.88 years prior.

Participants were categorized by their responses on the ISI and PSQI (Figure 6.1). Of the 111 participants, 26 (23%) met the cutoff for severe insomnia, 55 (50%) for moderate insomnia and 30 (27%) for sub-threshold insomnia. Higher scores on the PSQI indicate worse sleep quality. When broken down into subunits of 5, 19 (17%) individuals scored in the 5-9 range, 56 (51%) in the 10-14 range and 36 (32%) in the 15-20 range.

Correlations between insomnia severity, sleep quality, dysfunctional beliefs and attitudes about sleep, mindfulness, stress and mood disturbance are presented in Table 6.2. Acting with awareness was associated with less severe insomnia (r = -.280), better sleep quality (r = -.217) and less dysfunctional sleep beliefs (r = -.267), symptoms of stress (r = -.470) and mood disturbance (r = -.499). Not judging one's experience was associated with better sleep quality (r = -.243), and fewer dysfunctional beliefs about sleep (r = -.309), symptoms of stress (r = -.452), and mood disturbance. Finally, not reacting automatically was associated with better sleep quality (r = -.204) and less mood

disturbance (r = -.225). The describe and observe facets were not significantly related to any of the measured outcomes.

The hierarchical regressions are presented in Table 6.3. Pairwise plots of residuals of predicted values were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity prior to all of the regression analyses

Insomnia Severity

Symptoms of stress and mood disturbance were entered at Step 1, explaining 24% of the variance in insomnia severity (F (2, 108) = 16.924, p < .001). Acting with awareness, non-judging and non-reacting were entered at Step 2. These predictors did not account for a significant increase in the amount of variance (R^2 change = 0.026; F change (3, 103) = 1.241, p = .299). In the full model including the two covariates and three predictors, only mood disturbance accounted for significant variance in insomnia severity and contributed the most unique variance to the total R^2 (17%). Symptoms of stress (p = .056) and non-judging (p = .065) approached statistical significance.

Sleep Quality

When entered at Step 1, symptoms of stress and mood disturbance explained 31% of the variance in sleep quality (F (2, 108) = 23.714, p < .001). Acting with awareness, non-judging and non-reacting entered at Step 2 did not account for a significant increase in the amount of variance (R^2 change = 0.013; F change (3, 103) = 0.651, p = .584). In the model with all predictors entered, stress symptomotology was the only significant predictor of sleep disturbance and contributed the most unique variance to the total R^2 (29%).

Dysfunctional Beliefs and Attitudes about Sleep

When entered in Step 1, symptoms of stress and mood disturbance explained 18% of the variance in dysfunctional beliefs and attitudes about sleep (F (2, 108) = 11.961, $p <$ .001). Acting with awareness, non-judging and non-reacting did not account for a significant increase in the amount of variance when entered at Step 2 (R^2 change = 0.028; F change (3, 103) = 1.220, p = .306). Although not statistically significant, in the model with all predictors entered, non-judging contributed the most unique variance to the total R^2 (14%).

6.4 Discussion

This study was a cross-sectional examination of the association between dispositional mindfulness, insomnia severity, sleep quality and dysfunctional sleep beliefs in post-treatment cancer patients with clinical levels of insomnia. The only mindfulness facet significantly related to insomnia severity was acting with awareness; those who reported acting with more awareness had less severe insomnia symptoms. Higher levels of acting with awareness were also significantly related to less sleep disturbance, dysfunctional sleep beliefs, symptoms of stress and negative mood states. Acting with awareness can be contrasted with behaving mechanically while attention is focused elsewhere; a key component of mindfulness, and according to some researchers the central defining core of the mindfulness concept [235]. Being more aware of internal experiences may be required before one is able to modify subsequent thoughts or behavior and can be thought of as a foundational aspect of mindfulness.

Non-judging, described as taking a non-evaluative stance towards thoughts and feelings, was also significantly related to lower levels of sleep difficulty, stress symptoms

and mood disturbances. Of particular note, non-judging was associated with fewer dysfunctional beliefs and attitudes about sleep. Morin, Blais and Savard have demonstrated that a reduction in dysfunctional beliefs about sleep is related to improved insomnia severity, and suggested that addressing problematic sleep beliefs is required for successful treatment outcome [79]. Hence, the cultivation of a non-judging attitude may be one route to improved sleep through the reduction of dysfunctional sleep attitudes and beliefs.

Non-reacting was related to less sleep difficulty and mood disturbance. Allowing thoughts and feelings to come and go, without engaging in efforts to somehow change the experience, may be an important component of the sleep experience. Lundt suggests that sleep is facilitated by cognitive deactivation and a reduction in the amount of controlled and strategic information processing, paralleling physiologic deactivation characterized by a decrease in muscle tone and a slowing of the cardiovascular and respiratory systems [166]. In this way, mindfulness may help facilitate cognitive deactivation and physiological dearousal by allowing the individual to disengage from and/or not react to their daily concerns and strivings, particularly as they prepare for sleep.

Our study did not demonstrate significant associations between mindfulness facets of observing and describing and psychological outcomes, which is consistent with previous research [237,241]. Baer and colleagues have demonstrated a stronger associations between the observe facet and psychological outcomes in individuals with meditation experience, suggesting that this facet may only develop after meditation practice [250]. Potentially, the interpretation of the items on the *observe* and *describe* facets may require a familiarity with mindfulness. Items such as "When I am walking, I deliberately notice

the sensations of my body moving" (observe facet) and "I'm good at thinking of words to express my perceptions, such as how things taste, smell or sound" (describe facet) may not be easily understood by someone who is unfamiliar with the language of mindfulness training.

Furthering the debate on the definition and measurement of mindfulness, Grossman recommends that assessment of mindfulness in the general population employ measures to assess hypothesized components or products of mindfulness (i.e. bare attention, acceptance, self-compassion) as opposed to the overall construct of mindfulness, and employ qualitative or interview based methods to assess the more subtle aspects of mindfulness [232]. Alternately, MacCoon and colleagues published preliminary support for using a thermal pain test as an experimental paradigm of mindfulness in order to accurately measure this construct behaviorally in meditation-naive samples [154].

Previous research has established that increases in mindfulness - associated with participation in a mindfulness-training program such as MBSR - are related to improved psychological outcomes in cancer patients [246,251,253] and the general population [235,237-239,241]. This is the first study to examine relationships between dispositional mindfulness, insomnia severity, sleep quality, and dysfunctional beliefs and attitudes about sleep in cancer patients after accounting for the influence of levels of stress and mood disturbance, factors known to predict insomnia.

We did not find incremental support for the role of mindfulness on sleep measures above and beyond the contribution provided by symptoms of stress and mood disturbance, which were each associated with mindfulness scores. This highlights the importance of addressing mood symptoms in individuals with insomnia and symptoms of

stress as a predictor of sleep disturbance. However, this sample was selected based on the presence of clinical levels of insomnia, sleep disturbance, and dysfunctional sleep beliefs, and had not expressed an explicit interest in mindfulness training. Considering the demonstrated associations between certain mindfulness facets and sleep difficulty, it is possible that individuals with higher levels of dispositional mindfulness would be less likely to develop sleeping difficulty. Future research should compare levels of dispositional mindfulness in individuals with and without clinical levels of insomnia to determine whether people with higher levels of mindfulness are at decreased risk for sleep disturbances.

Figure 6.1: Insomnia Severity and Sleep Quality Scores (N=111)

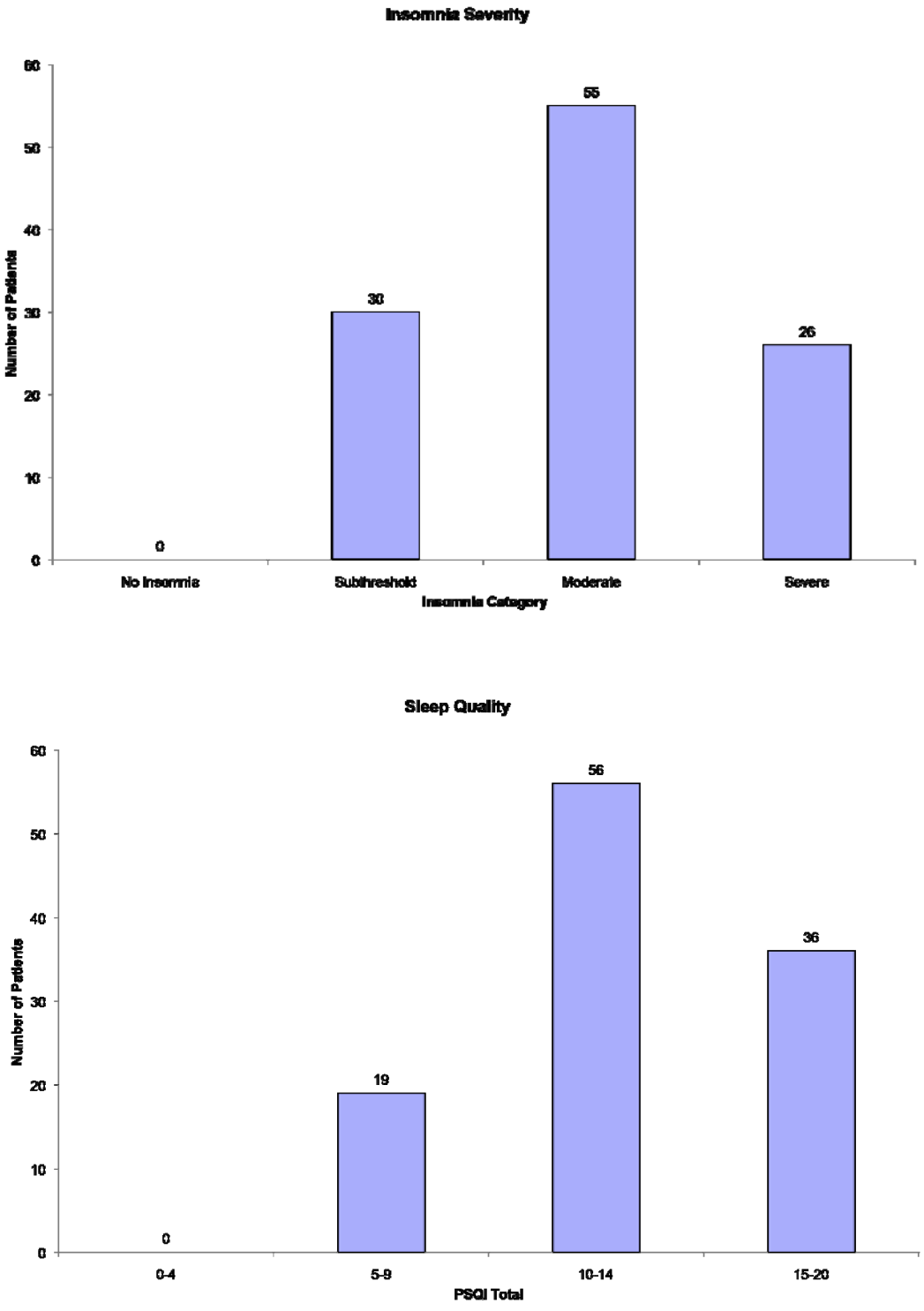


Table 6.1: Demographic Characteristics of Dispositional Mindfulness Sample

N=111	**Mean (SD)**	**Range**
Age	58.89 (11.18)	35-88
Education	15.14 (3.53)	6-33
Insomnia Duration (yrs)	6.88 (6.61)	.10-28.90
Disease Duration (yrs)	3.19 (4.03)	.17-28.90
	n	**%**
Sex		
Male	31	28%
Female	80	72%
Marital Status		
Single	20	18%
Married	72	65%
Other	19	17%
Employment		
Full-time	42	38%
Part-time	22	20%
Retired	35	32%
Disabled	12	11%
Insomnia Subtype		
Sleep Onset	13	12%
Sleep Maintenance	36	32%
Mixed	62	56%
Cancer Location		
Breast	53	48%
Prostate	12	11%
Female GU	11	10%
Blood/Lymph	10	9%
Lung	7	6%
Head/Neck	7	6%
Colorectal	5	5%
Other	6	5%

