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THE ASSOCIATION OF FREQUENCY, INTENSITY, AND DISTRESS OF FATIGUE, PAIN AND INSOMNIA FOR CHEMOTHERAPY PATIENTS

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THE ASSOCIATION OF FREQUENCY, INTENSITY AND DISTRESS OF FATIGUE, PAIN AND INSOMNIA FOR CHEMOTHERAPY PATIENTS

By

Jacquelyn Ann Keehne-Miron

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Abstract

THE ASSOCIATION OF FREQUENCY, INTENSITY AND DISTRESS OF FATIGUE, PAIN AND INSOMNIA FOR CHEMOTHERAPY PATIENTS

By

Jacquelyn Ann Keehne-Miron

Purpose/Objectives: The purpose of this research was to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized clinical trials (RCT's) of a cognitive behavioral intervention. This study will answer two questions. At baseline observation and at 10 weeks is there an association between the dimension of fatigue and the dimension of pain and/or insomnia for adults receiving chemotherapy? Also, can categories of response to fatigue management predict changes in the dimensions of pain and insomnia at 10 weeks? Co-variates examined include: age, site and stage of cancer, sex, and co-morbid conditions.

Setting/Methods: Seven cancer centers throughout the Midwest and East coast accrued patients. Descriptive, cross-tabs, t-tests and regression analyses were conducted using SPSS version 13.0.

Sample: Adults receiving chemotherapy for solid tumors or non-Hodgkin's lymphoma (n=671) participated. Seventy percent were female and 86.3% were Caucasian. Thirty-five percent had breast cancer and 21% had lung cancer. The mean age in this study was 57.6 years (range of 25-90).

Findings: At baseline and 10 weeks there is an association between the three dimensions of fatigue and the same dimensions for pain and insomnia. Categories of

response to fatigue management were capable of predicting changes in the dimensions of pain and insomnia at 10 weeks. For all dimensions of pain and insomnia, with the exception of 10 week frequency and distress of insomnia, younger age enhanced the dimension of pain or insomnia over and above the effect of fatigue. Co-morbid conditions also enhanced the dimensions of pain at both baseline and 10 weeks over and above the effect of fatigue. However, co-morbid conditions only influenced frequency of insomnia at baseline over and above the effect of fatigue. This study supported the appropriateness of the use of fatigue management categories as a research technique. Future studies should be directed toward the use of these categories to compare interventions aimed at various dimensions of multiple co-occurring symptoms such as fatigue, pain and insomnia in RCT's.

Dedication

This dissertation is dedicated to my husband and family, and to the cancer patients I have had the privilege of working with.

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Chapter 1

Overview

The American Cancer Society projects that there will be 1,444, 920 new cases of cancer diagnosed in the United States in 2007 (Jemal, Siegel, Ward, Murray, Xu, & Thun, 2007). It is estimated that 559,650 Americans will die of cancer in 2007, making it the second most common cause of death in the United States (Jemal et al., 2007). However, due to progress in early diagnosis and the implementation of new and improved treatments 5-year survival is at 65% for cancers diagnosed between 1995 and 2001, up from a 50% rate for cancers diagnosed between 1974 and 1976 (American Cancer Society, 2006). Although prevalence of cancer is high in the United States, survival rates are improving. The absolute number of cancer deaths in the United States decreased for the years of 2005 and 2006 by more then 3,000 cases from 2003 and 2004 (Jemal et al., 2007). The National Cancer Institute estimates that 10.5 million Americans are alive with some history of cancer (National Cancer Institute, 2007). Thus, cancer and the treatment of cancer is a major health concern in the United States.

The cancer treatment experience will be unique to each individual. For some patients a one-time surgical procedure may cure them of their disease. For others, cancer treatment may involve one or any combination of the following: surgery, chemotherapy treatments, bone marrow or stem cell transplantation, radiation therapy, biologic therapy and/or gene therapy. However, once experienced, it is not likely that one will forget the emotional and physical challenges associated with cancer.

Unfortunately, with a cancer diagnosis and treatment comes the advent of symptoms that can be troublesome to the patient, their caregivers and their practitioners. Rutledge

and McGuire (2004) supported that symptoms are a phenomena that are multidimensional, complex, and subjective changes in biopsychosocial functioning, sensations, or cognition. Symptoms may be present prior to diagnosis, during treatment, as well as upon the completion of treatment. Treatment may consist of any or a combination of the modalities listed previously. The treatment itself may cause symptoms, i.e., fatigue caused by chemotherapy or a skin reaction caused by radiation therapy. The cancer itself may also cause symptoms, i.e., pain caused by a colon cancer mass pressing on a nerve. It is not uncommon for patients to experience both symptoms caused by the disease process as well as the treatment regimen designed to fight the cancer. For some patients the best treatment option may be palliative care, which may also contain one of the previously mentioned treatment modalities. Even comfort measures such as pain medicines have the potential to produce unwanted symptoms on top of symptoms that may be present from the disease process itself. Symptoms are both related to the disease process as well as the treatment strategies designed to eliminate the cancer. Many patients will experience more then one symptom concurrently during the course of their disease treatment or after they have finished active treatment for their cancer.

It is due to the multiple nature of symptoms that patients are most likely to seek care from the health care team (Cleeland, Mendoza, Wang, Chou, Harle, Morrissey, & Engstrom, 2000; Rutledge & McGuire, 2003). Based on a 2001 study of newly diagnosed cancer patients (n=841), all 65 years of age or over, those diagnosed with lung cancer reported an average of 5.3 symptoms, breast cancer patients reported 3.6 symptoms, colon cancer patients reported 3.7, and prostate cancer patients reported an

average of 4.3 symptoms (Given, Given, Azzouz, Kozachik, & Stommel, 2001). The complex and dynamic nature of concurrent multiple symptoms pose significant challenges for patients and caregivers, as well as health care providers. The symptom experience will be unique to each patient. Each patient will experience varying degrees of frequency, intensity and distress of the symptoms (Dodd, Janson, Facione, Faucett, Froelicher, Humphreys, et al., 2001a; Lenz, Pugh, Milligan, Gift, & Suppe, 1997).

The dimensions of frequency, intensity and distress of symptoms are typically measured, researched and treated as they relate to each individual symptom. The majority of our research to date has focused on individual symptoms (Dodd et al., 2001a). The effect of the dimensions of symptoms as well as the symptoms themselves changing over time is of significant concern to patients, caregivers and members of the health care team. Patients may experience symptoms related to the disease and/or the treatment for their entire life. Although cancer/chemotherapy symptoms "wax and wane" over the course of their existence (Sarna, 1993), particular patterns are unknown.

Different dimensions of the symptom experience such as frequency, intensity, and distress, will also change over time. For example, Tishelman, Degner, Rudman, Bertilsson, Bond, Broberger, et al. (2005) found in a symptom study of lung cancer patients, completed over six different data collection points following diagnosis, that symptom intensity (frequency) and symptom distress (how disturbing or troubling a symptom was perceived to have been) were not equivalent over time. Actual symptom presentation as well as patient perceptions of the symptoms will change over time. Multiple, co-occurring symptoms will further complicate this scenario for patients as well as practitioners.

Researchers have descriptively studied multiple co-occurring symptoms throughout the chemotherapy experience (Cleeland et al., 2000; Dodd, Miaskowski, & Paul, 2001b; Kim, McGuire, Tulman, & Barsevick, 2005). In addition, researchers have begun to examine the effect of single or multiple symptoms as they change over time and their impact on outcomes such as physical functioning or quality of life (Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Cooley, Short, & Moriarty, 2003; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Gift, Stommel, Jablonski, & Given, 2003; Given, Given, Azzouz, Stommel, & Kozachik, 2000). The research that has been conducted on multiple, co-occurring symptoms has typically focused on symptoms and/or disease states identified a priori (i.e., pain and fatigue for only breast or lung cancer patients) and their relationship with an outcome (Bender, et al., 2005; Gift et al., 2003; Given, Given, McCorkle, Kozacik, Cimprich, Rahbar, & Wojcik, 2002).

As stated above, many patient present with a diagnosis or cancer or at the start of chemotherapy treatment with multiple co-occurring symptoms. The symptoms may "wax and wane" throughout chemotherapy or radiation treatment and even persist after the completion of therapy. Nursing interventions and studies have traditionally focused on individual symptoms. No randomized clinical trials (RCT) containing a nursing intervention have been identified that associate the dimensions of the frequency, intensity, and distress of one symptom with these same dimensions for additional symptoms that are co-occurring. No studies have been found that examine the potential of a change in dimension of one symptom being able to predict the co-occurrence of additional symptoms and/or changes in the dimensions of the other symptoms over time.

This study will examine multiple co-occurring symptoms in adults with various types of solid tumors as well as non-Hodgkin's lymphoma. The focus will be on three of the most common co-occurring symptoms associated with a cancer diagnosis and chemotherapy treatment; fatigue, pain and insomnia. This study will examine the frequency, intensity and distress for each symptom and associate these dimensions with the other symptoms presenting concurrently. Thus, as changes occur in one dimension of one of the symptoms of fatigue, pain, or insomnia, other dimensions of the other symptoms will be examined for possible changes. Due to the fact that fatigue is such a prevalent and persistent symptom with chemotherapy, the influence of fatigue and the management of fatigue as it is associated with the presence of and dimensions of the other symptoms of pain and insomnia will be of particular interest.

Fatigue

Fatigue has been one of the most widely studied cancer/chemotherapy symptoms. The symptom of fatigue has been defined as being subjective in nature with patients recalling sensations of weakness, lack of energy and/or tiredness (Cella, Lai, Chang, Peterman, & Slavin, 2002; Stone, Richards, & Hardy, 1998). Fatigue in the cancer patient is clinically different than fatigue experienced in the general healthy population. Cella et al. (2002) noted in a study comparing the general healthy United States population (n=1010) with non-anemic cancer patients (n=113) as well as anemic cancer patients (Hemaglobin < 11 g/DL) receiving chemotherapy (n=2369) that fatigue scores at baseline and upon completion of the study were significantly worse among the three groups respectively ($p < .001$).

However, Cella et al. (2002) noted that anemia is not the only variable that contributes to fatigue in the cancer/chemotherapy patient. Other possible causes include cytokine production, altered muscle metabolism, sleep deprivation, stress and depression. Nieboer et al. noted that joint ($p < .0001$) and muscle pain ($p < .0283$) were associated with greater amounts of fatigue in breast cancer patients (n=885) (Nieboer, Buijs, Rodenhuis, Seynaeve, Beex, van der Wall, et al., 2005). In addition, strong associations have been noted between increased severity of fatigue and poor performance status ($p < .001$), gastrointestinal symptoms ($p < .001$), pain ($p < .05$), and insomnia ($p < .05$) for patients receiving chemotherapy for non-Hodgkin's lymphoma (Wang, Giralt, Mendoza, Engstram, Johnson, Peterson, et al., 2002).

Fatigue is multifaceted and multidimensional. Fatigue is the most common symptom associated with cancer and its treatment (Cella, Davis, Breitbart, & Curt, 2001). Prevalence of fatigue for various cancer survivors either undergoing therapy or upon completion of therapy ranges from 25% to 99% as reported in different studies (Blesch, Paice, Wickham, Harte, Schnoor, Paul, et al., 1991; Irvine, Vincent, Graydon, Bubella, & Thompson, 1994; Servaes, Verhagen, & Bleijenberg, 2002). Fatigue has been recognized as the most distressing and the most unrelieved symptom of cancer as well as cancer treatment (Bower, 2005; Cella et al., 2002). Many studies have supported the negative effect of fatigue on personal, professional and social activities resulting in physical, psychologic, and economic issues influencing quality of life (Cella, 1997; Cella et al., 2001; Cella, Tulsky, Gray, Sarafian, Linn, Bonomi, et al., 1993; Ferrell, Grant, Funk, Otis-Green, & Garcia, 1996; Irvine et al., 1994; Nail & Jones, 1995; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). The Fatigue Coalition reported that 81% of

patients who have undergone chemotherapy reported diminished energy as the most common physical complaint. In addition, 78% of these patients stated that they consistently required more sleep and rest. The consequences of this fatigue was reported to have caused 88% of the respondents to alter their daily routines and 75% of those employed were required to change their work status due to the fatigue (Berndt, Kallich, McDermott, Xu, Lee, & Glaspy, 2005).

There is little doubt that the presence of fatigue is widespread and burdensome to patients undergoing chemotherapy. Cella et al. (2001) support that fatigue is typically the initial symptom experienced by patients. In addition fatigue increases with the progression of cancer and treatment (Cella et al., 2001). Tishelman et al. (2005) found in a study of lung cancer patients (n=400) that difficulty breathing, pain, and fatigue were the symptoms associated with the greatest amounts of distress (how disturbing or troublesome the symptom is to the patient). In this same study, fatigue remained the most distressing symptom throughout the entire study period (six time points over 1 year after diagnosis).

Gift et al. (2003) found in a study of newly diagnosed lung cancer patients (n= 112) that fatigue was the symptom with the highest ranking for incidence rate at baseline (upon diagnosis), three months later, and six months following diagnosis. Fatigue is problematic at baseline and may remain throughout and after the treatment period for cancer patients. However, fatigue is seldom a symptom appearing in isolation. Past research has supported that fatigue may effect the severity levels of additional symptoms experienced by the cancer patient (Given et al., 2001; Miaskowski & Lee, 1999). Pain

and insomnia are two symptoms that have been noted to co-occur with fatigue among cancer patients.

Pain and Insomnia Associated with Fatigue

Sarna (1993), noted in a study of women with lung cancer (n = 69) that the three most prevalent and distressing symptoms included fatigue, pain and insomnia. In fact, 41% of the women experiencing fatigue concurrently experienced pain and 31% experienced concurrent insomnia. Degner and Sloan (1995) validated this finding in their study with 434 newly diagnosed cancer patients with a variety of solid tumors. Degner and Sloan found that the most frequently occurring symptoms include fatigue, pain, loss of appetite, cough, and insomnia.

Beck and Schwartz (2000) found in a cross-sectional study (n=84) that pain intensity levels negatively influenced fatigue reports as well as "sleep quality." Likewise, Given et al. (2001) supported in a study of solid tumor patients (n= 841) age 65 and older, that those experiencing fatigue alone reported 4.4 additional symptoms. Those experiencing pain alone reported 3.8 additional symptoms. However, patients who experienced fatigue and pain concurrently reported an average of 6.3 "other" symptoms. Given et al. (2001) also found that 50% (n=161) of the patients that concurrently experienced pain and fatigue likewise experienced insomnia.

Fatigue, pain and insomnia were the three symptoms selected to examine in this study. The presence of multiple symptoms having a synergistic effect on outcomes such as morbidity has been discussed in the literature (Dodd et al., 2001a; Rutledge & McGuire, 2004). Although this study will not be examining morbidity as an outcome, the associations among three symptoms (fatigue, pain and insomnia) will be examined.

Fatigue appears to be a dominant symptom that may influence the occurrence of other symptoms, especially pain and insomnia due to their prevalence in the cancer and/or chemotherapy patient. To best describe and evaluate these symptoms the dimensions of frequency, intensity and distress were used to define each symptom cited above. Frequency was defined as the number of days out of seven days a patient reported the symptom as being present. Intensity was defined as a patient reported ranking of the symptom on a scale of 0 meaning symptom not present to 10 meaning the intensity of the symptom was the worst possible that the patient could imagine. Distress was defined as a self reported scale with 0 meaning the symptom does not bother the patient in any way to 10 meaning the symptom causes the worst bother for the patient that they can imagine. The higher the score, as reported by the patient in the 0-10 scale described above, assigned to the dimension (frequency, intensity and/or distress) the more problematic the symptom (fatigue, pain, and/or insomnia) is for the patient. It is assumed that appropriate and effective interventions may cause a change in the reported score for a dimension, thus, the score would decrease. Of course, the opposite may happen as well, if a patient's symptoms are not being properly managed or their condition is worsening their reported scores may increase. Due to the fact that this study contained an intervention component it was vital to examine changes in the symptom dimensions over time.

Due to the focus on the symptom of fatigue in this study it is important to examine the effect of fatigue management on the symptoms of pain and insomnia. To accomplish this, categories of response to fatigue management (none / mild, non-response, partial response, and full response), as established in the literature (Given, Given, Jeon, Sikorskii, in press), were examined as they were related to the dimensions of frequency,

intensity and distress for all three symptoms. These concepts will be further described in the Research Questions section.

Research Questions

Symptoms associated with cancer and chemotherapy seldom present individually. Multiple co-occurring symptoms may have a synergistic effect on each other (Rutledge & McGuire, 2004). Three of the most common symptoms associated with cancer/chemotherapy include fatigue, pain, and insomnia. Patients will experience varying degrees of frequency, intensity and distress associated with each symptom. These dimensions for each symptom and their associations among the symptoms of fatigue, pain and insomnia were explored in detail. The following research questions were addressed in this study.

Research Question 1

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *frequency* of fatigue and frequency of pain, as well as frequency of fatigue and frequency of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? The dimension of frequency is the number of days out of the past seven that a patient reports the symptom as present. This will be a continuous variable with a possible range of 0-7.

Research Question 2

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *intensity* of fatigue and intensity of pain, as well as intensity of fatigue and intensity of insomnia for adults receiving chemotherapy? Is this

association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? The intensity dimension is defined as a ranking of the symptom on a scale of 0 meaning not present to 10 meaning the intensity is the worst possible. This will be a continuous variable with a possible range of 0-10.

Research Question 3

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *distress* related to fatigue and distress related to pain, as well as distress related to fatigue and distress related to insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? The dimension of distress will be defined as a scale with 0 meaning the symptom does not bother the patient to 10 meaning the symptom causes the worst bother the patient can imagine. This will be a continuous variable with a possible range of 0-10.

Research Question 4

Using categories of response to fatigue management (none / mild, non-response, partial response and full response) established in the literature, determine how changes in the dimensions of frequency, intensity, and distress of pain and insomnia are predicted by categories of response to the management of fatigue between baseline and 10 weeks? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions?

Question 4 allowed the researcher to determine if the change in frequency of fatigue was predictive of a change in the dimensions of frequency, intensity and/or distress for the associated symptoms of pain and insomnia. For this question, fatigue intensity levels

were converted from continuous variables to categorical variables to facilitate comparison with fatigue response categories (Mendoza, Wang, Cleeland, Morrissey, Johnson, Wendt, et al., 1999). Fatigue response categories, as reported in the literature (Miaskowski, Dodd, West, Paul, Schumacher, Tripathy, et al., in press), define categorically the change in fatigue intensity levels after an intervention has been conducted. Response to fatigue management categories include: none / mild, non-response, partial response and full response. This question examined how changes in the dimensions of frequency, intensity, and distress of pain and insomnia at 10 weeks are predicted by a change in fatigue categories from baseline to 10 weeks. Specific measures will be further clarified in Chapter 4 of this dissertation. All four research questions contain the association of patient characteristics of age, site and stage of cancer, sex, and co-morbid conditions with the symptoms of fatigue, pain, and insomnia. These antecedents will be described in detail below.

Antecedents

Age

Demographic and/or disease characteristics may influence the research questions. A brief discussion supporting the selection of each variable; age, site and stage of cancer, sex, and co-morbid conditions follow. The variable of age as it effects a cancer diagnosis and treatment has received heightened awareness since the development of the National Cancer Institute Surveillance, Epidemiology, and End Result programs (NCI SEER). Insights from this program have determined that increasing age leads to the development of tumors, pharmacology may differ in an older population, as well as the effect of co-

morbidity, previous illness, and disabilities on the management of an older patient with cancer (Yancik & Ries, 2000).

Tishelman et al. (2005) noted that age (younger) and sex (women) were variables negatively influencing intensity (frequency) levels of fatigue throughout a study of adults with inoperable lung cancer (n=400). Age was examined in a study by Degner and Sloan (1995) (n = 434) with lung cancer to find that older patients experienced less symptom distress vs. younger counterparts.

Dodd et al. (2001b) studied the symptom cluster of pain, fatigue and sleep insufficiency in mainly breast and colon/rectal cancer patients during the first three chemotherapy treatments (n=93). Dodd et al. (2001b) found that age explained 11.8% of the change in functional status ($p < 0.001$) for these patients between baseline and the end of the third cycle of chemotherapy. Pain was able to explain 10.7% of the change ($p = 0.002$), fatigue explained 7.3% of the change in functional status ($p = 0.011$), and sleep insufficiency was statistically not significant ($p = 0.344$). On the contrary, Given et al. (2001) noted no relationship between advancing age and pain or fatigue in a sample of solid tumor chemotherapy patients all over the age of 65. Therefore, this conflicting information is rationale for the selection of age as an antecedent variable.

Stage of Disease

The stage of disease was noted by Gift et al. (2003) to be predictive of the number of symptoms that co-occurred with fatigue six months following a diagnosis of lung cancer (n=112). Gift et al. (2003) used a subset of lung cancer patients from the Given et al. (2001) study cited above. Given et al. (2001) reported in the larger data base including all tumor types that age, co-morbid conditions, and site of cancer failed to interact among

each other to produce a significant prediction of any combination of pain or fatigue. However, stage of disease when examined categorically as early or late stage was significant for predicting those who reported pain and fatigue vs. only those reporting pain alone (Given et al., 2001).

Sex

Sex has become a variable of interest in the cancer literature. Discussion related to sex ranges from examining how sex influences treatment choices to demographic findings supporting that male sex can be considered and independent negative prognostic factor for lung cancer survival (Fu, Kau, Severson, Kalemkerian, 2005; Moynihan, 2002). Numerous authors have found that women are more likely to experience pain and fatigue, or each alone when compared to neither symptom (Degner & Sloan, 1995; Given et al., 2001; Tishelman et al., 2005). Thus, the sex variable may indicate tolerance for therapy as well as provide prognostic value.

Co-morbid Conditions / Site of Cancer

The presence of co-morbid conditions were found to positively correlate with symptom distress and was found to be a significant predictor of symptom distress in women with lung cancer as reported by Sarna (1993). Given et al. (2001) noted that "patients with three or more comorbid conditions were more likely to report pain, fatigue, or their combination, when compared with those reporting neither symptom" (p. 462). Given et al. (2001) also noted mean number of symptom variations per differing sites of cancer. The variables of age, stage, sex, co-morbid conditions and site of cancer will be important variables in examining the effect of associations among the dimensions of frequency, intensity, and distress for fatigue, pain and insomnia.

It is essential to note that participation in a cognitive behavioral intervention is also a variable included in the data base for this study. This study examined data from 2 NCI supported longitudinal panel studies of adult cancer patients undergoing chemotherapy (RO1 CA-79280 {study number one} & RO1 CA-30724 {study number two}). Both studies contained cognitive behavioral interventions. These interventions will be described in detail in Chapter 4.

Purpose of the Research

The purpose of this research was to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occurred at two different data collection points in two randomized cognitive behavioral intervention clinical trials. This study answered the questions: At baseline observation and at 10 weeks is there an association between the dimension of frequency, intensity, and distress of fatigue and frequency, intensity and distress of pain and/or insomnia for adults receiving chemotherapy? Each dimension was analyzed in a separate question as described earlier. All research questions examined the association between the symptoms as possibly being influenced by the variables of age, site and stage of cancer, sex, and co-morbid conditions.

This research studied these variables within the context of an adapted Symptom Experience Model (SEM) (Armstrong, 2003). The SEM has been adapted to include the dimensions of time and an intervention to accommodate the chronic nature of the cancer diagnosis as well as the longitudinal, randomized control/intervention design of the studies used as the database for this study. In Chapter 2, the conceptual model and the adapted Symptom Experience Model by Armstrong (2003) will be presented and

discussed. The support for the adaptation of the model to include the dimensions of time and an intervention will be explained. In Chapter 3, a review of the oncology multiple, co-occurring symptom literature including the symptoms of fatigue, pain and insomnia will be described. The sample, recruitment process, measures, and methods for data collection will be presented in Chapter 4. The research findings will be presented in Chapter 5. Implications for clinical practice, study limitations and future direction for nursing research based on this work will also be presented in Chapter 5. Ultimately, this research may lead to future studies intended to design and test effective interventions to manage and/or prevent the individual and/or multiple, co-occurring symptoms of fatigue, pain and insomnia, in adult chemotherapy patients, thus, improving functional status, quality of life and/or economics (Kim et al., 2005).

Chapter 2

Conceptual Framework

In this chapter an adapted version of the Symptom Experience Model (SEM) by Armstrong (2003) will be presented and described. The rationale for selecting the SEM will be presented, followed by an explanation of the need to adapt it to this research. The adapted SEM includes the addition of a time and intervention component. The addition of the time and intervention components will be described in the context of the relationship of the co-occurring symptoms of fatigue, pain and insomnia within the cancer disease and treatment trajectory. The measurements of symptoms in this research occurred at two different data collection points; the effect of a cognitive behavioral intervention was also evaluated.

Intervention Adaptation to the Model

The addition of the intervention component to the SEM model will allow the model to guide this project. Two distinct interventions, a nursing intervention (Nurse Assisted Symptom Management, NASM) and/or an automated telephone symptom monitoring system (Automated Telephone Symptom Management, ATSM) intervention was implemented in the original studies that served as the database for this study. These interventions will be described in Chapter 4. The addition of the intervention will also promote utility of this adapted SEM for future studies as nursing research moves beyond descriptive symptom studies into randomized clinical trials designed to demonstrate the effect of antecedents and interventions on outcomes.

To begin, a brief look at the development of the SEM by Armstrong (2003). Figure 1 describes the SEM as created by Armstrong (2003). Armstrong used the Walker and

Avant (1995) method of concept analysis to examine the effect of multiple symptoms on the cancer patient's symptom experience. An extensive literature review was conducted examining the concept of the symptom experience, defining attributes, antecedents, consequences, a model case and other cases, and conclusions and implications for nursing and research. Four common themes guided by research conducted by Leventhal and Johnson (1983), Rhodes and Watson (1987), Lenz et al. (1997), and Lenz, Suppe, Gift, Pugh, & Milligan (1995) provided the foundation for the creation of the SEM. The themes included: symptoms are subjective in nature, symptoms are a departure from normal functioning, they are multidimensional, and they include an emotional response (Armstrong, 2003).

Armstrong used the classic Rhodes and Watson (1987) definition of symptoms as the foundation for her model; " . . . subjective, phenomena regarded by individuals as an indication of a condition departing from normal function, sensation, or appearance or as perceived indicators of change in normal functioning as experienced by patients" (2003, p. 601). In addition, the Armstrong model is rooted in the premise that symptoms occur concurrently and refers ". . . to the experience of multiple symptoms as the 'symptom experience'" (2003, p. 601). Similar to the work of Lenz et al. (1995, 1997) and Dodd (2001a), Armstrong included the dimensions of frequency, intensity, distress and meaning of the symptoms in the model. These dimensions are referred to as concepts that further delineate each symptom that make up the symptom experience. Armstrong applies the dimensions to each symptom in ". . . a multidimensional experience that can be measured separately or in combination with other symptoms" (2003, p. 602).

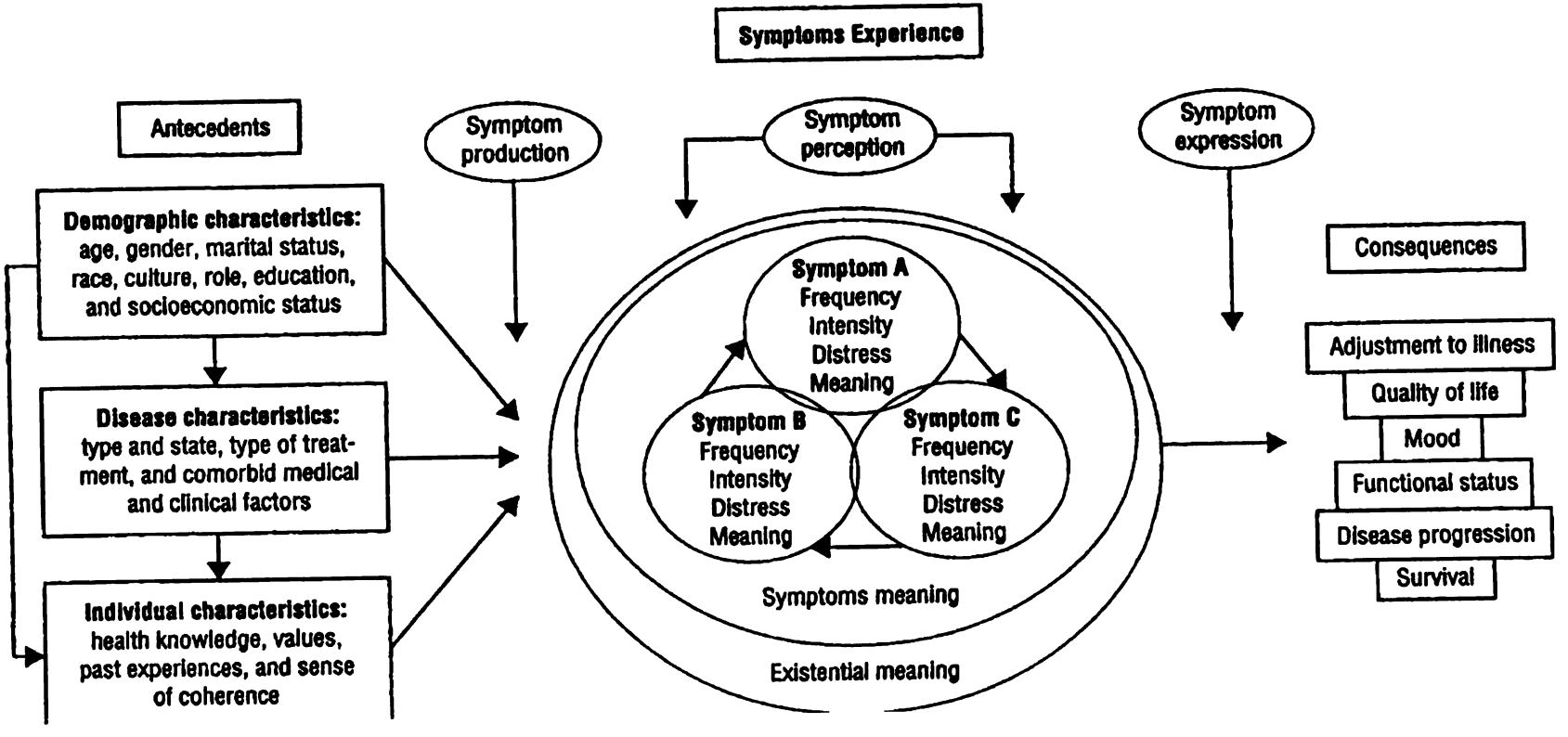


Figure 1. The Symptom Experience Model

The Symptom Experience: A Concept Analysis," by Armstrong, T.S., 2003, Oncology Nursing Forum, 30 (4), p. 603. Copyright 2003 by Oncology Nursing Society.

The SEM is designed to serve as a guide for supporting practice and research related to multiple, co-occurring symptoms. This model was originally created for application with an oncology population. These two statements represent rationale for selection of the SEM for this study. Additional rationale will be described while examining each component of the model. In addition, the elements of time and an intervention will be discussed. The following sections of this chapter will describe the model (from left to right) with application for this research identified within each component of the model.

The Symptom Experience Model

Antecedents

Various antecedents initiate the symptom experience when viewing the SEM from left to right. Antecedents are used to clarify both the attributes and the context in which the symptom experience is found (Armstrong, 2003; Walker & Avant, 1995). Antecedents are characteristics that the patient brings to the symptom experience such as demographic characteristics, disease characteristics, and individual characteristics (Armstrong, 2003). Theoretically, antecedent components include: physiologic, psychological, and situational factors that are the initial contributors to the symptom experience (Rhodes & Watson, 1987). Likewise, Lenz et al. (1997) incorporated physiologic antecedents into their classic symptom model, the middle range Theory of Unpleasant Symptoms (TOUS). Armstrong (2003) labeled the antecedents in the SEM as demographic characteristics, disease characteristics, and individual characteristics.

An additional classic model, the revised Symptom Management Model (SMM) by Dodd et al. (2001a) likewise depicts various domains that influence the symptom experience, management strategies and outcomes. An example from the SMM that is

closely replicated in the SEM is the environment domain that " . . . refers to the aggregate of conditions or the context within which a symptom occurs; that is, it includes physical, social, and cultural variables" (Dodd et al., 2001a, p. 671). Demographic characteristics in the antecedent section of the SEM include age, sex, marital status, race, culture, role, education, and socioeconomic status. Disease characteristics include type and state of the disease, type of treatment and co-morbid medical and clinical factors. As an example, in breast cancer the disease characteristics such as tumor size, disease stage, and HER2/neu status assists in determining the type of treatment a patient receives, thus, influencing the symptoms the patient may experience. Additional characteristics that are considered antecedents include such areas as health knowledge, values, past experiences, and sense of coherence. An example of the influence of health knowledge, values and past experiences may include the breast cancer patient who chooses a bilateral mastectomy although disease is found at an early stage in only one breast. This patient may feel very strongly per her health belief system that prophylaxis is an optimum approach for dealing with a possible future cancer, in addition, she may have an extensive family history of the disease that has influenced her values and past experience. Recall that the numerous antecedents cited in the SEM (demographic, disease characteristics, and individual characteristics) support the idea that multiple, co-occurring symptoms may or may not share the same etiology (Kim et al., 2005). The etiologies, as well as other antecedents, play a role in the production of symptom(s).

Symptom Production

Antecedents contribute to the production of the symptom. Symptom production is the next component of the model (moving left to right, after antecedents). Theoretically,

Armstrong (2003) cites the work of Leventhal and Johnson (1983) to define symptom production as an objective, concrete representation of the disease. Although not clearly articulated by Armstrong, the SEM likely depicts symptom production as the actual display of a physical response or a psychological reaction that takes into account the symptom antecedents. As noted in the model, antecedents lead to the production of a symptom and the perception of the symptom by the patient.

Symptom Perception

Symptom perception is multidimensional in nature. Theoretically, dimensions that are common across various symptoms and populations delineate symptom perception, for example, the frequency or intensity of the symptom. Dodd et al. (2001a) report that the ". . . gold standard for the study of symptoms is based on the perception of the individual experiencing the symptoms and his/her self-report" (p. 669). Within the Dodd et al. (2001a) SMM the symptom experience is composed of an individual's perception of the symptom as well as evaluation of the meaning and response to the symptom. McCorkle and Young (1978) provide an excellent example of the individualized perception of symptom assessment. These authors describe a nurses' perception of a lung cancer patient as struggling to breath and coughing, however, the patient does not acknowledge that these symptoms pose a problem. In this example, this patient's dyspnea has "become a way of life for him" (p. 375). Thus, patient perception of the distress created by the symptom is crucial for an accurate assessment and ultimately providing an optimal intervention and outcome. Patient perceptions of symptoms are typically assessed via three dimensions; frequency, intensity and distress (Armstrong, 2003; Lenz et al., 1997).

Similar to the SMM and TOUS models cited above, the SEM includes the three dimensions of the symptom experience; frequency, intensity and distress. Lenz et al. (1997) hypothesize that the dimensions of timing (frequency), intensity, and distress are ". . . assumed to be separable but related to one another" (p. 15). In addition, the concept of symptom meaning is considered a dimension of the symptom perception phase of the SEM model. The dimensions of frequency, intensity and distress will be applied to an adapted version of the SEM to be used with this research and described below.

Frequency

Conceptually, frequency has been defined by Lenz et al. (1997) as a component of a time dimension that notes the occurrence of the symptom in terms of being intermittent, persistent, or a combination of both. An example would appear as: "During the past seven days, how many days did you experience (the symptom)?" In this study frequency was represented as the number of days out of seven that each symptom was present. The range for frequency for each symptom was 0-7 with the exception being research question number four that converted the continuous variable into a categorical variable as described in Chapter 4. Note that this study was longitudinal in design; therefore, it is appropriate to evaluate frequency in terms of the "last seven days." The question was worded as: "During the past seven days, on how many days did you experience pain?" Frequency refers to an actual count of number of days that the patient experienced the symptom. In the case of this research the maximum value for the range will be seven, representing days experiencing the symptom in the past week.

Intensity

The second dimension evaluated as a component of the symptom perception in the SEM is intensity. Intensity was defined by Lenz et al. (1997), as the severity, strength, or amount of the symptom being experienced. In this study intensity was ranked by the patient describing the severity of the symptom on a scale of 0 – 10. Zero would mean that the symptom was "not present" to 10 meaning "worst possible." Again this is the patient's perception of how strong or severe the symptom is, for example; "On a scale of 0 = not present to 10 = the worst it could be, how severe is pain for you?" Intensity was the level of severity assigned to the symptom. This severity score was based on the patients' perception of past experiences with no severity (a 0) associated with a symptom with no intensity value versus their perception of what the worst possible level of severity may be (a 10).