Table 6.2: Correlations between Mindfulness, Insomnia Severity, Sleep Quality, Dysfunctional Beliefs and Attitudes about Sleep, Mood Disturbance, and Symptoms of Stress

Variables (N=111)	1	2	3	4	5	6	7	8	9	10
1. FFMQ Observe	-	**.213***	.093	-.146	**.222***	.047	.014	.058	.069	-.162
2. FFMQ Describe		-	**.326****	.035	**.399****	-.036	-.113	-.048	-.084	-.180
3. FFMQ Acting with Awareness			-	**.197***	.091	**-.280****	**-.217***	**-.267****	**-.470****	**-.499****
4. FFMQ Non-Judging				-	-.006	-.100	**-.243***	**-.309****	**-.452****	**-.475****
5. FFMQ Non-Reacting					-	-.115	**-.204***	-.175	-.178	**-.225***
6. ISI						-	**.683****	**.421****	**.469****	**.469****
7. PSQI Total							-	**.363****	**.546****	**.474****
8. DBAS Total								-	**.401****	**.407****
9. C-SOSI Total									-	**.809****
10. POMS Total										-

*p<.05; **p<.01
Variables 1-5 Higher scores are better (more mindful)
Variables 6-10 Higher scores are worse

Table 6.3: Hierarchical multiple regressions for insomnia severity, sleep quality and dysfunctional sleep beliefs

	Step	Predictor	B	SE	β	t	p	R^2	R^2 change	sr^2 inc
Insomnia Severity	1	POMS Total	.043	.024	.261	1.815	.072	.242		.153
		C-SOSI Total	.034	.019	.256	1.783	.077			.151
	2	POMS Total	.051	.025	.311	2.041	.044	.268	.026	.172
		C-SOSI Total	.037	.019	.284	2.041	.056			.163
		Acting with Awareness	-.024	.072	-.033	-0.333	.740			-.028
		Non Judging	.119	.064	.182	1.868	.065			.157
		Non Reacting	.011	.080	.012	0.132	.895			.011
Sleep Quality	1	POMS Total	.013	.019	.090	0.653	.515	.309		.053
		C-SOSI Total	.054	.015	.481	3.503	.001			.283
	2	POMS Total	.012	.021	.088	0.601	.549	.322	.013	.049
		C-SOSI Total	.056	.016	.500	3.536	.001			.287
		Acting with Awareness	.044	.059	.072	0.747	.457			.061
		Non Judging	-.001	.052	-.001	-0.016	.987			-.001
		Non Reacting	-.076	.066	-.097	-1.158	.249			-.094

DBAS Total	1	POMS Total	.014	.009	.236	1.581	.117	.184		.077
		C-SOSI Total	.010	.007	.215	1.444	.152			.097
	2	POMS Total	.008	.009	.140	.884	.379	.212	.028	.077
		C-SOSI Total	.008	.007	.170	1.113	.268			.097
		Acting with Awareness	-.017	.026	-.067	-.651	.517			-.057
		Non Judging	-.036	.023	-.157	-1.550	.124			-.136
		Non Reacting	-.035	.029	-.107	-1.187	.238			-.104

*Full model

CHAPTER 7: IMPACT OF MINDFULNESS-BASED STRESS REDUCTION ON MINDFULNESS AND DYSFUNCTIONAL SLEEP BELIEFS IN CANCER PATIENTS WITH INSOMNIA

7.0 Abstract

This study examined the impact of Mindfulness-Based Stress Reduction (MBSR) on insomnia severity, sleep quality, dysfunctional sleep beliefs, mindfulness, stress symptoms and mood disturbance in cancer patients with clinical insomnia. Patients (N=32) were assessed at baseline and 5-month follow-up to assess durability of treatment effect. Patients reported statistically and clinically significant reductions in overall insomnia severity, sleep disturbance, symptoms of stress and mood disturbance. After MBSR participation, 22% of the sample no longer reported insomnia symptoms. Acting with awareness, non-judging, and non-reacting were the facets of mindfulness associated with an overall reduction in dysfunctional sleep beliefs. This study provides initial support for the use of MBSR to improve sleep outcomes and address dysfunctional sleep-related beliefs.

7.1 Background

Sleep disturbances have been identified as an important but often overlooked side effect of cancer [18]. Prevalence rates for sleep disturbances in individuals with cancer range from 30-50%, depending on the definition, time of assessment and measurement tool used [19-21]. Longitudinal research conducted by Savard et al. established that insomnia symptoms persist in up to 21% of cancer patients 18 months post-treatment [22]. The increased rate of sleep difficulty experienced by cancer patients has been attributed to the emotional consequences of being diagnosed with cancer [33] and the effects of cancer treatment, particularly chemotherapy [34]. The inability to achieve restorative sleep can negatively impact energy levels [254], mood [29] and overall quality of life [38].

Mindfulness Based Stress Reduction (MBSR) is an intervention that is increasingly being offered to help people reduce perceived stress, manage negative mood states, and cope with physical illness. The intention of the MBSR program is to develop skills in mindfulness, described as non-judgmental awareness of the present moment, in order to self-regulate emotions and reactions to stress [122]. The tendency to be more mindful in daily life has been associated with better psychological functioning and reduced overall distress in people with [239,246,253] and without cancer [237,238,241]. Shapiro and colleagues suggest that mindfulness may increase self-regulation, clarify values, promote cognitive, emotional and behavioral flexibility and allow for the development of tolerance for difficult emotional states [177]. Potential mechanisms for how improved mindfulness leads to better overall psychological functioning are through decreases in ineffectual emotion regulation strategies such as rumination [175,178], worry [176], and experiential avoidance [130,176].

If mindfulness can increase emotional tolerance and cognitive flexibility, it follows theoretically that mindfulness training may also positively impact the tendency to hold rigid and dysfunctional beliefs about sleep. These include unrealistic expectations about sleep needs and daytime functioning, beliefs that sleep is unpredictable and uncontrollable, misconceptions and false attributions about the causes of insomnia, distorted perceptions of the consequences of poor sleep, and faulty beliefs about sleep promoting practices [73]. Research has established that a greater endorsement of dysfunctional sleep beliefs is a risk factor for the development, increased severity and maintenance of insomnia and sleep disturbances [75,76,79]. The modification of these problematic sleep beliefs with treatments such as Cognitive Behavior Therapy has been associated with improved sleep [78-82].

Several randomized controlled trials have established the utility of MBSR to improve psychological and physical outcomes in cancer patients [134-137]. Preliminary evidence suggests that MBSR may also have a positive impact on sleep quality and quantity in individuals with cancer [165,184,185]. MBSR has been hypothesized to improve sleep quality by the dual action of reducing stress induced arousal and maladaptive cognitions [185], but this remains to be conclusively demonstrated.

In addition to the lack of research on the effects of MBSR on sleep in cancer patients, the ability of mindfulness-based interventions to address dysfunctional sleep beliefs has yet to be thoroughly investigated. Gross et al. published the results of a randomized controlled trial of 30 individuals (22 women and 8 men) with chronic insomnia allocated 2:1 to MBSR or pharmacotherapy (3mg eszopliclone) [183]. Significant effects for both groups were reported on subjective measures of insomnia severity and

sleep quality, but only the MBSR group reported improvements in sleep self-efficacy and dysfunctional sleep beliefs. However, the authors did not include a measure of mindfulness, preventing the determination of whether improvements in dysfunctional sleep beliefs and sleep outcomes were related to an increase in mindfulness, the development of which is a central component of the MBSR program.

This study examined the impact of MBSR in cancer patients with clinical insomnia and addresses the limitations noted above by including validated measures of mindfulness and dysfunctional sleep beliefs. The following hypotheses were tested:

1. MBSR participation will improve subjective measures of sleep in cancer outpatients with clinical levels of insomnia.
2. Improvements in sleep quality and insomnia severity will be associated with increased mindfulness.
3. Increases in mindfulness will be associated with a reduction in dysfunctional beliefs and attitudes about sleep.

Additionally, we sought to explore whether improvements in sleep and psychological outcomes was associated with the number of classes attended and minutes spent in meditation (i.e. the "dose" of mindfulness). Previous research examining the relationship of attendance/home meditation practice and improved outcomes has produced conflicting results with some studies reporting no relationship and others suggesting greater improvement with more attendance and practice time [255].

7.2 Methods

Participants and Procedures

This study is a secondary analysis of a larger randomized controlled trial comparing the effect of MBSR to Cognitive-Behavioral Therapy for insomnia [223]. Ethical approval was obtained from the Conjoint Health Research Ethics Board of the University of Calgary/Alberta Health Services. Participants had attended at least 5 of the 9 MBSR sessions and were considered treatment completers. Patients were assessed at baseline and follow up (3 months post-program), as opposed to immediately after completion of the 8-week program, in order to assess the durability of treatment effect.

Patients were eligible for study inclusion if they met the following criteria: were over the age of 18; able to speak and read English; diagnosed with non-metastatic cancer and had finished chemotherapy or radiation at least one-month prior to study participation. They were required to meet a DSM-IV-TR diagnosis of primary or secondary insomnia. Patients were ineligible if they had another sleep or psychological disorder requiring alternate treatment or had previous experience with the practice of mindfulness. Patients were primarily recruited from outpatient oncology departments by self or physician referral, although the study was advertised through several other methods including: the distribution of posters and pamphlets throughout areas frequented by individuals diagnosed with cancer; television, radio, visual and print media advertising; and mailed invitations to eligible patients through the provincial cancer registry.

The study was advertised generally as the ***I-CAN*** *SLEEP Research Program: A study for individuals with* ***I****nsomnia and* ***CAN****cer* and did not refer to the specific treatment arms. As such, participants did not know when they consented to the study that they may be assigned to MBSR. Patients were told that the treatment they received may

include any or all of the following: modifying their sleep pattern, talking about how to manage stress, discussing how thoughts and habits may make it difficult to fall asleep at night, as well as practicing relaxation, meditation, gentle stretching exercises and completing some work at home. Hence, this sample is unique in that it is self-selected for having insomnia, rather than because the participants specifically wanted to learn meditation or yoga.

Mindfulness-Based Stress Reduction

The MBSR program has been offered as a no-cost clinical program at the Tom Baker Cancer Centre several times a year since 1997. It was adapted from the program developed by Jon Kabat-Zinn with added content specific to the needs of people with cancer, and clinically is called *Mindfulness-Based Cancer Recovery*. This version is described in detail in the treatment manual published by Carlson and Speca [126]. It comprises 8 weekly group classes of 90 minutes and is delivered to groups of up to 20 individuals. A 6-hour silent retreat is offered between weeks 5 and 6 as an opportunity for extended practice. During the program, participants are taught several types of mindfulness practices including the body scan, sitting meditation, walking meditation, mindful eating, mindful yoga and loving kindness meditation. This is combined with didactic instruction on the application of mindful attitudes to daily life, responding versus reacting to stress, and the mind-body connection. Participants are provided with a workbook and 2 CDs for home practice on the first day of the program but are also encouraged to read "Full Catastrophe Living" [122] and/or "Mindfulness-Based Cancer Recovery" [126]. The group delivery normalizes successes and struggles while allowing

individuals to receive support from others with similar and disparate experiences in a safe, professionally led intervention.

Measures

Demographic data: Each participant completed a form collecting information on demographic, disease and insomnia characteristics. Permission was obtained to access medical records to verify disease and treatment details.

The Insomnia Severity Index (ISI) is a 7 item screening measure of subjective insomnia symptoms, the consequences of insomnia, and the degree of distress elicited. Each item is rated on a 0-4 scale, with higher scores indicating more severe insomnia. The total score ranges from 0 to 28. The recommended cutoffs are: 0-7 no clinically significant insomnia; 8-14 subthreshold insomnia; 15-21 moderate clinical insomnia, and; 22-28 severe clinical insomnia. The ISI has established adequate concurrent and predictive validity with sleep diaries and PSG, and is sensitive to change. The ISI has been validated for use in cancer patients [214]. Further evaluation has established a change score of -8.4 to be associated with clinically significant improvement [202].

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item measure of sleep disturbance in the previous month [198]. It produces a total score and 7 subscales: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleeping medications and daytime dysfunction. Higher scores indicate the presence of sleep disturbances. A clinical cutoff of 5 was recommended to distinguish good sleepers from those with significant sleep disturbance. However, a cutoff of 8 has been recommended to distinguish poor sleep in clinical populations [36]. The PSQI has been validated for use in individuals with cancer [249].

The Five Facet Mindfulness Questionnaire (FFMQ) is a 39 item self-report measure of the tendency to mindful in daily life [201]. Items are rated on a 5-point Likert scale with higher scores indicating more mindfulness. The FFMQ summarizes five elements, or facets, important to the experience and development of mindfulness. These include: observing, describing, acting with awareness, non-judging and non-reacting. The sensitivity of FFMQ to measure changes in mindfulness resulting from MBSR participation has been demonstrated in individuals with and without cancer [130,246,251].

The Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) scale is a 16-item self-report measure of the extent to which individuals endorse unhelpful sleep beliefs [74]. Items are rated on a 0-10 Likert type scale, with higher scores indicating a stronger endorsement of the dysfunctional belief. A total score and the following four subscales are produced: consequences of insomnia, worry about sleep, sleep expectations and beliefs about sleep medication. Cronbach alpha values of 0.77 and 0.79 demonstrate acceptable internal consistency for clinical and research samples. A recommended clinical cutoff of > 3.8 on the DBAS-16 has been shown to provide maximum sensitivity and specificity [252].

The Profile of Mood States-Short Form (POMS-SF) is a 37-item measure of distinct mood states [226] that was shortened from the original 65-item version [218]. Response items range from ‘not at all’ to ‘extremely’ with higher scores indicating greater mood disturbance. A total score is produced, along with 6 subscales: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment. The POMS has been validated for use in individuals with cancer [200].

The Calgary Symptoms of Stress Inventory (C-SOSI) is a 56-item questionnaire assessing psychological and physiological responses to stress and validated for use in a cancer population [199]. Items are rated on 5-point Likert rating scale from 0-4 with higher scores indicating greater stress symptomotology. It produces a total score and 8 subscales: depression, anger, muscle tension, cardiopulmonary arousal, sympathetic arousal, neurological/GI, cognitive disorganization and upper respiratory symptoms.

Analysis

Hypothesis 1. Separate repeated measures analysis of variance (RM-ANOVA) were performed to determine the impact of participation in the MBSR program on levels of insomnia severity, sleep quality, mindfulness, beliefs about sleep, symptoms of stress and mood disturbance. Patients were assessed prior to program participation and 3 months following program completion (5 months after baseline). A Bonferonni correction was applied for multiple tests bringing the significance level to 0.005. Effect sizes (Cohen's d) were calculated by dividing the difference in baseline and follow up scores by the pooled standard deviation.

Hypotheses 2 & 3. Residualized change scores were calculated for each individual on measures of insomnia severity, sleep quality, symptoms of stress, mood disturbance, mindfulness and dysfunctional beliefs and attitudes about sleep. To calculate residualized change scores, baseline values were regressed onto follow-up values and the unstandardized predicted values were saved as a new variable. The predicted follow-up values were subtracted from the raw follow-up values to compute the residualized change scores [256]. Residual change scores were used instead of simple change scores to account for the variable's pre-treatment level and its potential for regression to the mean.

Considering the conservative nature of residualized change scores and the preliminary nature of these investigations, a correction for multiple comparisons was not employed.

Relationship to MBSR adherence. The associations between residualized change scores for each outcome, MBSR attendance and meditation practice were examined using Pearson product-moment correlation coefficients.

7.3 Results

Five individuals who attended the program did not provide follow up data. For these individuals, the last observation carried forward method was employed. Demographics are presented in Table 7.1. The participants consisted of 12 men and 20 women, totaling 32 individuals. The mean age was 60 years, with an age range of 36-87. Most of the participants were married (53%) and had a mean of 16 years education. The sample consisted primarily of individuals with breast (38%), followed by prostate cancer (16%) and blood/lymphatic cancers (16%). Patients had been diagnosed with cancer approximately 3 years prior to study participation. Most of the patients had difficulty initiating and maintaining sleep, beginning an average of 6 years prior.

Hypothesis 1

Results support the first hypothesis that MBSR participation would improve subjective measures of sleep in cancer outpatients with clinical levels of insomnia. Figure 7.1 demonstrates the categorical changes in insomnia severity after MBSR participation. The percentage of patients reporting severe insomnia dropped from 15.6% to 0%. The proportion of patients with moderate insomnia reduced 40.6% to 15.6% whereas sub threshold insomnia increased from 43.8% to 62.5%. At the 3-month assessment following

MBSR participation, 21.9% of patients no longer had clinically significant insomnia at all.

The overall impact of the MBSR program on mean scores for sleep, psychological variables and mindfulness is presented in Table 7.2. Reductions in overall insomnia severity and sleep disturbance from baseline to follow-up assessment were statistically significant and represented large effect sizes of 1.52 and 0.74 respectively. Participation in the MBSR program also accounted for significant reductions in symptoms of stress and mood disturbance with moderate effects sizes of 0.48 and 0.54. Changes in measures of overall dysfunctional beliefs and attitudes about sleep and the non-judging facet of mindfulness were significant at the $\alpha = 0.05$ level but no longer significant after a correction for multiple comparisons was employed.

Hypothesis 2

Associations between residualized change in subjective sleep measures and mindfulness are presented in Table 7.3. Although findings were in the hypothesized direction, there were no significant associations between changes in facets of mindfulness and improvements in insomnia severity. The correlation between an increase in non-judging and improved insomnia severity approached significance ($r = -.325$, $p = .070$). Increased awareness was related to reductions in daytime dysfunction ($r = -.411$, $p = .019$), and was the only facet of mindfulness associated with subjective sleep quality.

Hypothesis 3

The hypothesis that increased mindfulness would be associated with a reduction in dysfunctional belief about sleep was supported, with certain facets of mindfulness appearing more relevant than others. These associations are presented in Table 7.4.

Improved awareness was related to a reduction in sleep related worry and helplessness (r = -.398, p = .040), and overall dysfunctional sleep beliefs (r = -.386, p = .047). Increases in non-judging were related to reductions in unrealistic sleep expectations (r = -.470, p = .013) and a reduction in total negative sleep beliefs (r = -.400, p = .039). The tendency to not react automatically to experiences was associated with a reduction in unrealistic sleep expectations. An association between changes in the observe and describe facets of the FFMQ and dysfunctional sleep beliefs was not demonstrated.

Relationship to MBSR adherence.

The mean number of classes attended was 7 (range 5-9). The amount of meditation and yoga home practice ranged considerably from 90 to 3835 minutes with a median of 1296 minutes. This averages to 23.14 minutes per day during the 8-week intervention. The associations between residualized change scores for each outcome, MBSR attendance and meditation practice are presented in Table 7.5. Class attendance and the number of minutes spent in meditation and yoga were not significantly related to sleep or psychological outcomes.

7.4 Discussion

This study examined: 1) the impact of MBSR in cancer patients with clinical levels of insomnia, and 2) the associations between sleep outcomes, mindfulness, dysfunctional sleep beliefs, and home meditation practice. MBSR participation was associated with significant improvement in subjective assessments of insomnia (d = 1.53), sleep quality (d = 0.74), symptoms of stress (d = 0.54) and mood disturbance (d = 0.48). A moderate reduction in dysfunctional sleep beliefs (d = 0.44) was demonstrated but this was no longer statistically significant after a correction was employed. The mean

DBAS score at follow up was 4.42, still above the recommended clinical cutoff of 3.8 for the level of sleep beliefs deemed to be problematic.

The only other study to examine the impact of MBSR on dysfunctional sleep beliefs associated with chronic insomnia reported statistically significant improvement, however a correction for multiple comparisons was not employed. Values were also above the clinical cutoff (4.08), suggesting that problematic levels of negative sleep beliefs remained after MBSR program completion [183]. When mindfulness was added to standard cognitive behavioral treatment for insomnia in the general population, the improvement in dysfunctional sleep beliefs was clinically significant (2.83) with an effect size of 1.05 [167]. It may be the case that when there are efficacious CBT treatments for a disorder, the skillful addition of mindfulness components may improve treatment efficacy.