Distress

The concept of distress was conceptually defined by Lenz et al., as ". . . the degree to which the person is bothered by it" (1997, p. 16). This concept of distress has been used to define the "degree of discomfort" a patient is experiencing (McCorkle & Young, 1978). This study and the SEM viewed the distress dimension as a measurement of the patient's perception of the burden or interference that the symptom causes in their everyday life. In this study an example is; "How much did (the symptom) interfere in your life?" Patients rank their response on a scale of 0 – 10, 0 represents no interference to 10 meaning completely interfering. Interference in this study is in the context of; to what degree the symptom disrupted the patient's ability to do what they wanted to do. For example; "On a scale of 0 = did not interfere to 10 = completely interfered, overall,

how much did pain interfere in your life?" Armstrong (2003) noted that one's ability to perceive physical or mental distress is influenced by various factors; age, socioeconomic levels, culture, family role, education, health knowledge, values and past experiences. Distress is commonly associated with dimension of meaning.

Meaning

The dimensions of frequency, intensity and distress were included in this study. The dimension of meaning, although it is depicted in the SEM, will not be included in this study. The study was a secondary data analysis; the original data set did not contain items that specifically addressed situational and existential meaning. The concept of "meaning" is discussed only as a component of the SEM conceptual model. For the purpose of this study the dimension of distress is sufficient to cover the concept of interference or burden with daily life activities. These concepts are similar to situational and existential meaning.

Armstrong defines meaning as being assigned to physical sensations and ". . . may have profound implications for their physical and psychological health and, therefore their quality of life" (Armstrong, 2003, p. 602). The Armstrong SEM supports two types of meaning, situational and existential, this from the work of Richer and Ezer (2000). Situational meaning refers to the ". . . perception of a new event and their capacity to handle it" (Armstrong, 2003, p. 603). An example of situational meaning is the lack of ability to go to work due to fatigue caused by chemotherapy. Existential meaning refers to ". . . global representations of their places in the world" (p. 603). An example of existential meaning provided by Armstrong is the patient developing a sense of

vulnerability and mortality due to symptoms that remind them of the cancer diagnosis (p. 603). The dimension of meaning was not evaluated in this research.

Encapsulated within the meaning circles of the SEM, symptoms are perceived either individually or related to each other, refer to Figure 1. The SEM depicts multiple, co-occurring symptoms as three overlapping circles that include the underlying dimensions of frequency, intensity, distress, and meaning assessed for each symptom. The SEM depicts three overlapping circles not only as a means of defining that the dimensions must be assessed for each symptom, however, also as a representation of multiple, co-occurring symptoms being experienced by the patient.

Multiple Symptoms

Multiple symptoms co-occur, as noted by overlapping circles, see Figure 1. Each symptom individually possesses the dimensions of frequency, intensity and distress. However, the circles representing each individual symptom are connected with arrows and encapsulated as a group, thus, the theoretical perspective of multiple, co-existing chemotherapy/cancer symptoms. For this study fatigue, pain and insomnia will each have their own circle. The dimensions of frequency, intensity and distress will be identified for each symptom respectively. The associations between the symptoms will be evaluated as depicted by the arrows connecting the symptoms in the SEM, refer to Figure 2.

The numerous antecedents in the SEM may serve to clarify the etiology of the co-occurring symptoms. As an example the patient may present with pain, fatigue, and insomnia all co-occurring. The overlapping nature of the symptoms (represented by circles in the SEM) encapsulated in the symptoms and existential meaning circles depict

the stable and independent nature of the co-occurring symptoms. Arrows between the symptoms (circles) represent the strong relationship among the symptoms that are co-occurring. Understanding the symptom experience requires nurses to view symptoms as influencing and being influenced by other symptoms (Armstrong, 2003). This research examined changes in the frequency, intensity, and distress of symptoms (fatigue, pain and insomnia) that co-occur over time and have been affected by antecedents such as age, stage and site of cancer, sex, and co-morbid conditions.

Symptom Expression

The SEM depicts symptoms as influencing the expression of the symptom and ultimately the consequences section of the model, see Figure 1. Armstrong provided no definition for the symptom expression component of the model. However, the symptom expression component may be described as the physical, psychological, and emotional response to a symptom. In this study, one component of symptom expression was the response to fatigue management. Response to fatigue management was measured categorically as none / mild, non-responder, partial responder, or full responder. These categories will be described in detail in chapter 4. Symptom expression leads to consequences of the symptom.

Consequences

The SEM consequences include the concepts of: adjustment to illness, quality of life, mood, functional status, disease progression, and survival. Each concept cited as a consequence has its own theoretical definition. For example, quality of life may theoretically be described as the patient's perception of their ability to participate physically, emotionally, and socially in activities that promote well being (Cella &

Cherin, 1988). This study did not evaluate any consequences of the symptoms. This study focused on select antecedents and their influence on the frequency, intensity and distress associated with fatigue, pain, and insomnia.

Adaptation of the SEM

The SEM has been adapted to include only the elements needed to conceptually guide this research and the addition of the components of time and an intervention. The antecedents used in this study included: age, stage and site of cancer, sex, and co-morbid conditions. Refer to Figure 2 for the revised SEM including the antecedents listed above. As in the original model, symptom production will follow (from left to right) beginning with the antecedents. Symptom perception will follow symptom production and include the three overlapping symptom circles. Each circle will represent each of the symptoms of fatigue, pain, and insomnia. The dimensions of frequency, intensity and distress are represented for each symptom. The circles are connected by arrows and overlap representing the concept of multiple symptoms that co-occur.

Intervention

An additional adaptation for the SEM model is to include an intervention. As supported by the 2005 ONS White Paper for Nursing-Sensitive Patient Outcomes, ". . . nursing interventions play a vital role in preventing or minimizing symptoms and complications during all phases of cancer care (positive outcomes sensitive to nursing care)" (Given & Sherwood, 2005). The intervention for this study will be described in detail in Chapter 4. The intervention designed for the studies that were the source of data for this study were targeted directly at each symptom. For example, if a patient experienced fatigue, pain, and insomnia they would receive instruction per the nurse on

self care management for each symptom. Due to the fact that the intervention directly targets the symptom perception the intervention section of the model will follow (from left to right) the symptom perception component of the revised model, see Figure 2.

As stated previously, it is rare that a single symptom will present in the oncology population. The Symptom Experience in Time (SET) model by Henly, Kallas, Klatt, & Swenson (2003) describes interventions as ". . . operations that affect the target symptom or the symptom constellation. . ." (p. 413). The intervention may differ for each individual symptom or possibly one intervention may be appropriate to manage multiple, co-occurring symptoms. Interdisciplinary strategies may be used to intervene with symptom pairs or clusters due to the complex nature of co-occurring symptoms (Parker, Kimble, Dunbar, & Clark, 2005). Interdisciplinary involvement necessitates the need for conceptually derived clear documentation of the specifications of the intervention. The specifications will assist in the replication of studies that include interventions (Dodd et al., 2001a). Interventions are displayed in the Dodd et al. (2001a) SMM as symptom management strategies with "specifications" such as when, how much, and to whom.

In response to the need to include an intervention and specifications for use with the study data base, the SEM has been adapted to include an intervention component that consists of a set of thorough descriptors (what [nature of the strategy], when, where, why, how much [dose], to whom [recipient], and how [delivery means]) (Dodd et al., 2001a). Refer to Figure 2. The descriptors describe the intervention as well a means of facilitating study replication (Dodd et al., 2001a).

Time

The researcher is challenged as to the appropriateness of one time only measurements for co-occurring symptoms due to the chronic nature of cancer, treatment approaches that are delivered over time, and the knowledge that symptoms change over time. Issues to consider in examining symptoms over time include the timing of the symptom report in relation to the diagnosis and/or treatment plan. Patients diagnosed with advanced stage disease will likely present with a different symptom profile versus an early stage disease patient. The tumor type will also play a significant role. As stated earlier, Given et al. (2001), noted in a study (n=841) of newly diagnosed cancer patients that individuals diagnosed with lung cancer presented with an average of 5.3 symptoms versus those diagnosed with colon cancer presented with an average of 3.7 symptoms. In this study, the co-occurring symptoms of fatigue, pain and insomnia was evaluated over 2 different points in time. In addition, antecedents such as age, site and stage of cancer, sex, and co-morbid conditions were evaluated in relation to how they were associated with symptoms over time.

The site and stage of cancer were crucial pieces of data in this study. It is essential to understand the clinical context of the symptom (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). Symptoms may be indicative of the disease state, the treatment, or both. For example, fatigue may be associated with the lung cancer diagnosis or the myleo-suppressive effects of the chemotherapy. It may not even be possible to determine the etiology of the symptom. If the symptom is associated only with the treatment it is likely to predictably appear, remain, peak and/or dissipate (Barsevick et al., 2006). The symptom may be representative of a late effect of prior chemotherapy or radiation

therapy. For example patients with mantle field radiation for Hodgkin's disease may experience respiratory complications/symptoms later in life as a result of their field of radiation years prior. It is possible that some symptoms may be permanent, for example, hair loss due to radiation therapy. Therefore, the symptom assessment instrument as well as timing of the administration of this assessment instrument within the overall study design is crucial. These examples reinforce the need to acknowledge the concept of time in the adapted SEM model to guide this research.

Studying multiple symptoms requires examining the temporal nature of the symptoms across the specified study trajectory (Dodd et al., 2001a). Time plays a key role in symptom presentation as well as management for the oncology patient. Symptoms may change over time depending on if they are treatment or disease induced. As an example, dyspnea and loss of appetite due to a diagnosis of non-Hodgkin's lymphoma may be resolved after a few cycles of CHOP chemotherapy. The patient's bulky neck and chest disease may be decreased and the Prednisone may increase a patients' appetite. However this same patient may go on to experience fatigue and nausea as a result of the CHOP chemotherapy. Symptoms linked to the treatment (i.e., chemotherapy) may be dose dependent and/or schedule dependent. For example, a patient receiving a 28 day cycle of chemotherapy may experience less fatigue than a patient receiving dose dense (every 14-day) chemotherapy. Factors such as concurrent radiation therapy, growth factor administration, and if the chemotherapy is neo-adjuvant, adjuvant, or palliative may also impact the symptoms. Thus, antecedents such as stage of disease and treatment approach are very important, as well as the treatment and disease trajectory in effecting the identification and stability of the symptoms over time.

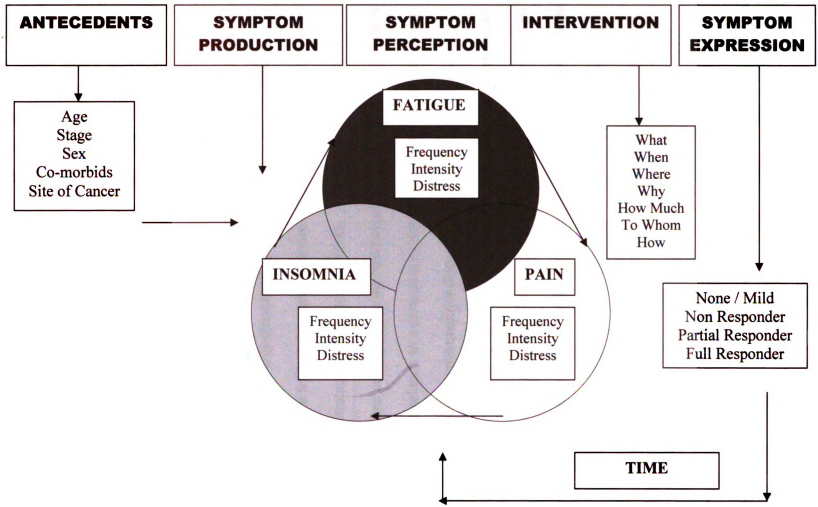


Figure 2: Adapted SEM

This SEM was adapted to include a time arrow reflective of a feedback loop from the symptom expression section of the model back to the symptom perception circles of the model, refer to Figure 2. The addition of the time component was influenced by the work of Henly et al. (2003) as stated above. Also, the TOUS by Lenz et al. (1997) was one of the first nursing models to represent multiple, co-occurring symptoms as well as a feedback loop from the outcome of performance back to the physiologic, psychologic, and situational factors and the symptoms. The Symptom Management Model depicts a feedback loop represented as a bi-directional arrow representing that the patient experiencing an outcome from the symptom necessitates that one will "modify" or "refine" intervention strategies (Dodd et al., 2001a).

The addition of a time component to the SEM allowed the researcher to evaluate a nursing intervention in relation to a particular symptom or group of symptoms at any given point in time along the treatment or disease trajectory. As applied to this longitudinal oncology nursing research, the time arrow would allow the researcher to evaluate the co-occurring symptoms of fatigue, pain, and insomnia at baseline and 10 weeks into therapy. The time arrow turns the previous static SEM model into a dynamic one that facilitates the evaluation of symptoms over time as well as the impact of a nursing intervention on the symptom dimensions (frequency, intensity, and distress).

Summary

The concepts of time and interventions are crucial when studying a treatment trajectory within a chronic illness, such as cancer, with multiple cycles of chemotherapy as a treatment. The adapted SEM, with the concepts of time and an intervention added describes multiple symptoms as well as nursing interventions over time. Timing of the

measurement of the symptoms as well as the intervention is dependent upon the clinical context of the subject group and research hypothesis. The clinical context determines when symptoms are likely to appear, peak and/or dissipate based on landmarks of the treatment and/or intervention and may be dependent upon how homogeneous the sample is (Barsevick et al., 2006). Thus, the revised SEM contains the essential elements to capture timing of the intervention as well as its effect on future symptoms.

The study of multiple symptoms requires a conceptual framework that matches the disease trajectory, over time, as well as interventions and their effects on future symptoms. It is essential for oncology nursing research to utilize a conceptual model that not only complements the research design, however, offers the closest representation to the clinical context of the multiple symptoms. The need for oncology nursing research as well as practice to comprehensively monitor and manage symptom clusters over the disease trajectory necessitates the use of a conceptual model that includes a time and intervention component (Kim et al., 2005). The SEM as adapted in this study may best address this need to monitor and manage multiple symptoms in the context of this study as well as future studies and clinical practice.

Chapter 3

Literature Review

This chapter will present a thorough review of the oncology literature published to date that is related to fatigue, pain, and insomnia as these three symptoms have the potential to occur together over time for the patient receiving chemotherapy. The adapted SEM will be used to guide this literature review. The components of the adapted SEM; antecedents (age, stage and site of cancer, sex, co-morbids) symptoms perception (fatigue, pain, insomnia) and the intervention and time components will serve as the headings for this literature review. Refer to Figure 2 for the adapted SEM. Descriptive studies as well as longitudinal randomized clinical trials (RCT's) including interventions will be included. The selection of studies/literature was based on scientific merit, congruence with the adapted SEM model, and similarity to the research questions.

Antecedents

When viewing the adapted SEM from left to right the first component is the antecedents. The antecedents of interest in this study include; age, sex, stage and site of cancer, and co-morbid conditions. These variables are frequently examined in the demographic sections of both descriptive as well as RCT's. The following literature review will examine each antecedent listed above as it relates to the symptoms of fatigue, pain, and insomnia, as well as the concept of co-occurring symptoms.

Age

This section will focus on the impact that age has on the symptoms of fatigue, pain, and insomnia as well as co-occurring symptoms in general. Physiologically, age has been linked to fatigue by factors such as decreased muscle mass, muscle morphology, as

well as changes in energy metabolism and neuromuscular activation (Ratel, Lazaar, Williams, Bedu, & Duche, 2003). Sarna (1993) was one of the first researchers to examine the effect of age on symptom distress. Sarna used the Symptom Distress Scale (SDS) to study 69 women diagnosed within 2 years with lung cancer, 43% were actively receiving treatment during the study period. The average age of women in this study was 61 years (SD = 11). The most prevalent and distressing symptoms were fatigue, pain and insomnia. Sarna found that symptom distress was not correlated with age when examined as a continuous variable or as a categorical variable with age 65 as the cut point (1993).

Degner and Sloan (1995) studied 434 newly diagnosed cancer patients, mean age 59.3 years (SD = 13.9), 52% were male and patients were diagnosed as having solid tumors or lymphomas. A weak correlation was noted between age and symptom distress, as evaluated by the SDS ($r = 0.11$). Younger patients experienced a greater reported amount of symptom distress vs. their older counterparts ($p = .02$).

Dodd et al. (2001b) studied a convenience sample for the identified symptom cluster of pain, fatigue and sleep insufficiency in mainly breast (45%) and colon/rectal (27%) cancer patients during the first three chemotherapy treatments (n=93). The average age of this sample was 55.4 years (SD = 14.6). The authors found that age explained 11.8% of the change in functional status ($p < 0.001$) for these patients between baseline and the end of the third cycle of chemotherapy. As an additional finding, pain was able to explain 10.7% of the change ($p = 0.002$) in functional status and fatigue explained 7.3% of the change ($p = 0.011$), sleep insufficiency was statistically not significant ($p = 0.344$) (Dodd et al., 2001b).

Given et al. (2001) studied an inception cohort of 841 patients from various community oncology centers throughout Michigan and one site in Indiana. All patients were age 65 or older and 31% of the patients were over the age of 75. Patients were receiving chemotherapy and were diagnosed with breast, lung, prostate or colon cancer. This study used The Symptom Experience Scale (SES), developed by the authors for this research project, to assess patients fatigue and pain. Although age was presented categorically, it was entered into the model as continuous data to reveal no relationship between age and fatigue or age and pain.

Tishelman et al. (2005) studied 400 patients in Sweden with inoperable lung cancer following diagnosis through the course of one year for a total of six different data collection periods. Two of the most prevalent symptoms identified in this sample were fatigue and pain. The purpose of the Tishelman et al. study was to determine if patients reported patterns of symptom frequency would be similar to patterns of symptom intensity. Tishelman et al. (2005) used the SDS instrument and reported that the mean age of their subjects was 64.5 years (SD = 10.0). The authors did report that their sample was younger than data provided by the cancer registry (mean age 68.8 years) and that the ages for males, 52% of the sample (mean age 66.2) and females (mean age 62.6) were statistically different ($p = .001$). Tishelman et al. (2005) noted that age (younger) and sex (women) were variables that negatively influenced intensity (frequency) levels of fatigue throughout their study.