In the best example of this, combining mindfulness with cognitive behavior therapy has led to improved relapse rates in individuals with depression [133,209]. Teasdale and colleagues suggest that mindfulness and cognitive approaches have a synergistic relationship in which cognitive therapy can allow for a modification of problematic thoughts and mindfulness practice allows the person to develop a less reactive relationship with those thoughts [257]. The co-morbidity between depression and sleep disturbances raises the possibility that a combined approach may also be beneficial for the treatment of insomnia.

This study did not demonstrate a strong effect of MBSR participation on all mindfulness facets in cancer patients with insomnia, apart from the non-judging facet (d = 0.36), which has been suggested as the heart of mindfulness practice by some authors

[123,231,234]. This is in contrast to other studies that have demonstrated increases in many mindfulness facets associated with MBSR participation in cancer patients [239,246,253]. The only other study to include a formal assessment of mindfulness (the KIMS: [258]) in individuals with insomnia also did not find a significant effect on mindfulness skills after participating in a treatment combining mindfulness meditation with cognitive behavioral therapy [167]. However this was not a formalized MBSR program and only the overall mindfulness score was reported, preventing a comparison between specific facets of mindfulness.

Validation of the ISI against other subjective and objective sleep measurements has established that a change score of -8.4 is associated with clinically significant improvement [202]. We observed an average ISI reduction of 6 points in this sample at the 5-month follow up assessment. When MBSR was compared to pharmacotherapy, Gross and colleagues observed a similar reduction (-6.89) when insomnia severity was measured immediately post-program (2 months), but when assessed at 5 months, the improvement had reached clinical significance [183]. Considering that our sample had chronic insomnia *and* were post-treatment for cancer, somewhat attenuated improvements might be expected because of persistent treatment side effects which negatively impact sleep, such as pain or menopausal symptoms. When the overall profile of ISI scores was examined, the number of patients with severe insomnia dropped from 16% to 0% and 22% of the sample was no longer reporting insomnia symptoms; arguably clinically important improvements.

Acting with awareness was the only facet of mindfulness that was significantly associated with a reduction in perceived daytime dysfunction. Decreased insomnia

severity was not highly correlated with mindfulness facets, apart from non-judging, which approached significance. This suggests that mindfulness may exert an indirect influence on insomnia severity through a reduction in symptoms of stress, improved emotional regulation, and potentially by allowing for the modification of rigidly held beliefs about sleep.

This is the first study to examine the associations between separate mindfulness facets and dysfunctional sleep beliefs. Acting with awareness, non-judging, and non-reacting facets appeared to influence overall dysfunctional sleep beliefs, particularly sleep related worries and unrealistic sleep expectations. Considering the evidence that modification of problematic sleep beliefs is associated with long-term recovery from insomnia [78,79,81], these preliminary findings may guide future research to examine the relevance of increasing awareness, not judging and not reacting habitually to unpleasant states or stimuli for addressing dysfunctional sleep beliefs.

Lastly, neither the number of classes attended nor amount of time spent in meditation home practice were associated with any of the outcomes measured. Gross and colleagues reported a relationship between home practice and reduced dysfunctional sleep beliefs [183]. The average meditation time reported in that study was 23.70 minutes, which is practically identical to our reported mean practice time of 23.14 minutes. Ong et al. also investigated associations between home practice and sleep outcomes in their pilot trial of a combined MBSR and cognitive behavioral treatment for insomnia [167]. A significant association was found between increased meditation and decreased arousal, but not between meditation time and sleep outcomes or dysfunctional sleep beliefs. Additional studies are warranted to address the conflicting evidence for the relationship

of meditation home practice to sleep outcomes. It has been recommended that future research use more detailed tracking of home practice, employ research designs that test differential homework regimes, and use qualitative methodology to assess the quality of home practice [255].

This study provides initial support for the use of MBSR to improve sleep outcomes and supports the role of mindfulness approaches in addressing dysfunctional sleep-related beliefs. However, the results of this study are preliminary and must be considered with the following limitations in mind. Without a control group it is not possible to evaluate the natural course of symptom severity. Although the observed improvements could be a result of extreme symptoms becoming better with time (regression to the mean), the fact that our sample reported having insomnia for an average of 6 years prior and that insomnia is known to be a particularly persistent condition in cancer patients makes this unlikely [22]. We also applied residualized change scores in the analyses, which would attenuate the statistical probability of regression towards the mean.

Despite the small sample size limiting the ability to assess more subtle psychological constructs and draw general conclusions about the benefits of MBSR for treating insomnia, demographically our sample was quite diverse in terms of cancer type and included both men and women with a significant insomnia history. Additional studies are required to confirm these initial findings with larger samples and more robust research designs. Lastly, the participants in this study were randomly assigned to MBSR and did not self-select a mindfulness-approach to their insomnia. It may be the case that participants who do not choose MBSR based on an interest in learning mindfulness may

not increase their self-reported levels of mindfulness as much as those who enter the program with a knowledge of its content and focus, and potentially higher motivation to cultivate mindfulness in their lives. Research comparing individual treatment preference would help determine the impact of this on treatment outcomes.

Figure 7.1: Insomnia severity scores before and 3 months after MBSR participation (n=32)

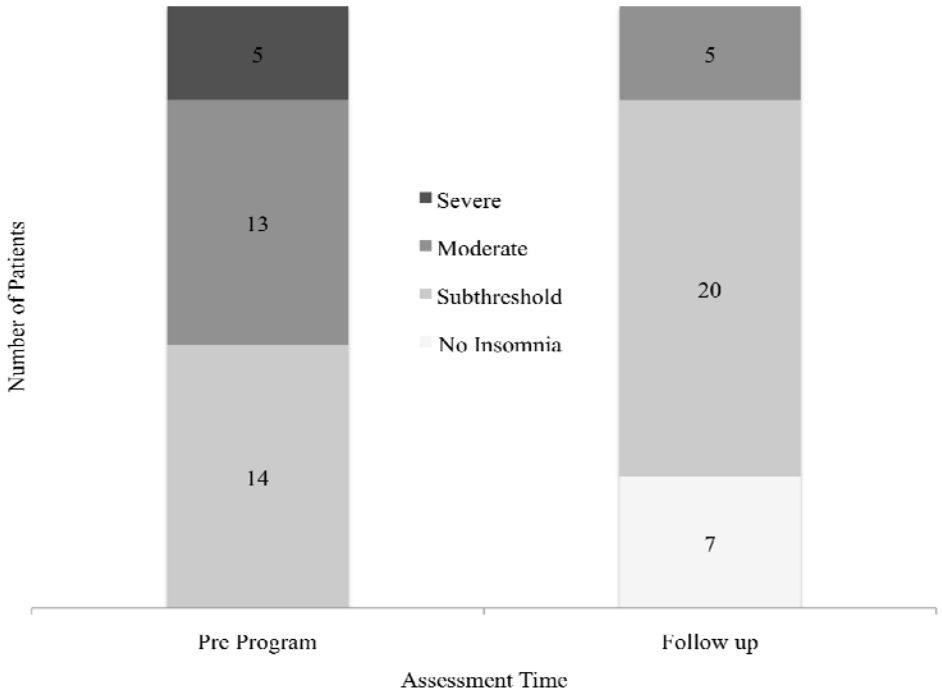


Table 7.1: Demographic Characteristics of MBSR Participants (N=32)

N=32	**Mean (SD)**	**Range**
Age	60.33 (12.21)	36-87
Education	15.77 (2.91)	11-25
Insomnia Duration (yrs)	6.67 (6.72)	.22-28.90
Disease Duration (yrs)	3.19 (3.81)	.17-19.90
	n	**%**
Sex		
Male	12	38%
Female	20	62%
Marital Status		
Single	9	28%
Married	17	53%
Other	6	18%
Employment		
Full-time	13	41%
Part-time	3	9%
Retired	13	41%
Disabled	3	9%
Insomnia Subtype		
Sleep Onset	1	3%
Sleep Maintenance	16	50%
Mixed	15	47%
Cancer Location		
Breast	12	38%
Prostate	5	16%
Female GU	2	6%
Blood/Lymph	5	16%
Lung	1	3%
Head/Neck	3	9%
Colorectal	1	3%
Other	3	9%

Table 7.2: Change over time in measures of insomnia severity, sleep quality, mood disturbance, symptoms of stress, dysfunctional attitudes and beliefs about sleep, and facets of mindfulness

	Assessment Time				
n=32	Pre Program	Follow Up (5 mo)	*F*	*p*	*ES*
ISI Total					
Mean	16.34	10.44			
SD	4.20	3.57	10.67	**.003***	1.52
PSQI Total					
Mean	11.44	9.00			
SD	3.60	2.98	14.80	**.000***	0.74
POMS-SF Total					
Mean	23.94	14.29			
SD	19.78	20.26	8.72	**.001***	0.48
C-SOSI Total					
Mean	60.44	46.97			
SD	27.13	22.60	8.72	**.001***	0.54
DBAS Total					
Mean	5.08	4.42			
SD	1.39	1.60	3.90	.032	0.44
FFMQ Scales					
Observe					
Mean	26.38	24.50			
SD	5.42	5.80	4.71	.013	-0.33
Describe					
Mean	26.56	26.44			
SD	4.94	5.12	0.07	.888	-0.03
Acting w/ Awareness					
Mean	28.19	28.63			
SD	5.33	5.00	0.37	.661	0.09
Non-Judging					
Mean	28.69	30.97			
SD	6.59	6.02	3.98	.029	0.36
Non-Reacting					
Mean	20.34	20.19			
SD	4.34	4.42	0.86	.422	-0.00

Bonferroni Corrected p-value = .005

Table 7.3: Correlations between Residualized Change in Insomnia Severity, Sleep Quality, and Mindfulness

	FFMQ				
n=32	Observe	Describe	Act with awareness	Non-Judging	Non-Reacting
ISI Total	-.099	.205	-.054	-.325	-.133
PSQI Total [a]	-.173	-.118	-.046	-.195	-.126
Sleep Quality	-.074	-.109	-.079	-.240	-.313
Sleep Duration	-.091	-.046	-.094	-.104	-.185
Sleep Onset Latency	-.152	.037	.220	-.154	.041
Sleep Efficiency	-.065	-.192	-.043	-.046	-.100
Sleep Disturbances	-.070	.097	.128	-.080	.115
Sleeping Medication	.085	.090	.123	.199	.073
Daytime Dysfunction	-.117	-.063	**-.411***	.071	-.033

*$p<.05$

[a] Higher scores indicate poorer sleep quality

Table 7.4: Correlations between Residualized Change in Mindfulness and Dysfunctional Beliefs about Sleep

n=32	FFMQ				
DBAS	Observe	Describe	Act with awareness	Non-Judging	Non-Reacting
Sleep Expectations	.116	.078	-.264	**-.470***	**-.395***
Worry	.257	.228	**-.398***	-.320	-.261
Consequence	-.015	.038	-.315	-.218	-.177
Medication	.187	.314	-.010	-.154	.110
Total	.187	.212	**-.386***	**-.400***	-.275

*p<.05; **p<.01

Table 7.5: Correlations between Number of Classes Attended and Minutes of Meditation Practice and Residualized Changes in Mindfulness, Sleep and Psychological Outcomes

Variables (N=111)	# Classes Attended	Min. practicing meditation/yoga
1. Observe	.103	-.045
2. Describe	-.195	.160
3. Awareness	-.096	-.141
4. Non-Judging	-.160	.041
5. Non-Reacting	.118	-.115
6. ISI	-.288	-.254
7. PSQI Total	-.046	.006
8. DBAS Total	.027	.003
9. C-SOSI Total	-.152	.106
10. POMS Total	-.077	-.225

*p<.05; **p<.01
Variables 1-5 Higher scores are better (more mindful)
Variables 6-10 Higher scores are worse

CHAPTER 8: OVERALL DISCUSSION

8.0 Summary of Main Findings

This thesis examined the use of non-pharmacological interventions to address insomnia in a heterogeneous sample of cancer patients. In the first chapter, the prevalence and contributing factors for the higher than average levels of sleep disturbance and insomnia in cancer patients are reviewed. Cancer patients are three times more likely than the general population to experience disturbed sleep and insomnia [22]. The higher prevalence of sleep disturbances and insomnia has been attributed to the physical (e.g. pain) and emotional consequences (e.g. cancer-related distress) of a cancer diagnosis and treatment [26,29]. Being treated with chemotherapy may make patients particularly vulnerable to disrupted sleep-wake rhythms [33,35]. In all, *the presence of persistent insomnia places patients at a higher risk for further psychological and physical morbidity and reduced quality of life; a problem warranting research and clinical attention* [38,39].

Chapter 2 discussed the theories of insomnia development and explored the breadth of biological, behavioral, psychological, cognitive and neurological features that may predispose, precipitate, and/or perpetuate insomnia. Research suggests that individuals with insomnia may be predisposed to "sleep reactivity" and a negative attributional style characterized by the tendency to experience sleep disruption in response to stressful life events and to rate those incidents as more problematic than other people [57,59,68]. There is also evidence that people who experience insomnia have higher levels of nighttime, as well as daytime, physiological, cognitive, and cortical arousal, which frequently presents as increased pre-sleep cognitive activity [51,66,83]. A key component of cognitive arousal is a focus on detecting potential sleep-related threats and scanning for evidence of consequences of poor sleep [77]. The is fed by the presence of

rigidly held dysfunctional beliefs and attitudes about sleep [73]. The research reviewed in Chapter 2 suggests that *the biological, behavioral, and cognitive aspects of insomnia are inseparable, with each contributing to development and maintenance of the others. Successful treatment should attempt to address these inter-related factors.*

The most common non-pharmacological treatment for insomnia (CBT-I) is described, the evidence for its efficacy is presented, and its limitations are introduced in Chapter 3. CBT-I employs sleep restriction and stimulus control in order to reduce conditioned arousal between sleep stimuli and arousal-producing activities by eliminating efforts to force or 'try harder" to sleep. These components are complimented by relaxation therapy and cognitive therapy to specifically address physiological arousal and beliefs about sleep that may contribute to worry and rumination. Despite being 1) informed by research; 2) recommended as a first line treatment by the American Academy of Sleep Medicine; and 3) considered well-established by the American Psychological Association, approximately *40% of people who participate in CBT-I do not experience a treatment response* [101], prompting interest in other treatment methods.

Chapter 3 then introduces the reader to MBSR, a well-established intervention that addresses psychological distress in medically and psychologically compromised populations [152], including cancer patients [155]. *MBSR is generating a considerable amount of research interest in the area of insomnia because of its demonstrated ability to reduce cognitive and physiological arousal* [178]. It is hypothesized that MBSR may facilitate cognitive deactivation and physiological dearousal by allowing the individual to disengage from dysfunctional thought patterns such as rumination and promote more flexible behavioral and emotional responses to events they appraise as stressful [166,167,174].

Preliminary evidence suggests that MBSR may produce beneficial effects in individuals with insomnia [183]*, but this remains to be adequately assessed in cancer patients.*

The published trial design manuscript comparing MBSR to CBT-I is included in Chapter 4. The use of *a non-inferiority design allowed for a direct comparison of the two treatments and a determination of whether the investigative treatment (MBSR) performs to the same standard as the established treatment (CBT-I) for insomnia while providing additional benefits of improved mood and subjective appraisals of stress.* The primary outcome was insomnia severity but secondary measures included: sleep indices measured with diaries and actigraphy as well as questionnaires assessing sleep quality, symptoms of stress, mood disturbance, dysfunctional beliefs and attitudes about sleep and mindfulness. Outcome assessments were completed immediately after finishing the interventions and then again at 3 months post-intervention to examine durability of treatment effect.

Chapter 5 presents the results of the non-inferiority study. Differential attrition was observed between the two interventions with more patients withdrawing from MBSR than CBT-I. The possible contributing factors and explanations for this result are discussed below. Despite the imbalance, randomization still produced groups equivalent on relevant measures at baseline. We found that *MBSR was non-inferior to CBT-I when assessed at 5 months but not immediately post-program. This result is attributed to MBSR producing slower but continual improvements over time while CBT-I generated rapid effects that were largely maintained.* The sleep diaries and actigraphy revealed differential effects by treatment arm with CBT having a larger impact on SOL and SE and MBSR positively affecting WASO and TST. *CBT-I uniquely improved sleep quality*

and dysfunctional sleep beliefs while both groups demonstrated the ability to reduce stress symptoms and mood disturbance. Several possibilities exist to explain the salutary effect of MBSR on sleep including: reduced physiological arousal, decreased rumination and worry, less experiential avoidance, improved mood and perceived stress levels. Future research is required to elucidate the precise mechanisms by which mindfulness may positively impact sleep.

The associations between dispositional mindfulness, insomnia severity, sleep quality, dysfunctional beliefs and attitudes about sleep, symptoms of stress and mood disturbance are examined in Chapter 6. Using the full baseline sample from Chapter 5 (N = 111) separate hierarchical regressions were performed to explore the impact of mindfulness facets on levels of insomnia severity, sleep quality and dysfunctional beliefs and attitudes about sleep after adjusting for of stress symptomotology and mood disturbance. We found that *acting with awareness, non-judging and non-reacting were associated with better sleep and psychological outcomes, but that mindfulness was not predictive of fewer sleep disturbances above and beyond the contribution provided by symptoms of stress and mood disturbance*. We suggest two possible explanations for these results: 1) using questionnaires to assess constructs of mindfulness in meditation-naive populations may not adequately capture the subtle qualities of dispositional mindfulness that are of interest to researchers, and 2) that selecting individuals based on the presence of insomnia would prevent the examination of whether lower levels of insomnia is associated with higher levels of dispositional mindfulness.

Chapter 7 extended the analysis of those participants who were randomized to, and completed, the MBSR program (n=32). The following hypotheses were tested: 1)

MBSR participation will improve subjective measures of sleep in cancer outpatients with clinical levels of insomnia; 2) Improvements in sleep quality and insomnia severity will be associated with increased mindfulness; and 3) Increases in mindfulness will be associated with a reduction in dysfunctional beliefs and attitudes about sleep. Patients reported statistically and clinically significant reductions in overall insomnia severity, sleep disturbance, symptoms of stress and mood disturbance (hypothesis 1) but improved sleep outcomes were not associated with increased mindfulness (hypothesis 2). In concordance with hypothesis 3, specific facets of mindfulness (acting with awareness, non-judging, and non-reacting) were associated with an overall reduction in dysfunctional sleep beliefs. This study provides initial support for theory that *one of the mechanisms by which MBSR improves sleep outcomes may be through a reduction in dysfunctional sleep-related beliefs*.

8.1 Challenges and Limitations of the Current Work

8.1.1 Blinding

Blinding is intended to reduce bias in the execution of research but because of difficulty in achieving and maintaining it, blinding is performed less frequently in non-pharmacological trials. Blinding refers to keeping participants, investigators, or assessors unaware of the assigned intervention so that they are not influenced (positively or negatively) by that information [259]. Participants may be impacted by expectations of the treatment effectiveness, leading to differential outcomes or difficulties with retention or adherence. If investigators or assessors are not blinded, their attitudes may be transferred to the participants. *The difficulty in blinding exists when the treatment requires*

awareness and active participation on behalf of the participants and the investigators who are delivering the intervention.

In order to quantify the frequency of blinding procedures and recommend innovative ways to incorporate this design feature, Boutron and colleagues conducted a systematic review of RCTs of non-pharmacological interventions published in 2004 that employed a blinding method [260]. The authors identified 1,040 articles, of which 123 were trials of non-pharmacological interventions that employed one of the following methods of blinding: sham procedures, blinding participants to study hypothesis, and blinding assessors of primary outcome. Of the included articles, 33 (27%) compared interventions that involved collaborations between participants and a care provider, 9 of which were in the domain of psychiatry/psychology. The remaining studies were trials of devices, surgeries or technical interventions. For the participative interventions, 12 (36%) used sham procedures and only 3 (10%) blinded participants to study hypotheses. This low prevalence rate may reflect the *perception that blinding in non-pharmacological trials is infeasible*. In a systematic review of 110 studies of non-pharmacologic treatments for osteoarthristis, blinding in trials was only considered possible with patients in 42%, care providers in 12%, and outcome assessors in 34% of studies compared to 96%, 96% and 98% in the respective categories in pharmacological trials [261]. Despite these challenges, researchers need to explore the most effective methods of balancing risk of bias and potential threats to internal and external validity.

The current study used a *partially blinded randomization paradigm, whereby patients were recruited for a study investigating non-pharmacological treatments for insomnia, but were neither aware of the particular interventions under investigation nor*

the study hypotheses. After baseline assessments were completed, participants were randomized and then given only the details about their specific treatment. This design characteristic was intended to reduce the impact of patient treatment preference and allow for more generalizable conclusions. What we observed was a differential drop out in the MBSR group. While it is not possible to determine the precise reason for this result (for the reasons discussed below), it does raise the *question of whether it is desirable to blind participants to behavioral interventions that require a significant investment of time and active participation, where personal preferences are likely to play a significant role in treatment adherence and outcome*.

Trials of mindfulness interventions typically have attrition rates ranging from 3-25% [262], but a few exceptions where substantial dropouts have occurred have been reported [263,264]. One such trial recruited patients with chronic obstructive lung disease and randomly assigned them to a mind-body breathing therapy (n=44) or a time-matched support group (n=42) [265]. Mind-body-breathing therapy was described as an 8-week program that combined the standard MBSR program designed by Jon Kabat-Zinn with relaxation response training developed by Herbert Benson [266]. The authors hypothesized that the ability of mindfulness to encourage re-appraisal of challenging physical and psychological states may have a positive impact on the primary outcome measure of dyspnea. Close to 60% of the entire sample reported high expectations for both the support and mind-body groups when beliefs were assessed prior to randomization. During trial execution, however, the support group experienced a 31% attrition rate compared to a 55% attrition rate in the mind-body intervention, with all of the drop outs occurring within the first three sessions.