Sex

Tishelman et al. (2005) found that female patients in their study reported significantly higher levels of fatigue and pain at the final data collection point (one year post

diagnosis) vs. their male counterparts. Women were more likely to be divorced and widowed vs. men. In addition, women were more likely to have received chemotherapy in this study, 84% vs. 72% ($p = 0.006$) of the men receiving some form of chemotherapy. No significant differences were noted for education level, type of lung cancer or stage of lung cancer.

Degner and Sloan (1995), noted that overall, women reported greater symptom distress than the male subjects in this lung cancer study ($t = -2.05$, $p = 0.04$). The Given et al. (2001) study, cited above, found that after controlling for other demographic variables such as co-morbid conditions, age, and site and stage of cancer, that women were more likely to experience pain with fatigue or each symptom alone when compared with neither symptom versus their male counterparts.

Cooley, Short and Moriarty, (2003) completed a secondary analysis from three different data sets (n=117) that used the SDS to study adults with lung cancer. The purpose of the Cooley et al. (2003) study was to describe which symptoms were reported as being the most distressing, what was the prevalence of these symptoms, how did the symptoms change over time, and examination of patient/clinical characteristics. The Cooley et al. (2003) study contained 54% men and found fatigue and pain to be the most distressing symptoms for all patients. Cooley et al. failed to support sex as a patient characteristic that was related to symptom distress over time. However, at baseline sex (being female) was noted to predict greater symptom distress at baseline (data was collected at baseline, three months and six months post diagnosis) (Cooley et al., 2003). Based on the data presented above, females experience higher levels of pain and fatigue. To further examine this association between sex and symptoms this current study

examined the association between sex and the symptoms of fatigue, pain and insomnia over time.

Stage and Site of Cancer

Early work in examining the effect of site of cancer on prevalence and intensity of symptoms was conducted by Vainio and Auvinen, (1996). Vainio and Auvinen together with the international members of the Symptom Prevalence Group prospectively studied 1840 cancer patients in seven hospices in the United States, Europe and Australia. The purpose of the Vainio and Auvinen study was to estimate the prevalence of pain and eight other common symptoms in a population with advanced cancer upon admission to a palliative care/hospice unit. Severe pain (using a scale with four grades: none, mild, moderate, severe) was noted in 51% of the sample. Statistically significant ($p = 0.003$) differences were noted in pain intensity according to primary site of the cancer. Severe pain was most commonly reported by prostate cancer patients. Gynecological cancer and head and neck cancer patients reported the greatest prevalence of moderate and severe pain. Overall, Vainio and Auvinen fount that ". . . there were statistically significant ($p < 0.0001$) differences between primary sites in the prevalence of all other symptoms except constipation, insomnia, and confusion" (1996, p. 6).

Dodd et al. (2001b) noted in their sample of 93 outpatients with various solid tumors, that the presences or absences of metastases did not have an effect on the severity of fatigue, pain or insomnia. However, stage of disease was noted by Gift et al. (2003) to be predictive of the number of symptoms that co-occurred with fatigue six months following diagnosis of lung cancer (n=112). Gift et al. stated; "The stage of cancer at diagnosis is the best predictor of symptoms later in the disease" (2003, p. 393).

Gift et al. (2003) used a subset of lung cancer patients from the Given et al. (2001) study cited above. Given et al. (2001) noted in the larger data base, including all tumor types, that site of cancer failed to interact among other demographic variables to produce a significant prediction of any combination of pain or fatigue. However, stage of disease when examined categorically as early or late stage was significant for predicting those who reported pain and fatigue vs. only those reporting pain alone. Given et al. (2001) also noted mean number of symptom variations per differing sites of cancer. Patients diagnosed with lung cancer reported an average of 5.3 symptoms, breast cancer patients reported 3.6 symptoms, colon cancer patients reported 3.7, and prostate cancer patients reported an average of 4.3 symptoms (Given et al., 2001).

The effect of histology on symptom distress was examined by Cooley (2002). Cooley found that histology of the lung cancer did influence symptom distress at baseline. Adults with non-small cell lung cancer experienced more symptom distress than their small cell lung cancer counterparts. Thus, site and stage of cancer significantly influenced symptoms experienced by the cancer patient and was explored in this study.

Co-morbid Conditions

The presence of the co-morbid condition of respiratory disease was found to positively correlate with a high level of symptom distress (chi square, 5.14; $p = 0.023$) in women with lung cancer as reported by Sarna (1993). Given et al. (2001) also noted that "patients with three or more co-morbid conditions were more likely to report pain, fatigue, or their combination, when compared with those reporting neither symptom" (p. 462). Refer to descriptions of both of these studies above.

Kurtz, Kurtz, Given & Given (1993) likewise noted a correlation between co-morbid conditions and symptoms, as well as with physical functioning. Kurtz et al. used a convenience sample of patients with various solid tumors as well as lymphoma (n=279) to examine the trajectory of symptoms and loss of physical functioning over a six month time span for patients initiating chemotherapy treatment. The most frequently appearing symptoms in this study were fatigue, pain, insomnia and nausea. These authors found that ". . . although co-morbidity was only modestly correlated with symptoms and loss of function for the total sample, it was highly correlated with both symptoms and loss of physical functioning for the younger patients (those younger than 60 years of age)" (Kurtz et al., 2003, p. 275). Co-morbidity consisted of a count of the number of physical co-morbid conditions as reported by the patient, range 0-13, examples include; arthritis, hypertension, diabetes, etc. (Kurtz, Kurtz, Stommel, Given, & Given, 1997).

Bower, Ganz, Desmond, Rowland, Meyerowitz & Belin (2000) studied the effect of co-morbid conditions in breast cancer survivors (n=1,927) as a component of a larger study to identify and describe the effects of fatigue on this population. To be eligible for this study women had to have stage II disease or lower within the past five years and received adjuvant therapy. Subjects in the study had to be free of disease at the time of the study to participate. The symptom assessment instrument used for this study was the Breast Cancer Prevention Trial Symptom Checklist. A logistic regression was completed to reveal that the co-morbid conditions of arthritis ($r = 1.35$, $p = .03$) and high blood pressure ($r = .99$, $p = .02$) emerged as significant predictors of fatigue group membership (Bower et al., 2000).

The presence of co-morbid conditions has been noted in the literature to impact symptom severity and distress. This study examined co-morbid conditions as antecedents. The next section of the adapted SEM model includes symptom production. Antecedents contribute to the production of the symptom. This section of the model is rooted in the work of Leventhal and Johnson (1983). Leventhal and Johnson define symptom production as an objective, concrete representation of the disease. As noted in Chapter 2, symptom production is not clearly articulated by Armstrong (2003). However, the Armstrong SEM likely depicts symptom production as the actual physical response or psychological reaction that takes into account the symptom antecedents and leads to symptom perception. The definition of the term symptom used for this research is from the work of Henly, Kallas, Klatt, & Swenson (2003): "Symptoms as experienced by individuals are unpleasant sensations or perceived changes in normal functioning or appearance" (p. 410). It is important to note that "symptoms are seldom solitary" (Kroenke, 2001, p. 848).

Symptom Perception

Symptom perception is multidimensional in nature. McCorkle and Young (1978) were among the first nursing authors to fully examine and develop a scale to research symptom perception. The scale was called the Symptom Distress Scale (SDS) and has been used in numerous studies; examples have been cited throughout this dissertation. McCorkle and Young define symptom distress as ". . . the degree of discomfort reported by the patient in relation to his/her perception of the symptoms being experienced" (1978, p. 373). This symptom perception section of the literature review will focus on research that has examined patient perceptions of the symptoms of fatigue, pain and insomnia.

Emphasis will be placed on the symptom of fatigue due to the significance of this symptom within the research questions.

Fatigue

The multidimensional nature of the concept of fatigue makes this concept one of the most interesting, yet difficult, areas of study. Fatigue is important to study for various physical, psychological and economic reasons. It is also important to study due to its impact on other chemotherapy symptoms, in particular pain and insomnia. Arronson, Teel, Cassmeyer, Neuberger, Palikkathayil, & Pierce, stated that "Fatigue is a universal symptom not only associated with most acute and chronic illnesses, but also with normal healthy functioning and everyday life"(1999, p. 45). Empirical evidence supports, patients with diagnoses such as: chronic obstructive pulmonary disease (COPD), human immunodeficiency virus disease (HIV), Addison's Disease, rheumatoid arthritis, multiple sclerosis, and cancer all experience fatigue, and most experience distress as a result (Aaronson, et al., 1999; Shaver, 1999; Breitbart, Rosenfeld, Kaim, & Funesti-Esch, 2001; Cleare, 2003; Theander & Unosson, 2004). This section will focus on the concept of fatigue from the perspective of oncology care.

The concept of fatigue is examined in the discipline of nursing via a bio-behavioral approach. This bio-behavioral approach is reflective of a level of understanding that is made up of the mental (psychological, cognitive, emotional, affective) and physiochemical elements that drive human interaction with the environment (Shaver, 1999). Fatigue is composed of behavioral, cognitive, somatic and affective domains (Stein, Jacobsen, Blanchard, & Thors, 2004). Congruent with the bio-behavioral approach, fatigue is classified as a symptom (Shaver, 1999).

Fatigue is the most common symptom associated with cancer and the treatment of cancer (Cella et al., 2001). Simon and Zittoun reported in their review of international, empirical chemotherapy studies that 60% to 96% of chemotherapy patients experienced fatigue (1999, p.244). Specific studies of the impact of fatigue as a symptom included the work of Ashbury, Findlay, Reynolds, & McKerracher (1998) who noted that of their 913 Canadian cancer patients surveyed, 78% reported fatigue and 52% actively sought out information to manage it. In addition, Vogelzang, Breitbart, Cella, Curt, Groopman, Horning, et al. (1997) reporting on behalf of The Fatigue Coalition, found that 78% of radiation and/or chemotherapy cancer patients experienced fatigue, and 32% of them experienced it on a daily basis. Fatigue is one of the most common symptoms associated with chemotherapy for both men and women. The prevalence and distress of fatigue for patients, caregivers and practitioners associated with fatigue due to cancer and cancer treatment necessitates continued study and conceptual understanding of this symptom. The conceptual definition of fatigue will follow.

Conceptual Definition of Fatigue

As noted above, fatigue is a serious, multifaceted, problematic symptom for many, especially cancer patients. A literature review of the concept provides numerous papers, reviews, and research findings that all share a common description of fatigue; it is complex, multi-dimensional, and universally experienced. However, no universal definition of fatigue was noted in the literature (Trendall, 2000). Most authors on this subject agree that the concept of fatigue involves biologic, psychosocial, and behavioral manifestations (Aaronson et al., 1999).

Fatigue may be viewed as a biological approach applied to a physical subsystem. An example of this would be "fatigue" of a muscle. In this context fatigue refers to the lack of ability of a muscle to contract after intense use (Shaver, 1999). Based on this biological and physiological approach the phenomena of fatigue may be referenced as functional organ failure (Berger, McCutcheon, Soust, Walker, & Wilkinson, 1991). Typically, the physiological context of fatigue is of concern to disciplines outside of nursing practice such as: biology, physiology, and medicine.

Disciplines outside of nursing studying fatigue examine mechanisms such as cytokine and immunoregulatory factors, the depletion of hormones, the role of neutrotransmitters, or dietary measures at the cellular level. An example of fatigue studied physiologically is the pathophysiological perspective of the influence of cortisol and the hypothalamic-pituitary-adrenal (HPA) axis. Cleare (2003) noted that low circulating cortisol levels mediate symptoms associated with fatigue syndromes. Cleeland, Bennet, Dantzer, Dougherty, Dun, Meyers et al. (2003) noted that cancer related symptoms such as fatigue and pain may involve actions of proinflammatory cytokines such as interleukin (IL) -1, tumor necrosis factor – α (TNF- α), IFN- α, and IL-2. The use of a physiological definition alone is limited for nursing clinical practice and research due to the applied nature of our practice and need for a bio-behavioral approach.

A psychological approach may be used to define the concept of fatigue. Lee, Hicks, and Nino-Murcia (1991) defined the state of psychological fatigue as one of weariness related to reduced motivation. Aaronson et al. (1999) defined fatigue within a psychological framework as a response to internal or external demands exceeding available resources. A qualitative study conducted in Britain compared cancer and

COPD patient responses to questions related to physical and psychological aspects of fatigue. Two psychological themes emerged for both groups; impact of fatigue on functionality and perceived control, and the emotional effect of the disease management (Ream & Richardson, 1997). Berger and Walker-Nobel (2001) also support the psychological approach to the concept in reference to mood and depression as components of mental health that influence the perception of fatigue. Fatigue is a complicated symptom consisting of physiological, psychological, and social components. The symptom of fatigue is thought to provide a possible synergistic effect on other chemotherapy symptoms. Fatigue as it presents with and possibly influences other symptoms will be examined below.

Co-occurring Symptom Studies Including Fatigue

Although symptom distress has been reported in the literature for three decades, it was Sarna (1993) who published one of the first oncology research papers to include fatigue as it was related to other co-occurring symptoms. Sarna hypothesized that some symptoms may "wax and wane during a course of treatment" (1993, p. 22). Sarna used the SDS in women with lung cancer (n=69). It was noted by Sarna that 61% reported more than one distressing symptom, in fact, 23% reported that they experienced four or more distressing symptoms concurrently. In addition, 41% experiencing fatigue also experienced pain.

Sarna was also one of the first authors to associate antecedents with the production of multiple symptoms. Sarna was interested in determining if multiple co-occurring symptoms could be predicted by the location and stage of the cancer. It was noted that antecedents such as treatment status, type of lung cancer, time since diagnosis, metastatic

disease, co-morbid conditions, education, marital status, and age did not effect ones perception of symptom distress in this study. However, the design of this study as a cross-sectional study with a small sample size of women at differing points in their disease and/or treatment process was a limitation.

Hickok, Morrow, McDonald, and Bellg (1996) described multiple co-occurring symptoms among male and female adult radiation therapy lung cancer patients (n=50) via a medical record audit. Hickok et al. noted that concurrently 78% of these patients reported fatigue, 80% reported pain, and 12 % had documented depression. Although this work was descriptive and retrospective, it did provide an early attempt to examine men and women with greater then two concurrent symptoms. The link between fatigue, pain and depression among these patients, regardless of sex, provided a significant replication of the findings of Sarna and lead to the future consideration of these multiple co-occurring symptoms a priori in study design.

Soon after, Gaston-Johansson et al. (1999) in their sample of 127 post adjuvant chemotherapy women with stage II-IV breast cancer, designed a study to specifically examine pain, fatigue and depression as co-occurring symptoms impacting the outcome of health status. Gaston-Johansson et al. found that fatigue, pain, and depression were present for 91%, 47% and 54% respectively. Fatigue, pain and depression were all significantly correlated to each other as well as participant's perception of their total health status. The pain-fatigue correlation was .34. Pain and depression correlated at .25 and accounted for 63% of the variance in total health as measured by the SF-36. Depression and fatigue correlated at .58 and accounted for 42% of the variance in the outcome of health status. Gaston-Johansson et al. supported a priori selection of

symptoms noted in past studies, offered a larger number of subjects and was one of the first to examine correlations among multiple co-occurring symptoms.

Beginning in the year 2000, Drs. Barbara and Charles Given began to publish work that supported the conceptual application of antecedents, the symptoms experience and outcomes/consequences. The Given work examined the impact of cancer and/or chemotherapy symptoms on physical functioning. The Given et al. (2001) study consisted of an inception cohort of 907 newly diagnosed solid tumor patients. The Symptom Experience Scale (SES) instrument was used. Four different patient interviews were completed at 6 to 8, 12 to 16, 26 to 30 and 52 weeks after the cancer diagnosis.

This study examined antecedents such as tumor type, stage of disease, age, education and marital status via a retrospective medical record audit. A prospective examination of the immediate, cumulative, and longer-term effects of chemotherapy on the dimensions of the symptom experience (frequency and severity) of multiple symptoms was completed at the time periods mentioned above. The outcome or consequence of physical functioning was measured by the SF-36. Given et al. noted that symptoms did not mediate between treatments and patient functioning. In this Given et al. (2001) study, the number of symptoms produced a significant effect, independent of surgery, radiation, and chemotherapy, for every additional symptom a decline of 2 units of physical functioning was noted. The symptoms of pain and fatigue and the total number of symptoms experienced by the subject were predictors of loss of function. Antecedent variables such as age, sex, co-morbid conditions, and the time of observation also had significant effects.

Kurtz, Kurtz, Stommel, Given and Given (2000) examined only the lung cancer patients from the above stated Given et al. (2001) data set. This sample of 133 patients was used to examine the effects of antecedents on the presence of multiple co-occurring symptoms. Kurtz et al. demonstrated that fatigue was the most universally reported symptom in this population regardless of age. Regardless of sex, five of the top six reported symptoms were the same (fatigue, cough, night urination, difficulty breathing, pain, and weakness), with some variation in order and frequencies. The antecedents of treatment type and stage of disease were responsible for the greatest variation in these six symptoms.

Later studies by Given et al. (2001) would use this same data set to study co-occurrence and patterns of change of pain and fatigue (n=841). Given et al. reported ". . . if patterns are found, then future work can focus on elaborating how levels of intensity or distress may moderate these patterns over time" (2001, p. 458). Findings of this study revealed that the occurrence of pain and fatigue were predictors of other reported symptoms among chemotherapy patients. Patients in this study who experienced pain and fatigue concurrently reported an average of 6.3 additional symptoms.

Building on the work of Gaston-Johansson et al. (1999) as well as the Given et al. (2001) work presented above, Dodd et al. (2001b) published one of the first studies based on a conceptual framework supporting a symptom cluster as defined by the authors. The Symptom Management Model as mentioned in Chapter 2 was the conceptual framework used for this study. Pain, fatigue and sleep insufficiency were determined a priori to be the symptom cluster of interest. The Karnofsky Performance Scale (KPS) measured the effect of this cluster on the outcome of functional status. A hierarchical multiple

regression model was used to explain variance in the KPS at the end of the patient's third cycle of chemotherapy adjusting for KPS at baseline. The authors found that pain explained only 10.7% of the change in KPS (p=0.002) and fatigue explained 7.3% (p=0.011). Sleep insufficiency failed to produce statistically significant findings with explanation of only 1% of the change overall (p=0.344). In addition, the Dodd et al. (2001b) study did not produce strong correlations between the three symptoms (pain to fatigue r = 0.22, pain to sleep insufficiency r = - 0.06, and fatigue to sleep insufficiency r = -0.13). The authors acknowledged this work as the "beginning insights" into the effects of symptom clusters.

An additional Given et al. (2002) study used a subset of the data presented in their studies that began in 2000 to include patients reporting concurrent pain and fatigue at baseline (n= 53 in the experimental arm, n=60 in the control arm) and a 10 contact nursing intervention over 20 weeks. The Given et al. (2002) publication was significant due to the emphasis on the randomized clinical trial design and inclusion of an analysis of the data related to the implementation of a nursing intervention for multiple symptoms. Review of this Given et al. (2002) study also supports the adaptation of the SEM to include a timeline as well as an intervention component.

The Given et al. (2002) prospective, randomized clinical trial (n=113) was part of the larger study described above that examined up to 14 different symptoms. The study focused on subjects who experienced both pain and fatigue at baseline. Given et al. (2002) used a cognitive-behavioral framework to guide the nursing intervention. Oncology Certified Nurses (OCN®) were provided study specific training to assess and intervene with identified symptoms in the experimental group of this study. The nursing

interventions consisted of patient problem solving techniques, the acquiring of information, symptom self-care management, and emotional and social support for patients. The effectiveness of supportive nursing interventions on symptom management, physical role impact and social functioning were examined. Nurse sensitive outcomes for this study included a reduction in the number of reported symptoms (measured by the Symptom Experience Scale) as well as social and physical functioning (measured by the SF-36).

The Given et al. (2002) longitudinal study contained baseline, 10 week, and 20 week observations. Effects for the group were noted as related to symptom count at the 20-week observation. At the 20-week observation, patients in the experimental group reported 3.3 (SD = 2.6) symptoms on average vs. the control group reporting 4.4 (SD = 2.7) symptoms. Similar statistically significant reductions were noted in physical role impact scores at 20 weeks. The experimental groups score mean was 50 vs. the control group mean score of 31 (Given et al., 2002). Social functioning produced similar findings with the experimental group having a mean score of 76 vs. the control group mean score of 63 (Given et al., 2002). These findings demonstrated that patients reporting pain and fatigue at baseline who received the nursing intervention reported fewer symptoms and improved impact on their physical and social role functioning. Work presented in the preliminary studies cited above shaped the development of the RO1 CA-30724 and RO1 CA-79280 studies, both of which were used as the database for this research.

In addition, a retrospective analysis completed by Cooley et al. (2003) studied prevalence, level of distress, and how symptoms change over time in 117 lung cancer

patients. The significance of the addition of the timeline to the SEM is also supported by this study. Cooley et al. (2003) combined three different data sets, all using a repeated measures design with use of the SDS to complete secondary data analysis. It was reported that fatigue, pain, and insomnia were among the most distressing symptoms at baseline and remained distressing at the three and six-month points of the study for patients receiving a combination of treatment modalities (n=51). Percentages of patients reporting the presence of the symptoms at the three different time periods are as follow: fatigue (65%, 61%, 43%), insomnia (45%, 27%, 22%), and pain (49%, 33%, 41%). Decreasing symptom reports over time for fatigue and insomnia were present, however, pain slightly increased by the 6-month point of the study. Cooley et al. (2003) imply that retrospective, longitudinal, descriptive studies of this nature are a starting point for studying multiple symptoms and have great relevance to the discipline of nursing and the development of nurse sensitive outcomes.

Bower et al. (2000) examined fatigue in breast cancer survivors. They compared a "fatigued" sample, all women scoring at or below 50 for the energy/fatigue subscale of the RAND 36-item Health Survey (mean age = 54.87, SD=11.91, mean years since diagnosis = 2.92, SD=1.18) to a "non-fatigued" sample of breast cancer survivors (mean age = 56.17, SD=11.04, mean years since diagnosis = 2.89, SD=1.19). The women with fatigue reported significantly more "severe" and "disabling" pain ($p < .0001$), greater menopausal symptoms ($p < .035$), and significantly greater levels of depression as measured by the CES-D (score > 16) ($p < .0001$). Logistic regression was completed on the total sample (n=1,927) to reveal that depression was the strongest predictor of fatigue group membership (odds ratio 1.13, $p < .0001$), followed by pain (odds ratio 0.97,

p <.0001) (Bower et al., 2000).

Two studies conducted with breast cancer patients and multiple co-occurring symptoms used different study designs. The first, Wilmoth, Coleman, Smith, and Davis (2004) provided an example of a priori establishment of a symptom cluster of fatigue, weight gain, and altered sexuality and examined it via a literature review of breast cancer publications. The second, Bender et al. (2005) used an exploratory secondary analysis approach to compare the prevalence of multiple symptoms associated with breast cancer. A pooled analysis was conducted by Bender et al. examining baseline assessments from 3 independent studies (combined n = 154 from the three studies). It is essential to note that each of the 3 studies contained women with differing stages of disease. Study 1 (n=40) were all early stage disease patients who had only completed surgery at the time of the study. Study 2 (n=88) were stage I, II, or III patients who had undergone surgery, adjuvant chemotherapy and were currently receiving hormonal therapy. Finally, study 3 (n=26) were all women with metastatic breast cancer. Bender et al. found that in all three studies a common "symptom cluster" existed that was composed of fatigue, cognitive impairment and mood problems.

We note from the above examples that cancer/chemotherapy patients exhibit both single and multiple, co-occurring symptoms at diagnosis, throughout treatment and even upon completion of therapy (Cleeland et al., 2000; Given et al., 2001). Fatigue is one of the most prevalent symptoms and is often associated with pain and insomnia (Cooley et al., 2003; Dodd et al., 2001b; Given et al., 2001; & Sarna, 1993). Although the significance of these co-occurring symptoms has been established, randomized clinical

trials involving interventions have been less plentiful. The following section will focus on the intervention component of the adapted SEM.

Interventions for Fatigue, Pain and Insomnia

Although the actual intervention for this study will be described in detail in Chapter 4. This section will review conceptual issues related to intervention studies that support the symptoms of fatigue, pain and insomnia. Recall that the interventions discussed here will target the symptom(s) directly. The adapted SEM draws from the SMM to include the intervention "specifications" of : what, when, where, why, how much, to whom, and how; to facilitate the literature review as well as study replication (Dodd et al., 2001a).

The Given et al. (2002) work as cited above (longitudinal, RCT with three observation periods), was one of the most significant intervention based nursing research studies conducted to date related to the symptoms of fatigue and pain in chemotherapy patients. Given et al. (2002) used a subset of the data presented above to include patients reporting concurrent pain and fatigue at baseline (n= 53 in the experimental arm, n=60 in the control arm) and a 10 contact nursing intervention over 20 weeks.

A description of the nursing intervention will follow. The intervention was comprised of evidence-based intervention strategies that were delivered to the nurse intervention group. Each intervention nurse had the same stepped cancer-nursing intervention software loaded onto a laptop computer. The Given et al. (2002) study software housed problem-specific, evidence-based intervention strategies that the nurse and patient could mutually elect for the patient to implement on his or her own behalf to move the problem toward resolution.

The nurse intervention was targeted to assess and intervene with previously identified symptoms. At each visit, the nurse assessed all symptoms. Any symptom that reached a severity level of 5 or higher on a 10-point scale or a reported impact of 3 or higher on a 5-point scale with respect to the impact on patients' quality of life were posted to the problem list. These patient assessments were part of the nursing intervention. Patient responses were selected from the options available in the intervention program and related to the impact that a particular symptom had on quality-of-life indicators (e.g., sleep, mobility, appetite). Patients were asked to rate their responses from 0 (no impact) to 10 (a great impact). For example, pain would be assessed according to its onset, duration, maximum severity, impact on daily activities, and other associated problems, such as fatigue or insomnia. All symptoms and functional health indicators that reached a threshold (i.e., either the current intensity self-rating of 5 or higher or quality-of-life indicators self-rating 3 or higher) were posted to the plan of care.

Once a symptom was posted the nurse and patient addressed it until the symptom was controlled or the intervention ended. At each intervention encounter, the nurse would ask the patient to evaluate the efficacy of the intervention strategy and the status of the problem resolution. Intervention strategies were modified, changed, or deleted depending on the result. Using a computer-assisted protocol, the intervention nurse was able to document in real time the interventions for each patient problem at each encounter in which the nurse and patient focused on the problem. Intervention fidelity was monitored by the nurse coordinator reviewing every encounter for each patient, as well as weekly meetings between the PI's and nurse interveners (Santacroce, Maccarelli, & Grey, 2004).

At baseline the experimental group in the Given et al. (2000) study presented with 7.3 (SD 2.8) symptoms and the control group 6.8 (SD 2.1). By the second observation (10 weeks into chemotherapy) the experimental group reported an average of 5.2 (SD 2.9) symptoms vs. 6.1 (SD 3.2). Upon completion of the nursing intervention the experimental group reported an average of 3.3 (SD 2.6) symptoms vs. 4.4 (SD 2.7) symptoms reported by the control group (p. 952).

The above data base was also used by this investigator to examine if symptom severity can be predicted by chemotherapy regimen 20 weeks following baseline assessment, after controlling for age, co-morbid conditions and experimental vs. control group membership in breast and lung cancer chemotherapy patients. The sample consisted of 71 females with breast cancer, 21 females with lung cancer and 23 men with lung cancer. A binary logistic regression was completed to support that co-morbid conditions and group assignment (experimental vs. control group membership) reliably predicted symptom severity. Chemotherapy category did not predict symptom severity at 20 weeks following baseline assessment. Symptoms related to toxicity profiles (i.e., nausea, mucositis, fever, diarrhea) of chemotherapy agents were not as prevalent as symptoms linked to the chemotherapy experience (i.e., fatigue, pain, insomnia). These data supported the significance of the co-morbid conditions, as mentioned above. However, the most significant contribution was the validation of significance of the impact of the nursing intervention on the outcome of decreasing symptom severity in the Given et al. (2002) study (Keehne-Miron, Given, Given, vonEye, & Doorenbos, 2005).

Yates, Aranda, Hargraves, Mirolo, Clavarino, McLachlan, et al. (2005) likewise implemented a nursing intervention in a RCT for cancer patients. Yates et al. studied

stage I or II breast cancer patients and fatigue. Subjects were recruited and randomized prior to their first chemotherapy treatment (n=109) to the control group (standard of care) or the intervention arm. The intervention was a psycho-educational intervention aimed at improving one's self-care skills and behaviors to minimize fatigue. Trained nurses used protocols to guide the structure, process and content of the intervention. All experimental group members also received a fatigue management booklet published by the Oncology Nursing Society. A baseline fatigue assessment was conducted on all patients with their first chemotherapy visit. The first intervention session took place for the experimental group in a face to face fashion at the clinic upon the subject's second course of chemotherapy. Two booster sessions were provided to the experimental group members one week post the second cycle of chemotherapy and the second booster took place two weeks post this same second cycle of chemotherapy.

It is important to note that no group differences existed at baseline between the groups. An immediate effect for the nursing intervention was noted upon the first follow-up assessment; this took place after the second booster session, prior to cycle three of chemotherapy. Estimated marginal change scores for severity scores for the experimental group from time one (pre chemotherapy) to time two (post cycle two chemotherapy and post intervention for the experimental group) was 1.0, for the control group, the mean change score was 2.6 ($p = .01$). This change score difference supported the nursing intervention. However, this finding was not supported in the remaining follow-up evaluations. Estimated marginal change scores for severity scores for the experimental group from time one (pre chemotherapy) to time three (post cycle three chemotherapy) was 1.6, for the control group the mean change score was 1.9 ($p = .59$). Time one to time

four (post cycle four of chemotherapy) was likewise non significant with the experimental group posting change scores of .6 and control group members with scores of 1.3 ($p = .26$). Thus, as stated by the authors, "no significant differences were identified for any pre-or post-test change scores for confidence with managing fatigue, cancer self-efficacy, anxiety, depression, or quality of life" (p. 6027). The effect of the nursing intervention did not withstand the time period of the study. Nursing interventions that were successful for reducing symptom severity between cycle one and cycle two were not successful at maintaining the reduction of symptom severity by cycle three. The importance of assessment, intervention and measurement of symptoms over time for chemotherapy patients is supported in this study. Variables influenced by time include the multiple cycles of chemotherapy and their possible influence on future cycles, chemotherapy dosing schedules (every 14 days vs. every 21 days), as well as timing of the measurements.

Likewise, Anderson, Lohen, Mendoza, Guo, Harle, and Cleeland, (2006) conducted a RCT to evaluate the efficacy of 3 brief cognitive–behavioral techniques (relaxation, distraction, and positive mood interventions) on cancer related pain. Patients were recruited from an outpatient clinic (n=57), patients had a solid or hematological malignancy and experienced daily pain reported between 4 and 7 on a 0-10 scale for intensity as their "usual" level of pain. All patients were using opioid medications and have reported a positive response (decrease in pain intensity by 1 point after the start of the opioid) to that therapy.

The interventions for the Anderson et al. (2006) study are described below. Patients in the relaxation group received a 20 minute audiotape containing positive mood

statements and positive imagery suggestions. The relaxation group received a 20 minute audiotape that contained progressive muscle-relaxation instruction. The distraction group selected an audiotape on various topics of their choice, i.e., history, geography, foreign language. The control group received standard of care.

The Anderson et al. (2006) study used the MD Anderson Symptom Inventory (MDASI) to measure cancer related symptoms and the Brief Pain Inventory (BPI) was used to measure pain at four different assessment points throughout the 9 week study period. The mean age of the sample was 52 years (range 30-80) with the majority (79%) of the participants being women, 58% of the sample had metastatic disease. The relaxation group reported a mean pain reduction level of .90 (CI: 0.16-1.65; p = .023) from time one to time two. The distraction group also reported a mean pain reduction level of 1.16 (CI: 0.47-1.85; p = .004) from time one to time two. The positive mood intervention actually caused a slight increase in pain intensity of 0.08 (CI: -1.53 – 0.138; p = .91) after the initial session. However, at all time periods beyond time two, no significant differences in pain intensity were noted between any of the groups. Thus, significant reports of pain reduction were only noted upon the first assessment immediately following either the relaxation and distraction interventions, over time the intervention was not effective.

This finding in the Anderson et al. (2006) study offers additional support for the diminished endurance of specific interventions over time for the cancer patient. It is important to note in this study that the control group members were more likely to be receiving chemotherapy (p = .04) as well as a non-significant difference in baseline severe pain levels between the intervention groups (81%) with the control group (55%) (p

= .09). What is demonstrated in the intervention studies described above is that when studying symptoms in cancer patients it is vitally important to monitor the symptoms as well as the effectiveness of the interventions over time. As noted above, an intervention can be considered effective and significant upon immediate implementation however, over time this effect may deteriorate. Thus, it is crucial to examine the effects of interventions within the context of the disease and treatment trajectory, over time.

This effect of the time element leads us to our final section of this chapter. According to the adapted SEM following the intervention is the symptom expression component of the model. The symptom expression is the physical display of the symptom(s) post intervention. The symptom express component is linked with a time arrow back to the symptom perception component of the adapted SEM, refer to Figure 2. We note following the intervention that the symptom(s) may stay the same, change in one or any of the dimensions, or no longer be perceived by the patient. The final concept of time will be reviewed below.

Time

The research presented above supports the appropriateness of measurements of symptoms over time due to the chronic nature of cancer, treatment approaches that are delivered over time, and the knowledge that symptoms change over time. Many cancer patients may experience symptoms for some time prior to diagnosis. The actual diagnosis of cancer can often take a significant amount of time to obtain with numerous visits to various specialists, miss diagnosis, and the numerous tests and procedures required to arrive at an accurate diagnosis. Often for patients symptoms continue or worsen during this time. Likewise, the treatments for cancer are administered over time.

Even surgery, although it may be considered a one time event, requires an extensive amount of time to recover from. Recovery of the blood cell values after surgery should be back to normal as well as incisions should be healing prior to the initiation of the next treatment such as chemotherapy or radiation therapy. Again, the variable of time needs to be considered as well as possible new or enhanced dimensions of symptoms due to the procedure and/or extension of time.

The concepts of dose and time are essential for optimum chemotherapy delivery. Optimum doses of chemotherapy due to body surface area and past clinical trials are intended to be delivered within specific time periods. These time periods are typically depicted as cycles. Standard time periods or cycles of chemotherapy are every week, every 14 days, every 21 days or every 28 days. Symptoms will be influenced by the selection of agents, the route of administration and the timing of the administration. It is also essential to recall that the symptoms associated with chemotherapy typically remain to various degrees upon completion of the treatment. Fatigue is one such symptom that has been found to persist over time following the completion of treatment for cancer.

Curt, Breitbart, Cella, Groopman, Horning, Itri, et al. (2000) offer support for this concept in their report for the Fatigue Coalition. The coalition conducted a telephone interview of 379 cancer patients having had a history of chemotherapy. Recruitment was from 6,125 households in the United States, the median patient age was 62 with the majority (79%) being women. Seventy six percent of this sample reported experiencing fatigue "at least a few days each month" during their most recent chemotherapy; 30% experienced the symptom on a daily basis. Women were more likely to experience daily fatigue vs. their male counterparts (33% vs. 22%, $p < .05$). Sixty two percent of patients

reporting fatigue during chemotherapy reported it as "lasting longer than four days" (p. 355). Curt et al. (2000) noted that of the patients who experience fatigue and pain, and either nausea or depression (a total of three symptoms) (n=198) the majority (58%) reported that fatigue was the symptom that had lasted the longest. This descriptive study emphasizes the importance of monitoring and accurately measuring symptoms, especially fatigue in combination with other co-occurring symptoms, over time.

Summary

Various studies cited in the sections above support the importance of the concept of time. The Curt et al. (2000) study exemplifies the "clinical context" of the symptom as described by Barsevick et al. (2006) in Chapter One. The Anderson et al. (2006); Given et al. (2002); and Yates et al. (2005) studies support the impact of interventions over time. Thus, the intent of this literature review was to not only examine the symptoms of fatigue, pain and insomnia, with an emphasis on studies that examine them as multiple, co-occurring symptoms, however, to also support the adaptation of the SEM as described in Chapter 2.