When the authors followed up with patients by phone to assess reasons for non-attendance, the majority cited time commitments and difficulty with transportation, but 15% endorsed the statement that they did not think the mind-body treatment was going to help. When looking specifically at the mind-body group, only 28 of the 44 participants randomized to this intervention reported high baseline expectations for the effect of treatment [265]. Fourteen patients assigned to the mind-body group did not attend a single class. One might hypothesize that the non-attending patients may have been in the group 16 individuals who did not rate the mind-body treatment favorably, but this was not formally assessed in the study. Thus, *instead of refusing to be randomized initially, patients who did not receive their desired treatment executed their preference by not participating. This emphasizes the need to consider patient preferences in trial design*.

8.1.2 Patient Preferences

Theoretically, randomized controlled trials should be employed when there is clinical equipoise (i.e. there is nothing to suggest that one treatment would be preferred over the other). This is frequently not the case in trials of psychological or behavioral interventions where one might reasonably believe that a person's values, expectancies and preferences may play a role in treatment selection and effectiveness. *When interventions cannot be completely blinded, patient preference for treatment can interact with the intervention to influence outcome and contribute to differential attrition, which may reduce internal validity* [267,268]. Preference-intervention interactions occur when a participant does not receive their preferred assignment and demonstrates demoralization and/or refuses to adhere to the treatment. *Studies that rely on subjective outcome measures are particularly susceptible to preference-intervention interactions because*

these measures are more easily effected by expectancy effects than objective outcomes [267].

Modifications to traditional RCTs have been recommended to incorporate participants' preference. These designs are frequently referred to as comprehensive cohort or patient preference trials. In these studies, patients with a preference for one treatment over the other are assigned to their preferred study arm while those participants without strong preferences are randomized in the usual fashion, resulting in a four-armed trial. The strength of this design is that almost all eligible participants will enter the study and preference effects can be statistically controlled, however larger samples will likely be required and power may be more difficult to calculate due to difficulty estimating treatment preferences [269].

To examine the impact of patient preference on attrition and outcome measures, the Preference Collaborative Review Group conducted a systematic review and meta-analysis of 8 fully randomized patient preference trials published between 1996 and 2006 [270]. The studies included were primarily comparing different musculoskeletal treatments for pain. The overall preference rate for all the studies was 56%, indicating that just over half of patients were generally partial to one treatment over another. Patients who were randomized to their preferred treatment reported better outcomes than those who were not, although the between group effect sizes were small. Although the research is not entirely consistent on the impact that patient preference may have on outcomes [267], Udell suggests that *RCTs require patients to disregard inherent preferences which can underestimate possible gains, making the findings of research less representative of, and applicable to, real-world settings* [268].

Research has typically employed simple treatment preference evaluations (i.e. Which of treatments A or B would you favor?), however new information suggests that preference may not be this straightforward to assess. Much of the attention has focused on personal beliefs, but how the information is presented and discussed can also play an important role in preference. Mills and colleagues describe a qualitative analysis of 93 audio recordings of recruitment appointments for men considering enrolling in a RCT of localized prostate cancer treatments [271]. The possible treatments included radical prostatectomy, radical conformal radiotherapy and active monitoring of prostate specific antigen. The majority of patients were found to express preferences early in the appointments (69%). Despite these initial opinions, in many cases, *preferences were demonstrated to change after detailed discussion of treatments and trial rationale with study personnel. This may be particularly important in the evaluations of interventions, such as meditation, that may not be as readily understood, patients may hold misconceptions of the treatment, or where patients may have biases or strong opinions for, or against, the use of that treatment.*

Espie, Barrie and Forgan explored the treatment preferences of patients with different insomnia phenotypes [272]. Patients with psychophysiologic insomnia (n=51) were compared to patients with idiopathic insomnia (n=50). As described in Chapter 2, individuals with psychophysiologic insomnia can often attribute their sleep disturbance to identifiable events and exhibit hyperarousal, sleep incompatible behavior and excessive focus and anxiety about sleep. Idiopathic insomnia occurs in less than 10% of patients with insomnia, is characterized as a chronic complaint with few periods of sustained remission and is considered more resistant to treatment. Patients completed a scenario-

based treatment acceptability scale rating comparing pharmacological, cognitive-behavioral and acceptance-based approaches. Approximately 65% of the entire sample rated acceptance-based treatments favorably, with higher levels observed in the idiopathic group. *The authors recommend that acceptance-based methods be compared to standard CBT-I, as we have done in this study, but note that patients' expectations are likely to have an important impact on outcomes* [272].

8.1.3 Treatment Credibility and Expectations

The absence of an assessment of treatment credibility and expectations is a limitation in the design of this trial. *Treatment credibility has been defined as "how believable, convincing and logical the treatment is", whereas expectancy refers to "improvement that participants feel will be achieved"*. Devilly and Borkovec have validated a credibility/expectancy questionnaire that assesses thoughts and feelings about treatments for use in a variety of populations [273]. The six questions included in the questionnaire are: 1. How *logical* does the therapy offered to you seem? 2. How successfully do you *think* this treatment will be in reducing your symptoms? 3. How *confident* would you be in recommending this treatment to a friend? 4. How much improvement in your symptoms do you *think* will occur? 5. How much do you really *feel* that this treatment will help you reduce your symptoms? and 6. How much improvement in your symptoms do your really *feel* will occur? It has been recommended to assess treatment credibility soon after initiation and following completion to determine whether beliefs change with additional exposure to the intervention. *Had this been employed in the current study, we would have been able to assess whether patients' beliefs about the*

utility of MBSR for treating insomnia was different than for CBT-I and whether this impacted attrition and outcomes.

Arch and colleagues used the Devilly and Borkovec scale to assess treatment credibility in a RCT comparing CBT to Acceptance and Commitment Therapy (ACT) for mixed anxiety disorders [274]. ACT is a mindfulness-based therapy that encourages acceptance, among other strategies, to increase behavioral flexibility and improve psychological functioning. Initial treatment credibility scores differed significantly by group, with CBT evidencing higher scores than ACT, however this did not appear to impact attrition rates. Despite initial differences in beliefs about the effectiveness of the treatments, the two groups did not differ on general anxiety outcomes. The authors suggested that abstract ideas such as acceptance in the ACT treatment, compared to concrete skills in CBT, might have initially contributed to a diminished sense of treatment credibility. Unfortunately, this study did not include a post treatment assessment of credibility to determine whether the belief in the value of ACT improved over time with increased exposure. One might hypothesize that the patients in our trial may have experienced a similar skepticism about MBSR. *Additional research is required to address the question of treatment credibility in comparative trials of mindfulness-based interventions.*

8.2 Strengths of the Current Work

8.2.1 Non-Inferiority Research Design

Non-inferiority trials are becoming more common in behavioral research when investigators are interested in knowing whether a new treatment is at least as effective as an existing one, especially if it is purported to have additional benefits [224]. These

advantages may include a reduction of cost, patient or provider burden and/or side effects. *Non-inferiority trials can also efficiently evaluate the extent to which an investigative treatment compares to an already established treatment, bypassing the relevance of placebo, usual care and waitlist randomized trials, and speeding up the translation of this knowledge into action* [227]. Ethical considerations also frequently prevent the comparison of new treatments to placebo or no-treatment controls when effective interventions exist for the condition under examination, as is the case for insomnia.

The hypotheses and method of data analysis in non-inferiority trials is opposite of what would be recommended in traditional RCTs, which can create confusion for those not familiar with the design. In a traditional superiority design, the null hypothesis assumes no difference, whereas the null hypothesis in a non-inferiority trial states that a difference exists. As such, *non-inferiority researchers are seeking to accept the alternate hypothesis that there is no significant difference between the two groups, as specified by the margin of non-inferiority.* Intent-to-treat analyses are the recommended method of data analysis in a traditional RCT. When ITT is used in non-inferiority trials, however, they typically reduce the difference between the two groups, making it harder to reduce the null hypothesis and increasing type I error. To address this design concern, many non-inferiority trials only include participants that were adherent to treatment protocol, but this may bias the results in the opposite direction. *The PP and ITT analyses in our study (Chapter 5) were largely consistent, increasing the confidence with which we can conclude that our results were neither impacted by Type I or II errors*.

The determination of a non-inferiority margin is an especially important design aspect, as it has a direct influence on statistical power and sample size. We based our margin of non-inferiority on a well-validated measure of insomnia severity with statistical *and* clinical reference categories. This allows us to make claims about the actual impact of the intervention on the patients' sleep experience. *The results of our trial suggest that both CBT-I and MBSR are capable of producing significant statistical and clinical benefit in cancer patients with insomnia.* An additional novel finding was that CBT-I was not significantly different from MBSR in reducing symptoms of stress and mood disturbance. This result requires additional research to determine the directional relationship between stress, mood disturbance, and insomnia in cancer patients.

8.2.2 The Use of Actigraphy

One of the strengths not fully emphasized in Chapter 5 was the use of actigraphy to measure objective sleep outcomes. Actigraphy is a method of assessing sleep or wakefulness based on the presence or absence of movement. Actigraphy is a small device, typically worn on the wrist and has the ability to record days or weeks of data in the patient's home environment. This is an advantage over PSG, which in most cases requires extensive equipment, can be cost prohibitive, necessitates that the patient must spend several nights in a sleep laboratory and produces results that may not be representative of normal sleep. The use of ambulatory monitoring of sleep via wrist actigraphy is considered a reliable and valid method of measuring sleep in normal, healthy populations and it is recommended for the assessment of treatment effects in people with insomnia [193,230,275]. Actigraphy has been used in several studies with cancer

patients prior to and during treatment, and has been included as an outcome measure in trials of behavioral interventions [31,33,37,208,276-278].

The inclusion of actigraphy is recommended in the evaluation of insomnia interventions and provides a superior approximation to PSG than sleep diaries [275]. One area where actigraphy may not accurately represent the sleep experience is sleep onset latency. When compared to PSG, actigraphy tends to underestimate SOL because people with insomnia may lie motionless awake in bed, which the actigraph scores as sleep [229,230]. So not unexpectedly, a discrepancy between subjective and objective reports of SOL and WASO was observed in the study reported in Chapter 5. Patients reported an additional 15-30 minutes of sleep onset and 20-50 minutes more time awake on sleep diaries than what was recorded by actigraphy. However, subjective report of improvements in WASO, TST and SE were confirmed by the inclusion of actigraphy in both the PP and ITT analyses. This strengthens the confidence with which we can conclude that both interventions are able to produce beneficial sleep effects.