The purpose of this research is to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized clinical trials that include a cognitive behavioral intervention. The literature review above provided an opportunity to discover some inconsistent findings in past work as well as provide conceptual and historical guidance leading to the development of the research questions for this study. These studies have also provided direction for the development of the research design and

methods that will be used for this study. In Chapter 4 a through description of the research design and methods will be provided.

Chapter Four

Design and Methods

This chapter will present and describe the sample and setting, the intervention, experimental variables, instruments, data analysis plan, and human subject protection plan for this research. The purpose of this research is to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized cognitive behavioral intervention clinical trials. The two trials are both NCI supported longitudinal panel studies of newly diagnosed adult cancer patients (RO1 CA-79280 {study number one} & RO1 CA-30724 {study number two}).

Research Questions

Overall, this study will address the question: At baseline observation and at 10 weeks is there an association between the dimensions of frequency, intensity, and distress of fatigue and frequency, intensity and distress of pain and/or insomnia for adults receiving chemotherapy? The effect of fatigue management will be evaluated as well as each question will be examined for a possible influence on the association by the variables of age, site and stage of cancer, sex, and co-morbid conditions. The specific research questions will follow.

Research Question 1

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *frequency* of fatigue and frequency of pain, as well as frequency of fatigue and frequency of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid

conditions? The dimension of frequency is the number of days out of the past seven that a patient reports the symptom as present. This will be a continuous variable with a possible range of 0-7.

Research Question 2

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *intensity* of fatigue and intensity of pain, as well as intensity of fatigue and intensity of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? The intensity dimension is measured on a rating scale of 0 meaning not present to 10 meaning the intensity is the worst possible. This will be a continuous variable with a possible range of 0-10.

Research Question 3

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *distress* related to fatigue and distress related to pain, as well as distress related to fatigue and distress related to insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? The dimension of distress will be measured on a rating scale with 0 meaning the symptom does not bother the patient to 10 meaning the symptom causes the worst bother the patient can imagine. This will be a continuous variable with a possible range of 0-10.

Research Question 4

Using categories of response to fatigue management (none / mild, non-response, partial response and full response) established in the literature, determine how changes in

the dimensions of frequency, intensity, and distress of pain and insomnia are predicted by categories of response to the management of fatigue between baseline and 10 weeks. Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions?

Question 4 will examine if a change in frequency of fatigue is capable of predicting a change in the dimensions of frequency, intensity and/or distress for the associated symptoms of pain and insomnia. For this question, fatigue intensity levels will be converted from continuous to categorical variables to facilitate the comparison with fatigue response categories (Mendoza, Wang, Cleeland, Morrissey, Johnson, Wendt, et al., 1999). The fatigue response categories will be 0 = none 1 = mild fatigue, 2-4 moderate fatigue, 5-10 severe fatigue.

Response categories for the management of fatigue will be determined by comparing the baseline fatigue severity category with the 10 week fatigue severity category. Response categories for the management of fatigue will be as follows: None/mild = patient stays within the same none or mild category at the baseline measurement as well as the 10 week measurement. A patient can move from none to mild or from mild to none in this category. Non-responder = a patient who stays within the same category (excluding none/mild) from the baseline measure of fatigue to the 10 week measurement, (i.e., severe at baseline and severe at 10 weeks). Partial responder = A patient who goes from severe to the moderate level of fatigue between baseline and 10 weeks. Full responder = A patient who goes to the none or mild category of fatigue from moderate or severe between baseline and 10 weeks (Given et al., in press; Miaskowski, et al., in press; Paul, Zelman, Smith, & Miaskowski, 2005).

Sample and Settings

The two randomized cognitive behavioral intervention clinical trials database from which will be used for this research started accruing patients in 2004. Subject accrual was completed in June of 2006 at which time a total of 671 cancer patients participated in both studies. All patients were over the age of 21, undergoing chemotherapy for a solid tumor or lymphoma and being treated at one of seven community or academic cancer centers throughout the Midwest and East coast. Study sites included: Yale University in Connecticut, Indiana University in Indiana, and Michigan State University/Breslin Cancer Center/Great Lakes Cancer Institute, Saint Joseph Mercy Oakland Hospital, Saint Mary's Health Care, William Beaumont Hospital, and Holy Cross Cancer Center all in Michigan. Subjects were accrued to one of four different arms (groups) that made up the two studies, study one (n= 235) and study two (n=437). See Appendix A for the Study Schema. Potential subjects were recruited at each center by trained recruiters.

Once patients were enrolled and consented, in either study, they completed twice-weekly automated telephone calls for up to six weeks assessing chemotherapy symptoms. In study one, patients who had advanced disease and reported a 2 out of 10 for both pain and fatigue or a 3 for either pain or fatigue entered the trial, received a baseline interview, and were randomized to either the NASM group to receive an eight week, six contact stepped-approach cognitive behavioral intervention implemented by an oncology nurse as well as a symptom management toolkit, or to the group involving a similar number of encounters with a trained non-nurse intervener (non nurse symptom management [NNSM]) who provided a self-management intervention based on a symptom management toolkit.

In study two, patients who reported a 2 or higher for a severity rating for one or more symptoms entered the trial, received a baseline interview, and were randomized to one of two arms (groups) of the study. Patients in group one received six weekly calls by an automated system (ATSM) with reference to a symptom toolkit based on the severity of the symptoms reported. Patients in group two received an eight-week, six contact stepped-approach cognitive behavioral intervention implemented by an oncology nurse as well as the toolkit (NASM). Patients never reaching a 2 or higher on any symptom at screening did not enter the trial, and were sent a letter thanking them for participation.

Both randomization procedures balanced the groups with respect to site of cancer and recruitment location. All patients from both studies, all groups, will be used in this research. The rationale for the various academic and community sites involved in this study is to provide a mix of academic and community cancer center patients, rural and urban participants, and to promote ethnic and cultural diversity based on geography.

The Intervention

Study number one contained two arms, each with an intervention. Upon randomization patients and caregivers could be placed in the NNSM group or the NASM group. The NNSM group intervention consisted of the patients and caregivers receiving a symptom management toolkit (book that provided detailed instruction and reference for management of common chemotherapy/cancer symptoms) and six calls over an eight week time period by a research assistant who would listen to concerns and advise participants to reference the appropriate section in the toolkit.

Study number two contained an ATSM group as one of the two groups of this study. This group likewise received the toolkit, however, instead of a research assistant making

the call, as in the example cited above; an automated telephone system contacted the patient for six calls over eight weeks at times per the patient's pre-determined preference. The automated telephone system required patients to respond to symptom assessment questions by ranking the symptoms 0-10 on their telephone keypad, based on responses the automated system would direct them to appropriate sections of the toolkit and/or refer the patient to their oncologist if the symptom met a threshold pre-determined by their oncologist.

Both studies contained NASM groups. Participants in these groups also received the toolkit and six calls over eight weeks by an oncology nurse. The nursing intervention was comprised of evidence-based intervention strategies that were delivered to the nurse intervention group. Each intervention nurse had the same stepped cancer-nursing intervention software loaded onto a laptop computer. This software housed problem-specific, evidence-based intervention strategies that the nurse and patient could mutually elect for the patient to implement on his or her own behalf to move the problem toward resolution.

The intervention for all of the groups described above was targeted to assess and intervene with previously identified symptoms. At each visit, the nurse, research assistant (non-nurse), or automated telephone system assessed all symptoms. In addition to severity rated on a scale from 0 = not present to 10 meaning the worst severity possible, patients were asked to rate their responses from 0 (no impact) to 10 (great impact) on quality of life indicators (e.g., sleep, mobility, appetite). Any symptom that reached a level of 4 or higher in severity or impact on quality of life indicators was posted to the problem list. In the NASM groups, once a symptom was posted the nurse

and patient addressed it until the symptom was controlled or the intervention ended. In the NNSM and ATSM groups, the patients were directed to the toolkit as described above.

At the next intervention encounter, the patients were asked to evaluate the efficacy of the intervention strategy and the status of the problem resolution. In the NASM groups the intervention strategies were modified, changed, or deleted depending on the result. Using a computer-assisted protocol, the intervention nurse was able to document in real time the interventions for each patient problem at each encounter in which the nurse and patient focused on the problem. Intervention fidelity was monitored by the nurse coordinator reviewing every encounter for each patient, as well as weekly meetings between the PI's and nurse interveners (Santacroce, 2004).

Patients in both studies were very similar. The distributions of age, race/ethnicity and level of education did not differ between the two studies. Study number one had a higher percent of lung cancer patients, lower percent of breast cancer patients, and higher percentage of late stage cancer patients. Because of disease severity, patients in study number one had higher severity symptoms at intake, including pain and fatigue. Preliminary analysis revealed that both studies demonstrated decreased summed symptom severity at the ten week analysis with no differences by group in each study. The data from both studies will be combined. This study will not be looking for a group effect. Demographic data will be presented in Chapter 5. All analyses will adjust for group and study membership. The main interest of this study is the frequency, intensity and distress of fatigue, pain and insomnia, the effect of a fatigue intervention, and the testing of other covariates. Refer to Appendix A for the study schema.

Due to the extensiveness of the data and the large number of subjects, unique aspects of this study include: the impact of variables such as age, site and stage of disease, sex, and co-morbid conditions, the ability to examine symptoms for a change in pattern of frequency, intensity, and distress over time, and, the ability to assess the relationships among symptoms.

Experimental Variables

The outcome variables for this study arise from the adapted SEM and include the frequency, intensity, and distress of the symptoms of fatigue, pain, and insomnia, refer to Figure 2. All results will be adjusted for study membership and group. Additional covariates that will be examined include: age, site and stage of disease, sex, and co-morbid conditions. The randomized clinical trial design was closely monitored throughout the original studies resulting in a minimal amount of missing values.

Measures

Demographic data such as site of cancer, stage of disease, and treatment protocol were obtained from a medical record audit after patients signed consent forms and completed the study.

The Symptom Experience Scale (SES). The SES was developed by Drs. Barbara and Charles Given for the Family Home Care for Cancer: A Community –Based Model study (1993), it is based on the Symptom Distress Scale (SDS) by McCorkle & Young (1978). The SES is an interview guide that prompts trained interviewers to ask patients if they had experienced symptoms commonly associated with cancer or their cancer treatment in the previous two weeks. Frequency was recorded as the number of days out of the past seven a particular symptom was experienced, thus, used 0-7 scale. Intensity

was recorded as the severity level and was ranked on a scale from 0 = not present to 10 = the worst it can be. Distress referred to the extent to which the symptom caused an "interference with life" and also used a 0-10 scale. Cronbach's alpha has been established for this instrument as .90 in previous studies (Wyatt, Friedman, Given, Given, & Beckrow, 1999). The SES has consistently measured symptoms within the theoretical definition by Armstrong (2003), thus, establishing construct validity. Content validity has been examined and established by reviewing the literature and surveying chemotherapy symptom assessment/management experts as to the degree to which the items cover the domain of chemotherapy/cancer symptoms.

Data Collection Schedule and Procedures

Nurse recruiters were trained from each of the participating sites to identify eligible patients, explain the study to potential subjects, and obtain signed informed consents. Upon receipt of signed consent, all patients were monitored and screened into the study via the automatic telephone system as described previously. All study participants, regardless of random assignment completed the telephone interviews. Trained personnel who were not nurses conducted all of the telephone interviews. If a patient was randomized to a NASM group the nurse was contacted by the project coordinator. The intervention nurse then contacted the patient via telephone to introduce herself, review the consent, and the patients' role in the study and schedule a time to conduct the baseline intervention session. All intervention contacts were conducted via the telephone.

Telephone interviews included the SES at baseline, 10 weeks and 16 weeks and were conducted from a central location. Each interviewer was trained and followed an explicit quality assurance protocol. The non-nurse intervention group received telephone calls of

similar frequency that provided an automated version of the SES. All patients received conventional care as prescribed by their oncology team. Medical record audits were completed at the end of the study.

Data Analysis and Interpretation

The outcome measures for this study included symptom frequency, intensity and distress. The purpose of this research was to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized cognitive behavioral intervention clinical trials. The following statistical approaches were applied to the research questions.

Descriptive analyses of the outcome measures (symptom frequency, intensity and distress of each symptom) were obtained by group, and by age, site, stage of cancer, sex, and co-morbid conditions at baseline and ten weeks. Distributions of the outcome measures were evaluated. Regression analysis was conducted at baseline and 10 weeks for each of the following research questions: Research Question 1: At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *frequency* of fatigue and frequency of pain, as well as frequency of fatigue and frequency of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Research Question 2: At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *intensity* of fatigue and intensity of pain, as well as intensity of fatigue and intensity of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer,

sex, and co-morbid conditions? Research Question 3: At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *distress* related to fatigue and distress related to pain, as well as distress related to fatigue and distress related to insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions?

Analysis conducted for baseline measurements were performed using the following statistical models: 1) Frequency of pain at baseline related to frequency of fatigue at baseline and 2) Frequency of pain at baseline related to frequency of fatigue at baseline add covariates. The covariates for all of the following models included age, site and stage of cancer, sex, and co-morbid conditions. Models 1) and 2) were also fit with frequency of insomnia as an outcome. Similar analyses were preformed for the intensity and distress dimensions:

Intensity of pain at baseline related to intensity of fatigue at baseline;

Intensity of pain at baseline related to intensity of fatigue at baseline add covariates;

Intensity of insomnia at baseline related to intensity of fatigue at baseline;

Intensity of insomnia at baseline related to intensity of fatigue at baseline add covariates;

Distress of pain at baseline related to distress of fatigue at baseline;

Distress of pain at baseline related to distress of fatigue at baseline add covariates;

Distress of insomnia at baseline related to distress of fatigue at baseline;

Distress of insomnia at baseline related to distress of fatigue at baseline add covariates.

The essential parameters tested in these models were regression coefficients for the frequency, intensity and distress of fatigue at baseline.

Analysis conducted at 10 weeks was performed using the same statistical models as at baseline with baseline measures replaced by 10 week measures. Covariates in the 10 week analyses were the same as in the baseline analyses with study membership and group added to adjust for their effect on the outcomes. The essential parameters tested in these models were regression coefficients for the frequency, intensity and distress of fatigue at 10 weeks.

Regression analysis was also conducted to answer research question number four: Research Question 4: Using categories of response to fatigue management (none / mild, non-response, partial response and full response) established in the literature, determine how changes in the dimensions of frequency, intensity, and distress of pain and insomnia are predicted by categories of response to the management of fatigue between baseline and 10 weeks? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Analysis were performed by fitting the following statistical models: 1) Frequency of pain at 10 weeks related to frequency of pain at baseline add category of response to fatigue management and 2) Frequency of pain at 10 weeks related to frequency of pain at baseline add category of response to fatigue management add covariates. The covariates include age, site and stage of cancer, sex, co-morbid conditions, study membership and group. The essential parameters tested in these models are the regression coefficients for the variables representing different categories of response to fatigue management. Following the analysis of frequency of pain, statistical models 1) and 2) were fit for the intensity and distress of pain, and for the frequency,

intensity and distress of insomnia. Note that the above models included group and study membership; therefore, the results were adjusted for these variables. Analyses were performed using SPSS ® Version 13.0 Graduate Pack for Windows statistical software package.

Power

Following completion of the data analysis post hoc power analysis was performed for each research question. From the results of fitting each statistical model, the observed effect sizes for the essential parameters tested in the models were determined, and based on the magnitude of the effect size and the sample size, the statistical power to detect each effect size was calculated. The final power analysis is displayed in a Table 14; see Chapter 5, page 112.

Protection of Human Participants

This study (approval # 06-130, Michigan State University Institutional Review Board [IRB]) as well as the two studies that this data analysis is based upon have successfully completed full IRB review at Michigan State University (MSU). The two studies (RO1 CA-79280 {study number one} & RO1 CA-30724 {study number two}) providing the data for this research received full review at each of the 7 clinical sites recruiting for the studies. Informed consent written materials were presented to prospective patients by trained nurse recruiters at each clinical site. Upon receipt of signed written consent patients were enrolled in the automated telephone screening system. Upon reaching threshold for study participation patients were reminded of the study procedures and their informed consent.

If patients wished to continue with the study at this time they were given a baseline interview. Following the baseline interview patients were randomized to the study groups by the site study coordinator. At any time a patient was allowed to withdraw from the studies. All patients were given a study code, no names or other identifying characteristics were used in the analytical datasets. The list of codes to identify patients is kept in a locked file drawer with access to the key only available to the study PI's.

Data Security

All patient data was recorded and stored via a web based data collection program. This program was backed up on a nightly basis and stored on a secure server in a fire retardant room located outside MSU. All members of the research team have completed mandatory MSU IRB training related to patient consent, confidentiality, quality assurance, and data safety and security on a yearly basis.

Recruiter Training

Nurses from the clinical trials offices of participating sites were hired and trained to implement the recruitment protocol. The PI's for the two studies Dr. Barbara Given and Dr. Charles Given interviewed all recruiter candidates and made the final selection for hire of one recruiter per site. All of the nurse recruiters were experienced in clinical trial recruitment, most were oncology nurses familiar with the cancer centers practitioners and their patients.

Prior to initiation of recruitment, all nurse recruiters were extensively trained in interactive sessions the included discussion of the objectives and schema of the studies (RO1 CA-79280 [study one] and RO1 CA-30724 [study two]), inclusion and exclusion criteria, policies and procedures for identifying and recruiting participants,

confidentiality, MSU IRB policies, their local institution's IRB policies, and completion of the study forms, web-based tracking system, and symptom severity screening system. Secure computer passwords were provided to each nurse recruiter for entering sociodemographic information into the web-based tracking system. A recruiter manual was used for training as well as provided for future reference to each nurse recruiter. The recruiter manual contained information on the research team and contact information, overall study goals and objectives, inclusion and exclusion criteria, screening and recruitment procedures, and a recruitment script.

The Recruitment Process

The nurse recruiters evaluated patients based on the inclusion criteria. Inclusion criteria consisted of: being over the age of 21, diagnosed with a solid tumor cancer or non-Hodgkins lymphoma, currently receiving chemotherapy, able to speak and read English, and had a touchtone telephone. Nurse recruiters presented the study and informed consent verbally and provided a study packet that included a description of the studies, contact information, and the informed consent forms to potential subjects and their caregivers. Nurse recruiters completed screening/enrollment forms for each patient approached. Every screening/enrollment form was faxed to the PI's office at MSU. Upon obtaining a signed informed consent, sociodemographic information was entered into the web-based system. Patients were screened at this time for symptom severity. Recall that patients needed to have a 2 or higher level of severity (range 0-10) on any of the 13 symptoms assessed via the M.D. Anderson Symptom Inventory (MDASI) to enter into study one or study two or higher for both pain and fatigue or a 3 or higher for either pain or fatigue on the MDASI to enter into study two (Cleeland et al., 2000). Symptom

severity screening took place via an automated voice response version of the MDASI. Patients were called weekly for up to 6 weeks.