8.2.3 Additional Strengths

This body of work has several additional strengths including: 1) the recruitment of a relatively heterogeneous sample; 2) a rigorous selection procedure; 3) the addition of instruments to measure outcomes not yet assessed in the research literature (mindfulness and dysfunctional sleep beliefs); and 4) the inclusion of a 3-month post-treatment assessment. Although the majority of patients in this study had been diagnosed with breast cancer, the sample also included a substantial portion of men and patients with a variety of other cancer types. The groups were not large enough to perform subgroup

analyses but this does speak to the *wide prevalence of insomnia in cancer and the generalizability of CBT-I and MBSR for improving sleep in cancer patients*.

The sleep and insomnia literature has been criticized for employing broad and/or vague inclusion criteria and diagnostic definitions such as "self-defined poor sleepers" as was evident from the review provided in Chapter 2 [193]. *This research complies with the recommendations for a standard research assessment of insomnia provided by an expert panel of 25 insomnia researchers.* The recommendations begin with the application of a quantitative criterion for insomnia (i.e. greater than 30 minutes SOL and/or WASO with less than 85% SE), which provides maximum sensitivity and specificity to detect effects. To this end, we even excluded 16 patients whose sleep diaries did not confirm the severity of their sleep disturbance reported in the interview. Secondly, we conducted a clinical interview to evaluate the presence of other sleep and/or psychological disorders. Although PSG would be required to provide a definitive diagnosis of sleep disorders such as sleep apnea or periodic limb movement disorder, symptom self-report is increasingly being used to rule out sleep disorders other than insomnia in primary care clinics [279]. Lastly, we included what the expert panel considered to be essential measures of global sleep (PSQI) and insomnia symptoms (ISI) as well as measures of the consequences of insomnia (CSOSI and POMS-SF). Following these recommendations *allows the comparison of our findings to other studies conducted in cancer populations and the more general insomnia literature*.

The theoretical relevance of mindfulness to the treatment of insomnia stems from the ability of mindfulness-based interventions to help people reframe obsessive and intrusive thoughts, thereby reducing cognitive and physiological arousal [179]. Previous

studies of MBSR and sleep have not included measures of dysfunctional sleep beliefs or mindfulness, preventing the examination of these variables. Studies that have evaluated mindfulness-based interventions in insomnia patients without medical co-morbidities, have also not been able to sufficiently investigate associations between mindfulness and dysfunctional sleep beliefs. The study by Gross and colleagues included a measure of dysfunctional sleep beliefs but not mindfulness [183]. Ong and colleagues included measures of mindfulness and beliefs about sleep but they did not report (or perhaps conduct) these associations [167]. As such, the studies reported in *Chapters 6 and 7 represent what will be the first published examinations of the association between mindfulness and sleep beliefs, which may inform future research investigating mechanisms with larger samples and more robust research designs.*

Without the inclusion of a 3-month assessment point, we would not have been able to fully evaluate the ability of MBSR to improve insomnia. Our study confirms previous research that *MBSR can have positive effects on general measures of cancer-related distress, but suggests that longer-term follow ups may be required to observe changes in disorders like insomnia, which is characterized by its chronicity*. This represents a particularly important design characteristic and efforts should be made to include additional post-treatment assessments in trials of MBSR whenever possible.

8.3 Implications and Directions for Future Research

Several research and clinical applications arise from these findings. Firstly, the appropriateness of random assignment (blind or not) in trials of psychological and/or behavioral interventions deserves further consideration. There is an inherent tension between establishing the efficacy of a treatment and determining whether that treatment

is going to be effective in clinical practice. In the real world, people typically make decisions about what they are and are not going to do based on a complex system of beliefs, attitudes, and values. There is an increasing recognition that *psychological and behavioral trials cannot and should not be compared to the gold standard double-blind placebo-controlled RCT.* The recognition of the differences between pharmacological and non-pharmacological trials is evidenced by the publication of specific CONSORT guidelines to strengthen the reporting for non-pharmacological trials [280].

Despite the findings of non-inferiority between MBSR and CBT-I, it is premature to recommend MBSR as an intervention for insomnia with broad application. The differential attrition between the two groups only allows for the determination that *MBSR may be an effective treatment for people with insomnia and cancer who are seeking, or are willing to try and stick to, that approach*. Whether recruiting for a research study or suggesting a treatment for a patient in clinical practice, it is recommended that study or clinical staff take time to fully describe the study/program and explore the patient's beliefs, reasons for seeking treatment, and expectations for outcome. Although this process may take more time initially, *matching the patient to the most appropriate treatment may result in better study and clinical results*. It would be relevant to conduct trials to determine whether patients who are fully informed and participate in a treatment that was consistent with their preferences and expectations would have better results.

There remains the question of how mindfulness-based interventions like MBSR may work to impact sleep outcomes. Several mechanisms may exist, including direct effects via a reduction of cognitive and physiological arousal or indirectly through the development of more cognitive, emotional and behavioral flexibility and the reduction of

negative mood states. Sophisticated dismantling and mediation trials are required to answer this foundational question.

In sum, this randomized, controlled non-inferiority trial represents the first study to directly compare CBT-I to MBSR for the treatment of insomnia in patients with cancer. We also examined associations between dispositional mindfulness and sleep outcomes in cancer patients with insomnia who had not yet been exposed to meditation. Further, we examined whether changes in mindfulness resulting from MBSR participation were associated with modifications in problematic sleep-related beliefs. This body of work emphasizes the need to conduct patient-centered research, expands treatment options for patients with insomnia, and potentially reduces the symptom burden experienced by patients, for whom cancer has created or exacerbated their insomnia.

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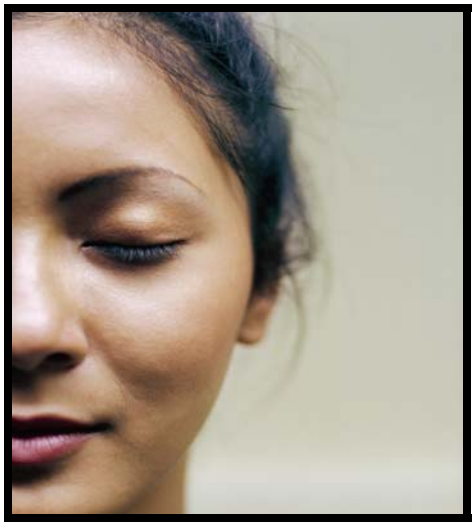
APPENDICES

I-CAN Sleep Research Program

*A Study for Individuals with **I**nsomnia and **Can**cer*

Questionnaire Package



Demographic Information

Study Identification Number _____

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

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

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

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

Self Identified Ethnic Origin: _____

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

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

Height: _____ **Weight:** _____ **BMI:** _____

Type of Cancer and Stage: _____

Treatments previously received: ☐ Surgery ☐ Chemotherapy ☐ Radiation ☐ Hormonal (please Indicate: □ Past or □ Present)

Medications

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

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

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

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

Alcohol Consumption (beer, wine, liquor)

Amount of drinks_____ per/ Day ☐ Week ☐ Month ☐

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

Number of times_____ per/ Day ☐ Week ☐ Month ☐

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

Number of times_____ per/ Day ☐ Week ☐ Month ☐

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

Minutes of activity_____ per/ Day ☐ Week ☐ Month ☐

Vitamins, Dietary Supplements & Herbs

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

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

Other Complementary Therapies

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

☐ **Meditation**
Times used last month _____

☐ **Yoga**
Times used last month _____

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

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

☐ **Chiropractic**
Times used last month _____

☐ **Homeopathy**
Times used last month _____

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

☐ **Prayer**
Times used last month _____

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

☐ **Naturopathy**
Times used last month _____

☐ **Reflexology**
Times used last month _____

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

Psychological Therapies

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

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

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

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

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

☐ **Hypnosis**
Times used last month _____

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

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

Sleep History

1. I have had sleeping problems since (approximately):

Month_____/Year_____ (e.g. June/2006)

2. When do you think your sleeping problems began?

a) I had problems sleeping before my cancer diagnosis and they have remained constant (not changed)

b) I had problems sleeping before my cancer diagnosis and they have become worse

c) My sleeping problems began when I was diagnosed with cancer

d) My sleeping problems began when I started treatments. Please specify:
   a. Surgery
   b. Chemotherapy
   c. Radiation
   d. Hormonal

e) My sleeping problems began after my cancer treatments were finished

3. I have/had more problems with (choose one answer):

a) Falling asleep at the beginning of the night

b) Staying asleep during the night

c) Both falling asleep and staying asleep

d) Waking up too early in the morning and not able to fall back asleep

Calgary Symptoms of Stress Inventory (cSOSI)

This questionnaire is designed to measure the different ways people respond to stressful situations. The questionnaire contains sets of questions dealing with various physical, psychological and behavioral responses. We are particularly interested in the frequency with which you may have experienced these stress related symptoms during the **past week**.

Never	***Infrequently***	***Sometimes***	***Often***	***Very Frequently***
0	***1***	***2***	***3***	***4***

Stress is often accompanied by a variety of emotions.
During the last week, have you felt:

1. Like life is entirely hopeless	0	1	2	3	4
2. Unhappy and depressed	0	1	2	3	4
3. Alone and sad	0	1	2	3	4
4. That worrying gets you down	0	1	2	3	4
5. Like crying easily	0	1	2	3	4
6. That you wished you were dead	0	1	2	3	4
7. Frightening thoughts keep coming back	0	1	2	3	4
8. You suffer from severe nervous exhaustion	0	1	2	3	4

Does it seem:

9. You become mad or anger easily	0	1	2	3	4
10. When you feel angry, you act angrily toward most everything	0	1	2	3	4
11. You are easily annoyed and irritated	0	1	2	3	4
12. That little things get on your nerves	0	1	2	3	4
13. Angry thoughts about an irritating event keep bothering you	0	1	2	3	4
14. You let little annoyances build up until you just explode	0	1	2	3	4
15. Your anger is so great that you want to strike something	0	1	2	3	4

Never	*Infrequently*	*Sometimes*	*Often*	*Very Frequently*
0	*1*	*2*	*3*	*4*

Muscle tension is a common way of experiencing stress. Have you noticed excessive tension, stiffness, soreness or cramping in the muscles in your:					
16. Shoulders	0	1	2	3	4
17. Neck	0	1	2	3	4
18. Back	0	1	2	3	4
19. Jaw	0	1	2	3	4
20. Forehead	0	1	2	3	4
21. Eyes	0	1	2	3	4
22. Hands or arms	0	1	2	3	4
23. Tension headaches	0	1	2	3	4
Does it seem:					
24. Thumping of your heart	0	1	2	3	4
25. Rapid or racing heart beats	0	1	2	3	4
26. Rapid breathing	0	1	2	3	4
27. Irregular heart beats	0	1	2	3	4
28. Difficult breathing	0	1	2	3	4
29. Pains in your heart or chest	0	1	2	3	4
Do you experience:					
30. Difficulty in staying asleep at night	0	1	2	3	4