Patients that never met the symptom severity inclusion criteria described above were thanked for participating and not entered into the trial. Patients that did meet all inclusion criteria were randomized into one of the two studies based on their symptom severity screening. Refer to Appendix A for the study schema. Randomization to one of the two arms of each study was completed using a computer minimization program balancing cancer site within each arm by recruitment location (Taves, 1974).

Recruiter Quality Assurance

The PI's reviewed each screening/enrollment form submitted by the nurse recruiters. The forms were reviewed for missing data and to verify inclusion criteria. Nurse recruiters participated in regularly scheduled conference calls with the PI's to discuss and troubleshoot recruiting issues. Regularly scheduled meetings at MSU were conducted in which all recruiters were expected to attend. All recruiters were required to submit a weekly web-based recruitment summary that was reviewed by PI Dr. Barbara Given. Dr. Barbara Given personally called the nurse recruiter with any questions or concerns related to patient recruitment.

Intervention Nurse Training

Experienced oncology nurses from Michigan, were hired and trained to implement the intervention protocols for the nurse intervention arms of both studies (RO1 CA-79280 [study one] and RO1 CA-30724 [study two]). The PI's for the two studies Dr. Barbara Given and Dr. Charles Given interviewed all intervention nurse candidates and made the final selection for hire. Prior to initiation of the study, all intervention nurses were

extensively trained in interactive sessions the included discussion of the objectives and schema of the studies (RO1 CA-79280 [study one] and RO1 CA-30724 [study two]), policies and procedures for intervening and interviewing participants, confidentiality, MSU IRB policies, and completion of the web-based data management system. Training sessions involved classroom interactive sessions with the study PI's as well as practice taped telephone intervention sessions with MSU College of Nursing doctoral students acting as patients.

Secure computer passwords were provided to each intervention nurse for entering information into the web-based system. A computerized stepped intervention protocol was used for training as well as study intervention. Study manuals were provided that contained information on the research team and contact information, overall study goals and objectives, inclusion and exclusion criteria, intervention policies, procedures, and scripts.

The Intervention Process

The intervention nurses intervened with patients randomized to the nursing arms of both studies based on the stepped nursing interventions contained in the web-based system. A total of 17 symptoms were evaluated they included: fatigue, pain, dyspnea, insomnia, distress, nausea, fever, difficulty remembering, lack of appetite, dry mouth, vomiting, numbness and tingling, diarrhea, cough, constipation, weakness, and alopecia. Six contacts were made over an 8 week time period of the study. Patients reporting a symptom severity of 1 or higher were asked to respond to how that symptom interfered with daily activities, emotions, enjoyment of life and relationships (Daut, Cleeland, & Flanery, 1983). Patients randomized to the nurse intervention arm that reported a

symptom severity of 4 or higher (range 0-10) received the intervention from the nurse. Up to 4 strategies were used for each symptom with a severity score of 4 or higher. The strategies included: teaching, prescribing, communicating with the provider, and counseling and support. Patients in the nurse intervention arms were also directed to refer to their symptom management toolkit. At all later contacts the intervention nurse evaluated the strategies used. The nurse asked if the strategy was tried or not and if helpful or not. If the strategy was not helpful it was altered and/or a new strategy proposed.

Intervention Nurse Quality Assurance

Throughout the training periods PI Dr. Barbara Given listened to each practice tape and monitored the corresponding web-based documentation and provided feedback to the intervention nurses. Throughout the study The PI's randomly reviewed tapes and the web-based documentation completion by the intervention nurses. The PI Dr. Barbara Given randomly reviewed the web-based data management system to review nursing interventions for appropriateness and documentation based on the study protocols. The intervention nurses participated in regularly scheduled conference calls with the PI's to discuss and troubleshoot issues. Regularly scheduled meetings at MSU were conducted in which all intervention nurses were expected to attend.

Interviewer Training

Interviewers were hired and trained to implement the interview protocols for all arms of both studies (RO1 CA-79280 [study one] and RO1 CA-30724 [study two]). The PI's for the two studies Dr. Barbara Given and Dr. Charles Given interviewed all interviewer candidates and made the final selection for hire. Prior to initiation of the study, all

interviewers were extensively trained in interactive sessions the included discussion of the objectives and schema of the studies (RO1 CA-79280 [study one] and RO1 CA-30724 [study two]), policies and procedures for interviewing participants, confidentiality, MSU IRB policies, and completion of the web-based data management system. Training sessions involved classroom interactive sessions with the study PI's as well as practice taped telephone interviews with MSU College of Nursing doctoral students acting as patients. A minimum of 3 practice interviews were conducted with different doctoral students acting out the roles of a depressed and very distraught patient, a patient that is very talkative and easily distracted, and a very angry and upset patient.

Secure computer passwords were provided to each interviewer for entering information into the web-based system. Study manuals were provided that contained information on the research team and contact information, overall study goals and objectives, inclusion and exclusion criteria, interview policies, procedures (ie., probing and clarification), and scripts. Many of the interviewers were MSU graduate students in a health care related field.

The Interview Process

Interviews were conducted via telephone calls by the trained interviewers at baseline (after symptom screening and prior to intervention), 10 weeks and 16 weeks. Interviewers used interview software to direct the interview process. Each interview took approximately 45 minutes to complete. Interviews were scheduled at the patient's convenience.

Interviewer Quality Assurance

The PI Dr. Barbara Given listened to each of the 3 taped practice interviews for content, technique, and confidentiality. The web-based documentation for each of the 3 practice interviewer sessions was also evaluated by Dr. Barbara Given. Dr. Given provided feedback and coaching to each interviewer based on this evaluation. Throughout the study every 10^{th} interview with the patient's audible permission was reviewed by the PI Dr. Barbara Given. Dr. Barbara Given critically evaluated the quality of the interview (pace of the interview, probing and clarification techniques, and attention to distress experienced by the patient). Feedback was provided to the interviewer.

Women and Minority Inclusion in Clinical Research

The past NCI (RO1 NR/CA 01915) funded study completed by Drs. Barbara and Charles Given (Given et al., 2000; Given et al., 2001; Given et al., 2002) served as a benchmark for subject recruitment and retention. This past study included 763 patients at its preliminary study point, 367 of these patients were male and 337 were female. However, minority recruitment was low in this past study with approximately 92% of the patients being white. This value was consistent with the socio-demographic profile of Michigan and the participating centers in this study. Therefore, some different clinical sites were recruited for participation in the two current studies (RO1 CA-79280 & RO1 CA-30724) to improve minority recruitment. The addition of Holy Cross (a metro-Detroit clinical site in Michigan) as well as the Yale academic site enhanced minority recruitment for these two studies. Demographics for this research will be presented in Chapter 5.

Facilities and Resources

All support for the facilities, computer, telephone, and human resources are provided by two RO1 grants from NCI, as cited above. This study involved analysis of data generated by these two funded studies and was supported by The Oncology Nursing Foundation Trish Green Research Grant and Michigan State University College of Nursing. Nursing intervention and telephone interviews were conducted at a research office on the campus of MSU; the automated telephone system is also housed there. Trained recruiters used phones, faxes, and computers at the clinical sites that are property of the studies.

Summary

This chapter presented the design and methods that were used for this study as well as human subject protection and data safety. The purpose of this research was to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized cognitive behavioral intervention clinical trials. Descriptive demographic statistics, generalized linear regression model analysis, and statistical power for this study will be presented in Chapter 5. Chapter 5 will also include a discussion of the findings, strengths and limitations of this study, and implications for clinical practice and research.

Chapter 5

Findings

This longitudinal study was designed to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized clinical trials of a cognitive behavioral intervention. This study will answer the questions: At baseline observation and at 10 weeks is there an association between the dimension of frequency, intensity, and distress of fatigue and frequency, intensity and distress of pain and/or insomnia for adults receiving chemotherapy? Also, can categories of response to fatigue management predict changes in the dimensions of frequency, intensity and distress of pain and insomnia at 10 weeks? Covariates examined included: age, site and stage of cancer, sex, and co-morbid conditions. Participants were recruited from seven academic and community cancer centers.

Sample

A total of 671 adult chemotherapy patients participated in this study. The majority of participants (37.4%, n=251) were recruited from Indiana University and the Hosier Oncology Group in Indiana. Grand Rapids, Michigan recruited 14.2% of the participants (n=95) and 34.3% were from the Pontiac/Detroit city/Detroit suburban area (n=230). Yale University in Connecticut recruited 8.0% of the participants (n=54) and the remaining 6.1% (n=41) were recruited in the Lansing or Flint Michigan locations. A total of 37.5% (n=252) of the participants were recruited from university cancer centers, the remaining 62.5% (n=419) of the patients were recruited from community cancer centers.

The sociodemographic and disease characteristics of the participants are presented in Table 1. Females made up 70% (n=467) of the patients in this study due to a large number of breast cancer patients in this study. Thirty percent of the sample were male (n=204). The mean age of the participants was 57.6 years (SD = 11.79, range 25-90 years). Age distribution is presented in Figure 3. The predominant race of participants was Caucasian (86.3%, n =579), African Americans accounted for 9.8% (n = 66) of the participants, and 2.7% (n = 18) were other races such as Mexican Americans, Chicanos, Native American Alaskans, Oriental Asians, and Pacific Islanders. Race data was missing for 8 patients (1.2%). Note: the race categories were taken directly from the data collection instrument, categories were not altered or adapted to adjust for race or ethnicity standards per NCI or other agencies.

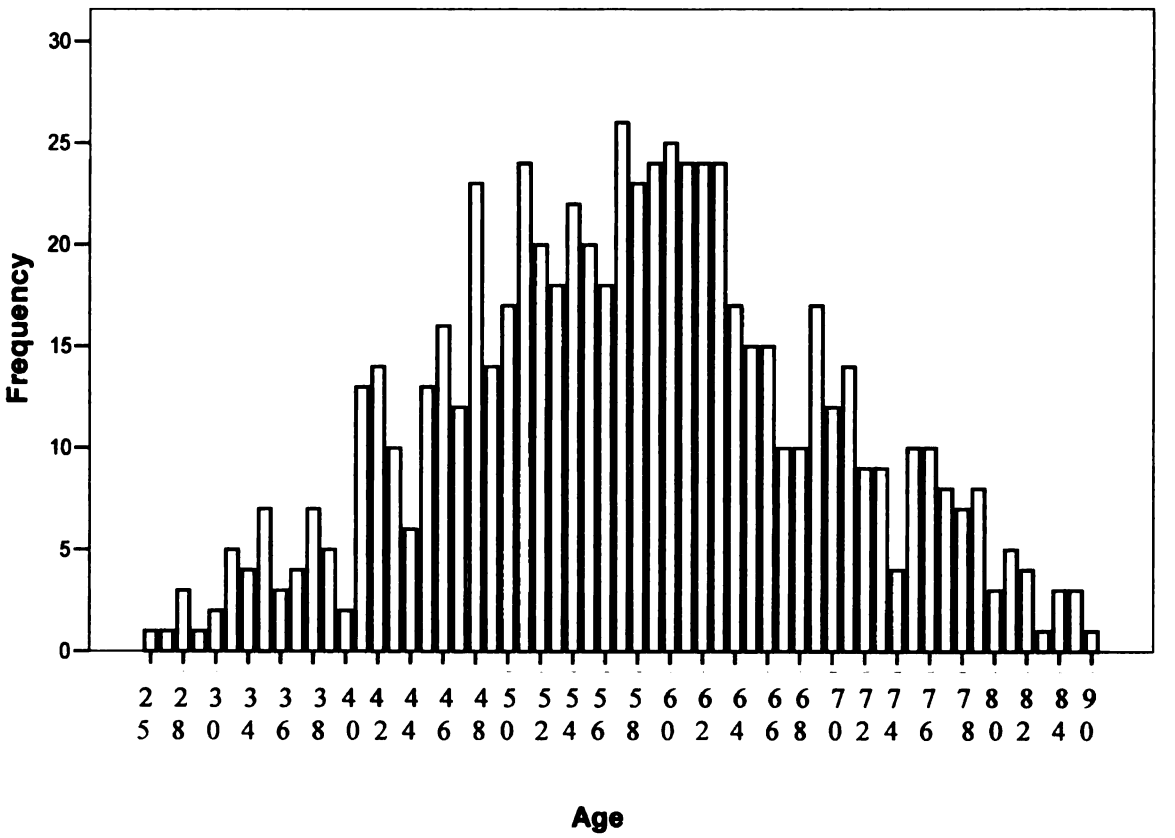


Figure 3. Frequency Distribution of the Variable of Age for Study Participants

The majority of patients were married, (65.3%, n = 438), 10.3% were never married (n = 69) and 15.4% (n = 103) were divorced or separated. Fifty patients (7.5%) in this study were widowed. The education experience of this sample consisted of 118 patients (17.6%) with a graduate or professional degree, 332 (49.5%) had completed college or experienced some college or technical training as their highest level of education. One hundred and sixty-one (24%) participants had completed their education through high school and the remaining 60 (8.9%) completed grade school or some high school as their highest level of education.

The most common tumor type of patients in this study was breast cancer (n = 234, 34.9%). There were no males with breast cancer in this study. Non-small cell lung cancer was the second most common tumor type (n = 113, 16.8%) and 27 (4.0%) of the participants had small cell lung cancer. Eighty (11.9%) patients had colon cancer. Fifty-one (7.6%) of the patients had a genitourinary malignancy and 33 (4.9%) experienced a gastrointestinal malignancy. The remaining patients had a gynecological malignancy, non-Hodgkin's lymphoma, pancreatic cancer or other cancers. Nineteen (2.8%) patients experienced some other form of cancer not mentioned above.

Cancer diagnosis as it relates to sex was also examined. Females with breast cancer represented the largest percentage of the sample (34.9%, n = 234). Refer to Table 2 for cancer site by sex data. Data representing cancer stage in this study is depicted as early (stage one or two) or late (stage three or four). Overall, the majority (n = 569, 85.6%) of the patients in this study experienced late stage disease. For 23.2% (n = 156) of patients in this study this cancer diagnosis represented recurrent disease.

Table 1

Descriptive Statistics of Sociodemographic and Disease Characteristics of Patients

Characteristic	N	%
Patient Gender		
Female	467	70.0
Male	204	30.0
Patient Ethnicity		
Caucasian	579	86.3
African American	66	9.8
Other	18	2.7
Missing	8	1.2
Marital Status		
Married	438	65.3
Divorced or Separated	103	15.4
Never Married	69	10.3
Widowed	50	7.5
Living Together	10	1.5
Education		
Did not completed high school	60	8.9
Completed high school	161	24.0
Some college or technical training	202	30.1
Completed college	130	19.4
Completed graduate degree	118	17.6
Cancer Site		
Breast	234	34.9
Non-small cell lung	113	16.8
Colon	80	11.9
GU	51	7.6
Gynecological	47	7.0
GI	33	4.9
NHL	38	5.7
Small cell lung	27	4.0
Pancreas	21	3.1
Mesothelioma	8	1.2
Other	19	2.8
Stage of Cancer		
Early (stage 1 or 2)	96	14.4
Late (stage 3 or 4)	569	85.6
Disease Recurrence		
Yes	156	23.2
No	515	76.8

	Range	Mean (SD)	Median
Patient Age	25-90 years	57.6 (11.79)	58.0
Number of Co-Morbid Conditions	0-9	2.07 (1.61)	2.00

Table 2

Number / % Statistics of Cancer Site by Sex

Cancer Site and Sex	N	%
Breast – Female	234	34.9
Lung – Female	77	11.5
Lung – Male	63	9.4
Colon – Female	53	7.9
Colon – Male	27	4.0
Other Cancer – Female	103	15.4
Other Cancer – Male	114	16.9

Co-morbid conditions were evaluated for this study. Eighty-one percent of the participants in this study experienced one or more co-morbid conditions upon entry into this study. The mean number of reported co-morbid conditions was 2.07 (SD 1.61, range 0 – 9). Only 125 patients (18.6%) reported 0 co-morbid conditions. See Table 3 for a list of co-morbid conditions identified in this study. The most commonly reported co-morbid condition in this study was high blood pressure (n = 285, 42.5%) followed by emotional problems (n = 175, 26.1%) and another cancer (n = 134, 20%), 118 (17.6%) reported urinary incontinence and 116 patients reported heart problems (17.3%).

Measures

Descriptions of the measures used in this study were provided in Chapter 4. A discussion of the mean values for the dimensions of frequency, intensity and distress for the symptoms of fatigue, pain and insomnia at baseline and 10 weeks will be presented here. Recall that frequency was described as the number of days out of the past seven that the symptom was present. Intensity was described as a ranking of the symptom on a scale of 0 meaning not present to 10 meaning the intensity is the worst possible. Distress was recorded as a scale with 0 meaning the symptom does not bother the patient to 10

meaning the symptom causes the worst bother the patient can imagine. See Table 4 for the mean values, standard deviations and possible ranges for each symptom (fatigue, pain, and insomnia) at baseline and 10 weeks for all subjects (n = 671) regardless of group membership.

Table 3

Number / % Statistics of Co-morbid Conditions

Co-morbid Condition	N	%
High Blood Pressure	285	42.5
Emotional Problems	175	26.1
Other Cancer	134	20.0
Urinary Incontinence	118	17.6
Heart Problem	116	17.3
Diabetes	84	12.6
Cataract Surgery	70	10.4
Emphysema	67	10.0
Arthritis	62	9.2
Hearing Aid	41	6.1
Replace Joint	37	5.5
Chest Pain	25	3.7
Stroke	20	3.0
Fractured Hip	7	1.0
Other Major Health Problem	151	23.3

Group Membership and Attrition

Group membership was not expected to result in statistically significant differences based on previous work with this same data set. Sikorskii, Given, Given, Jeon, Decker & Decker (in press) noted that both the NASM and the ATSM groups achieved significant reductions in symptom severity over baseline and at 10 weeks (post intervention) with effect sizes exceeding .5 and no differences by group. This study will adjust for group membership and examine group effect via generalized linear regression models.