Never	*Infrequently*	*Sometimes*	*Often*	*Very Frequently*
0	*1*	*2*	*3*	*4*

31. Hot or cold spells	0	1	2	3	4
32. Having to get up in the night to urinate	0	1	2	3	4
33. Sweating excessively even in cold weather	0	1	2	3	4
34. Having to urinate frequently	0	1	2	3	4
35. Early morning awakening	0	1	2	3	4
36. Flushing of your face	0	1	2	3	4
37. Difficulty in falling asleep	0	1	2	3	4
38. Breaking out in cold sweats	0	1	2	3	4
Have you experienced:					
39. Feeling faint	0	1	2	3	4
40. Feeling weak and faint	0	1	2	3	4
41. Spells of severe dizziness	0	1	2	3	4
42. Nausea	0	1	2	3	4
43. Blurring of your vision	0	1	2	3	4
44. Severe pains in your stomach	0	1	2	3	4
Does it seem:					
45. You must do things very slowly to do them without mistakes	0	1	2	3	4
46. You get directions and orders wrong	0	1	2	3	4
47. Your thinking gets completely mixed-up when you have to do things quickly	0	1	2	3	4

Never	*Infrequently*	*Sometimes*	*Often*		*Very Frequently*		
0	*1*	*2*	*3*		*4*		
48. You have difficulty in concentrating			0	1	2	3	4
49. You become suddenly frightened for no good reason			0	1	2	3	4
50. You become so afraid you can't move			0	1	2	3	4
Have you experienced:							
51. Colds			0	1	2	3	4
52. Hoarseness			0	1	2	3	4
53. Colds with complications (e.g. Bronchitis)			0	1	2	3	4
54. Nasal stuffiness			0	1	2	3	4
55. Having to clear your throat often			0	1	2	3	4
56. Sinus headaches			0	1	2	3	4

5-FACET M QUESTIONNAIRE

Please rate each of the following statements using the scale provided. Write the number in the blank that best describes your own opinion of what is **generally** true for you.

Never True	*Rarely True*	*Sometimes True*	*Often True*	*Always True*
1	*2*	*3*	*4*	*5*

1. When I'm walking, I deliberately notice the sensations of my body moving.	1	2	3	4	5
2. I'm good at finding words to describe my feelings.	1	2	3	4	5
3. I criticize myself for having irrational or inappropriate emotions.	1	2	3	4	5
4. I perceive my feelings and emotions without having to react to them.	1	2	3	4	5
5. When I do things, my mind wanders off and I'm easily distracted.	1	2	3	4	5
6. When I take a shower or bath, I stay alert to the sensations of water on my body.	1	2	3	4	5
7. I can easily put my beliefs, opinions, and expectations into words.	1	2	3	4	5
8. I don't pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted.	1	2	3	4	5
9. I watch my feelings without getting lost in them.	1	2	3	4	5
10. I tell myself I shouldn't be feeling the way I'm feeling.	1	2	3	4	5
11. I notice how foods and drinks affect my thoughts, bodily sensations, and emotions.	1	2	3	4	5
12. It's hard for me to find the words to describe what I'm thinking.	1	2	3	4	5
13. I am easily distracted.	1	2	3	4	5
14. I believe some of my thoughts are abnormal or bad and I shouldn't think that way.	1	2	3	4	5
15. I pay attention to sensations, such as the wind in my hair or sun on my face.	1	2	3	4	5
16. I have trouble thinking of the right words to express how I feel about things	1	2	3	4	5

Never True	*Rarely True*	*Sometimes True*	*Often True*	*Always True*
1	*2*	*3*	*4*	*5*

17. I make judgments about whether my thoughts are good or bad.	1	2	3	4	5
18. I find it difficult to stay focused on what's happening in the present.	1	2	3	4	5
19. When I have distressing thoughts or images, I "step back" and am aware of the thought or image without getting taken over by it.	1	2	3	4	5
20. I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing.	1	2	3	4	5
21. In difficult situations, I can pause without immediately reacting.	1	2	3	4	5
22. When I have a sensation in my body, it's difficult for me to describe it because I can't find the right words.	1	2	3	4	5
23. It seems I am "running on automatic" without much awareness of what I'm doing.	1	2	3	4	5
24. When I have distressing thoughts or images, I feel calm soon after	1	2	3	4	5
25. I tell myself that I shouldn't be thinking the way I'm thinking.	1	2	3	4	5
26. I notice the smells and aromas of things.	1	2	3	4	5
27. Even when I'm feeling terribly upset, I can find a way to put it into words.	1	2	3	4	5
28. I rush through activities without being really attentive to them	1	2	3	4	5
29. When I have distressing thoughts or images I am able just to notice them without reacting.	1	2	3	4	5
30. I think some of my emotions are bad or inappropriate and I shouldn't feel them.	1	2	3	4	5
31. I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow.	1	2	3	4	5
32. My natural tendency is to put my experiences into words.	1	2	3	4	5
33. When I have distressing thoughts or images, I just notice them and let them go.	1	2	3	4	5
34. I do jobs or tasks automatically without being aware of what I'm doing.	1	2	3	4	5

Never True	*Rarely True*	*Sometimes True*	*Often True*	*Always True*
1	***2***	***3***	***4***	***5***

35. When I have distressing thoughts or images, I judge myself as good or bad, depending what the thought/image is about.	1	2	3	4	5
36. I pay attention to how my emotions affect my thoughts and behavior.	1	2	3	4	5
37. I can usually describe how I feel at the moment in considerable detail.	1	2	3	4	5
38. I find myself doing things without paying attention.	1	2	3	4	5
39. I disapprove of myself when I have irrational ideas.	1	2	3	4	5

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

Profile of Mood States-Short Form

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

		Not at all	***A Little***	***Moderately***	***Quite a Bit***	***Extremely***
		0	***1***	***2***	***3***	***4***
1.	Tense	0	1	2	3	4
2.	Angry	0	1	2	3	4
3.	Worn-out	0	1	2	3	4
4.	Unhappy	0	1	2	3	4
5.	Lively	0	1	2	3	4
6.	Confused	0	1	2	3	4
7.	Peeved	0	1	2	3	4
8.	Sad	0	1	2	3	4
9.	Active	0	1	2	3	4
10.	On edge	0	1	2	3	4
11.	Grouchy	0	1	2	3	4
12.	Blue	0	1	2	3	4
13.	Energetic	0	1	2	3	4
14.	Hopeless	0	1	2	3	4
15.	Uneasy	0	1	2	3	4
16.	Restless	0	1	2	3	4
17.	Unable to concentrate	0	1	2	3	4
18.	Fatigued	0	1	2	3	4
19.	Annoyed	0	1	2	3	4
20.	Discouraged	0	1	2	3	4
21.	Resentful	0	1	2	3	4
22.	Nervous	0	1	2	3	4
23.	Miserable	0	1	2	3	4
24.	Cheerful	0	1	2	3	4
25.	Bitter	0	1	2	3	4
26.	Exhausted	0	1	2	3	4
27.	Anxious	0	1	2	3	4
28.	Helpless	0	1	2	3	4
29.	Weary	0	1	2	3	4
30.	Bewildered	0	1	2	3	4
31.	Furious	0	1	2	3	4
32.	Full of pep	0	1	2	3	4
33.	Worthless	0	1	2	3	4
34.	Forgetful	0	1	2	3	4
35.	Vigorous	0	1	2	3	4
36.	Uncertain about things	0	1	2	3	4
37.	Bushed	0	1	2	3	4

Beliefs and Attitudes about Sleep (DBAS-16)

Several statements reflecting people's beliefs and attitudes about sleep are listed below. Please indicate to what extent you personally agree or disagree with each statement. There is no right or wrong answer. For each statement, circle the number that corresponds to your own personal belief. Please respond to all items even though some may not apply directly to your own situation.

Strongly Disagree — Strongly Agree

0 1 2 3 4 5 6 7 8 9 10

1. I need 8 hours of sleep to feel refreshed and function well during the day.

0 1 2 3 4 5 6 7 8 9 10

2. When I don't get proper amount of sleep on a given night, I need to catch up on the next day by napping or on the next night by sleeping longer.

0 1 2 3 4 5 6 7 8 9 10

3. I am concerned that chronic insomnia may have serious consequences on my physical health.

0 1 2 3 4 5 6 7 8 9 10

4. I am worried that I may lose control over my abilities to sleep.

0 1 2 3 4 5 6 7 8 9 10

5. After a poor night's sleep, I know that it will interfere with my daily activities on the next day.

0 1 2 3 4 5 6 7 8 9 10

6. In order to be alert and function well during the day, I believe I would be better off taking a sleeping pill rather than having a poor night's sleep.

0 1 2 3 4 5 6 7 8 9 10

7. When I feel irritable, depressed, or anxious during the day, it is mostly because I did not sleep well the night before.

0 1 2 3 4 5 6 7 8 9 10

8. When I sleep poorly on one night, I know it will disturb my sleep schedule for the whole week.

0 1 2 3 4 5 6 7 8 9 10

9. Without an adequate night's sleep, I can hardly function the next day.

0 1 2 3 4 5 6 7 8 9 10

10. I can't ever predict whether I'll have a good or poor night's sleep.

0 1 2 3 4 5 6 7 8 9 10

11. I have little ability to manage the negative consequences of disturbed sleep.

0 1 2 3 4 5 6 7 8 9 10

12. When I feel tired, have no energy, or just seem not to function well during the day, it is generally because I did not sleep well the night before.

0 1 2 3 4 5 6 7 8 9 10

13. I believe insomnia is essentially the result of a chemical imbalance.

0 1 2 3 4 5 6 7 8 9 10

14. I feel insomnia is ruining my ability to enjoy life and prevents me from doing what I want.

0 1 2 3 4 5 6 7 8 9 10

15. Medication is probably the only solution to sleeplessness.

0 1 2 3 4 5 6 7 8 9 10

16. I avoid or cancel obligations (social, family) after a poor night's sleep.

0 1 2 3 4 5 6 7 8 9 10

Pittsburgh Sleep Quality Index (PSQI)

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

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

BED TIME: _____

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

NUMBER OF MINUTES: _____

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

GETTING UP TIME: _____

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

HOURS OF SLEEP PER NIGHT: _____

For each of the remaining questions, check the one best response. Please answer all questions.

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

Cannot get to sleep within 30 minutes

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

Wake up in the middle of the night or early morning

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

Have to get up to use the bathroom

not during the	less than	once or twice	three or more

past month	once a week	a week _____	times a week
_____	_____		_____

Cannot breathe comfortably

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

Cough or snore loudly

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

Feel too cold

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

Feel too hot

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

Had bad dreams

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

Have pain

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

Other reason(s), please describe _____

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

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

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

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

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

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

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

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

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

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