Table 4

Mean Values, Standard Deviations and Possible Ranges of the Symptoms per Dimension

	Fatigue Baseline	Fatigue 10 weeks	Pain Baseline	Pain 10 weeks	Insomnia Baseline	Insomnia 10 weeks
Frequency						
mean	4.70	3.68	2.28	1.93	3.07	1.62
(SD)	(2.49)	(2.85)	(2.77)	(2.77)	(2.74)	(2.41)
(range)	(0-7)	(0-7)	(0-7)	(0-7)	(0-7)	(0-7)
Intensity						
mean	4.71	3.22	2.32	1.63	3.77	1.87
(SD)	(2.69)	(2.67)	(2.81)	(2.41)	(3.27)	(2.74)
(range)	(0-10)	(0-10)	(0-10)	(0-10)	(0-10)	(0-10)
Distress						
mean	4.18	2.52	2.02	1.31	3.03	1.31
(SD)	(3.06)	(2.78)	(2.88)	(2.40)	(3.08)	(2.33)
(range)	(0-10)	(0-10)	(0-10)	(0-10)	(0-10)	(0-10)

A total of 1605 cancer patients were eligible and approached by nurse recruiters for either of the two studies, 815 signed informed consent forms, and 806 patients initiated the symptom screening (Sikorskii et al., in press). Seven hundred and twenty-eight met the inclusion criteria to enter into one of the two trials. A total of 671 patients completed baseline interviews, and 533 completed 10 week interviews. Sikorskii et al. (in press) examined attrition with this data set; they found that patients who attrited did not differ significantly on summed symptom severity at baseline. In study number 2 attrited patients averaged 42.32 for summed symptom severity, NASM patients averaged 41.47 ($p = 0.89$).

Results

Regression analysis was conducted for each research question using SPSS ® Version 13.0 Graduate Pack for Windows statistical software package. Minimal missing data was

noted in the final data set, n=671, therefore, all cases were used for final analysis with no missing data procedures used. All regression models for all research questions will include group assignment (experimental or control) and study name (ATSM or Pain and Fatigue [NASM]) to allow adjustment for these variables. Recall differing inclusion criteria for the two different studies. To enter into the NASM group's patients needed to report a 2 out of 10 for frequency of pain and fatigue at baseline or a 3 out of 10 for pain or fatigue on the MDASI screening instrument used for study participation. ATSM group inclusion criteria required that the patient reported a 2 or higher on any one of the 13 symptoms assessed in the MDASI. Symptoms assessed in the MDASI include: fatigue, pain, disturbed sleep, distress (emotional), nausea, shortness of breath, lack of appetite, dry mouth, drowsy, emesis, numbness or tingling, bloated, sad (Cleeland et al., 2000). Thus, in this study examining the symptoms of fatigue, pain, and insomnia patients in the NASM study were expected to experience a greater effect of pain and fatigue at baseline vs. their ATSM counterparts. It is possible that ATSM patients may not even experience fatigue, pain or insomnia and participate in this study due to the inclusion criteria that allowed any report of a 2 or higher for any one of the 13 symptoms from the MDASI listed above.

The outcome variables examined in this study include frequency, intensity and distress of fatigue, pain and insomnia as described previously. The covariates included: age, site and stage of cancer, sex, and co-morbid conditions. Age will be the age of the patient at baseline of the study and represents a continuous variable. Co-morbid conditions will be represented by a continuous variable and be the total number of co-morbid conditions that the patient reports at baseline. Stage of cancer was determined in the NASM and

ATSM studies to be a categorical variable. Early stage represents cancer stages 1 or 2 per the TNM staging system and late represents stages 3 or 4 per the TNM system at baseline of the study as determined per the medical record audit. Site of cancer was originally examined in this study as a categorical variable that combined sex and cancer site, for example, females with colon cancer, males with lung cancer, females with an "other" cancer, a total of 8 categories were developed. This variable was not statistically significant in the regression models, with the exception of females with lung cancer being different form the referent category on baseline insomnia. Based on this finding as well as a review of the literature, the cancer site category for this study was represented as lung cancer or other cancer (Cooley, 2002; Cooley & Moriarty, 2003; Fu et al., 2005; Gift et al., 2003; Given et al., 2001; Given et al., 2002; Kurtz et al., 2000). Sex was a categorical variable as male or female.

The following format guided the data input and interpretation of the generalized linear regression model analysis for research questions 1-3. Frequency, intensity, or distress level of pain or insomnia was the outcome for each model respective of the question or portion of the question being examined. Covariates for all models included the dimension of fatigue, group assignment, and study name. Covariates examined when the portion of the question sought to examine influencing variables included: age, site and stage of cancer, sex, and number of co-morbid conditions. Models were constructed for baseline findings as well as 10 week findings. Results of the data analysis for research questions 1-3 will be presented below. Research question 1 will be described in detail, research questions 2 and 3 were conducted in the same manner, for the sake of avoiding

redundancy the results will be outlined. Research question 4 design and results will be described in detail below.

Research Question 1

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *frequency* of fatigue and frequency of pain, as well as frequency of fatigue and frequency of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? As noted above, generalized linear regression model analysis was conducted with frequency of pain at baseline as the dependent variable, study name, group assignment and frequency of fatigue at baseline as covariates. This model supported that there is an association between the dimensions of frequency of fatigue and frequency of pain at baseline ($\beta = .38$, SE = .04, $t = 9.40$, $p < .01$, not in tables). Generalized linear regression model analysis was also conducted with frequency of pain at 10 weeks as the dependent variable, study name, group assignment and frequency of fatigue at 10 weeks as the covariates. This model supported that there is an association between the dimensions of frequency of fatigue and frequency of pain at 10 weeks ($\beta = .27$, SE = .04, $t = 6.75$, $p < .01$, not in tables). Refer to Table 5 for results of the regression analysis for the pain and fatigue model with all covariates added to the model.

To examine the effects of the covariates a generalized linear regression model examined pain at baseline as the dependent variable and the covariates as cited above. The model included the frequency of pain at baseline as the dependent variable, the covariates: sex, cancer site as a categorical variable of lung cancer or other cancer, stage of disease as a categorical variable as early or late, patient age and number of co-morbid

conditions were continuous variables as well as frequency of fatigue at baseline. This model demonstrated that there remains an association between the dimensions of frequency of fatigue and frequency of pain at baseline when the covariates are included in the model ($\beta = .35$, SE = .04, $t = 8.64$, $p < .01$). Age ($\beta = -.04$, SE = .01, $t = -3.78$, $p < .01$) demonstrated a negative association with this model and the number of co-morbid conditions ($\beta = .21$, SE = .07, $t = 2.98$, $p < .01$) demonstrated a positive association.

Table 5

Regression Analyses for Relating Frequency of Pain to Frequency of Fatigue and Other Covariates at Baseline and 10 Weeks

	Baseline				10-Weeks			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Fatigue Frequency	.35	.04	8.64	< .01	.29	.04	7.10	< .01
Age	-.04	.01	-3.78	< .01	-.03	.01	-2.42	.02
Comorbids	.21	.07	2.98	< .01	.24	.08	2.96	< .01
Sex								
Male	.09	.22	.39	.70	-.17	.26	-.66	.51
Female	000	.	.	.	000	.	.	.
Stage								
Early	-.24	.29	-.83	.41	-.17	.31	-.55	.58
Late	000	.	.	.	000	.	.	.
Cancer								
Lung	.28	.25	1.11	.27	-.06	.31	-.20	.85
Non-Lung	000	.	.	.	000	.	.	.

Ten week data were also examined via a generalized linear regression model with the effects of the covariates cited above. This model demonstrated that there remains an association between the dimensions of frequency of fatigue and frequency of pain at 10 weeks ($\beta = .29$, SE = .04, $t = 7.10$, $p < .01$). Again, age ($\beta = -.03$, SE = .01, $t = -2.42$, $p = .02$) demonstrated a negative association and the number of co-morbid conditions ($\beta =$

.24, SE = .08, t = 2.96, p < .01) demonstrated a positive association. Thus, being younger and having more co-morbid conditions at baseline was associated with a higher frequency of pain at baseline and 10 weeks over and above the frequency of fatigue at baseline or 10 weeks.

An additional model was developed that examined the frequency of insomnia at baseline as the dependent variable and the frequency of fatigue at baseline. This model supported an association between the dimensions of frequency of fatigue and frequency of insomnia at baseline (β = .21, SE = .04, t = 4.92, p < .01, not in tables). The frequency of insomnia at 10 weeks as the dependent variable and the frequency of fatigue at 10 weeks as the independent variable were also examined via generalized linear regression. This model supported that there is an association between the dimensions of frequency of fatigue at 10 weeks and frequency of insomnia at 10 weeks (β = .24, SE = .04, t = 6.70, p < .01, not in tables). Refer to Table 6 for results of the regression analysis for the insomnia and fatigue model with all covariates added to the model.

A generalized linear regression model was run with frequency of insomnia at baseline as the dependent variable and included all of the covariates cited above. This model demonstrated that there remains an association between the dimensions of frequency of fatigue at baseline and frequency of insomnia at baseline that is not significantly affected by the addition of the covariates (β = .18, SE = .04, t = 4.32, p < .01). Age demonstrated a negative association with this model (β = -.04, SE = .01, t = -4.39, p < .01). The number of co-morbid conditions (β = .20, SE = .07, t = 2.71, p < .01) demonstrated a positive association. Differing from the models with pain at baseline as the dependent variable cited above, over and above other covariates in the model lung cancer patients had

significantly lower frequency of insomnia compared to non-lung cancer patients, (β = -.52, SE = .26, t = -1.99, p = .05). See Table 6.

Table 6

Regression Analyses for Relating Frequency of Insomnia to Frequency of Fatigue and Other Covariates at Baseline and 10 Weeks

	Baseline				10-Weeks			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Fatigue Frequency	.18	.04	4.32	< .01	.25	.04	7.03	< .01
Age	-.04	.01	-4.40	< .01	-.02	.01	-1.56	.12
Comorbids	.20	.07	2.71	< .01	.02	.07	.25	.81
Sex								
Male	.18	.23	.79	.43	.11	.23	.49	.63
Female	000	.	.	.	000	.	.	.
Stage								
Early	.13	.30	.44	.66	.17	.28	.63	.53
Late	000	.	.	.	000	.	.	.
Cancer								
Lung	-.52	.26	-1.99	.05	.11	.23	.49	.63
Non-Lung	000	.	.	.	000	.	.	.

The same model was run with frequency of insomnia at 10 weeks as the dependent variable; all other variables were the same as noted above. This model with frequency of insomnia at 10 weeks as the dependent variable and all covariates demonstrated that there remains an association between the dimensions of frequency of fatigue at 10 weeks and frequency of insomnia at 10 weeks (β = .25, SE = .04, t = 7.03, p < .01). However, all other covariates were not significantly associated with frequency of insomnia in this model. Age, co-morbid conditions and lung cancer no longer had a significant association with the outcome, frequency of insomnia, at 10 weeks. Thus, being younger, having more co-morbid conditions, and not having lung cancer diagnosis at baseline was

associated with a higher frequency of insomnia at baseline over and above the frequency of fatigue at baseline, however, age, number of co-morbid conditions, and site of cancer did not influence insomnia over and above the frequency of fatigue at 10 weeks. See Table 6.

Research Question 2

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *intensity* of fatigue and intensity of pain, as well as intensity of fatigue and intensity of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Generalized linear regression model analysis was conducted with intensity of pain at baseline as the dependent variable. This model supported that there is an association between the dimensions of intensity of fatigue and intensity of pain at baseline ($\beta = .40$, $SE = .04$, $t = 10.81$, $p < .01$, not found in tables) and at 10 weeks ($\beta = .31$, $SE = .04$, $t = 8.22$, $p < .01$, not found in tables). Refer to Table 7 for results of the regression analysis for the pain and fatigue model with all covariates added to the model.

Examination of the covariates resulted in a model that continued to support an association between the dimensions of intensity of fatigue and intensity of pain at baseline ($\beta = .37$, $SE = .04$, $t = 9.61$, $p < .01$). Similar to the findings noted above with frequency of pain, age ($\beta = -.04$, $SE = .01$, $t = -3.76$, $p < .01$) demonstrated a negative association within this intensity of pain model and the number of co-morbid conditions ($\beta = .19$, $SE = .07$, $t = 2.74$, $p < .01$) demonstrated a positive association. See Table 7.

Table 7

Regression Analyses for Relating Intensity of Pain to Intensity of Fatigue and Other Covariates at Baseline and 10 Weeks

	Baseline				10-Weeks			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-Value
Fatigue Intensity	.37	.04	9.61	< .01	.30	.04	8.16	< .01
Age	-.04	.01	-3.76	< .01	-.03	.01	-3.59	< .01
Comorbids	.19	.07	2.74	< .01	.25	.07	3.62	< .01
Sex								
Male	.08	.23	.34	.74	-.14	.22	-.62	.54
Female	000	.	.	.	000	.	.	.
Stage								
Early	-.03	.29	-.11	.92	-.32	.27	-1.19	.24
Late	000	.	.	.	000	.	.	.
Cancer								
Lung	.02	.26	.06	.96	-.17	.26	-.64	.52
Non-Lung	000	.	.	.	000	.	.	.

A model was also conducted with intensity of pain and fatigue at 10 weeks and all covariates. This model supported an association between the two variables at 10 weeks ($\beta = .30$, SE = .04, $t = 8.16$, $p < .01$). Age ($\beta = -.03$, SE = .01, $t = -3.59$, $p < .01$) demonstrated a negative association and the number of co-morbid conditions ($\beta = .25$, SE = .07, $t = 3.62$, $p < .01$) demonstrated a positive association. Younger age and having more co-morbid conditions at baseline were associated with a higher intensity of pain over and above the intensity of fatigue at baseline and 10 weeks. Refer to Table 7.

The intensity of insomnia and fatigue at baseline were also studied. An association between the dimensions of intensity of fatigue and intensity of insomnia was supported at baseline ($\beta = .35$, SE = .05, $t = 7.76$, $p < .01$, not in tables) and at 10 weeks ($\beta = .40$, SE =

.04, t = 9.73, p < .01, not in tables). See Table 8 for the regression analysis for the intensity of insomnia and fatigue model with all covariates added.

The baseline model with all the covariates added demonstrated that an association between the dimensions of intensity of fatigue and intensity of insomnia at baseline remains (β = .32, SE = .05, t = 6.83, p < .01). Age was the only covariate that demonstrated a significant association (β = -.04, SE = .01, t = -3.37, p < .01).

Table 8

Regression Analyses for Relating Intensity of Insomnia to Intensity of Fatigue and Other Covariates at Baseline and 10 Weeks

	Baseline				10-Weeks			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Fatigue Intensity	.32	.05	6.83	< .01	.41	.04	9.95	< .01
Age	-.04	.01	-3.37	< .01	-.02	.01	-1.98	.05
Comorbids	.12	.09	1.36	.176	.03	.08	.34	.73
Sex								
Male	-.02	.28	-.06	.95	-.04	.25	-.18	.86
Female	000	.	.	.	000	.	.	.
Stage								
Early	.22	.35	.62	.54	.25	.30	.83	.41
Late	000	.	.	.	000	.	.	.
Cancer								
Lung	-.45	.31	-1.44	.15	-.20	.29	-.68	.50
Non- Lung	000	.	.	.	000	.	.	.

Intensity of insomnia and intensity of fatigue with all covariates added at 10 weeks was also studied. This model supported that there is an association between the dimensions of intensity of fatigue and intensity of insomnia at 10 weeks (β = .41, SE = .04, t = 9.95, p < .01). Age continued to demonstrate a negative association (β = -.02, SE = .01, t = -1.98, p = .05). Younger age was associated with a higher intensity of insomnia

at baseline and 10 weeks over and above the intensity of fatigue at baseline or 10 weeks. See Table 8.

Research Question 3

At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *distress* related to fatigue and distress related to pain, as well as distress related to fatigue and distress related to insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Generalized linear regression model analysis was conducted with distress related to pain at baseline and distress of fatigue at baseline. This model supported an association between the dimensions of distress of fatigue and distress of pain at baseline ($\beta = .38$, SE = .03, $t = 11.46$, $p < .01$, not in tables). See Table 9 for results of the regression analysis for the distress of pain versus distress of fatigue model with all covariates added to the model.

The effects of the covariates were also examined. This model demonstrated that there remains an association between the dimensions of distress of fatigue and distress of pain at baseline with the covariates ($\beta = .35$, SE = .03, $t = 10.20$, $p < .01$). Age ($\beta = -.04$, SE = .01, $t = -3.70$, $p < .01$) demonstrated a negative association and the number of co-morbid conditions ($\beta = .30$, SE = .07, $t = 4.23$, $p < .01$) demonstrated a positive association with level of pain at baseline.

Generalized linear regression model analysis was conducted with distress of pain versus distress of fatigue at 10 weeks. This model supported an association between distress of fatigue and distress of pain at 10 weeks ($\beta = .34$, SE = .04, $t = 9.87$, $p < .01$, not found in tables). The effects of the covariates were examined. An association

between the dimensions of distress of fatigue and distress of pain at 10 weeks was maintained with the covariates in the model ($\beta = .34$, SE = .04, $t = 9.70$, $p < .01$). Again, age ($\beta = -.03$, SE = .01, $t = -3.20$, $p < .01$) demonstrated a negative association and number of co-morbid conditions ($\beta = .16$, SE = .07, $t = 2.38$, $p = .02$) demonstrated a positive association. Younger age and a greater number of co-morbid conditions at baseline were associated with a higher distress of pain at baseline and 10 weeks over and above the distress of fatigue at baseline or 10 weeks. See Table 9.

Table 9

Regression Analyses for Relating Distress of Pain to Distress of Fatigue and Other Covariates at Baseline and 10 Weeks

	Baseline				10-Weeks			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Fatigue Distress	.35	.03	10.20	< .01	.34	.04	9.70	< .01
Age	-.04	.01	-3.70	< .01	-.03	.01	-3.20	< .01
Comorbids	.30	.07	4.23	< .01	.16	.07	2.38	.02
Sex								
Male	.14	.23	.62	.54	-.19	.22	-.87	.38
Female	000	.	.	.	000	.	.	.
Stage								
Early	-.11	.29	-.38	.71	-.25	.26	-.94	.35
Late	000	.	.	.	000	.	.	.
Cancer								
Lung	-.06	.26	-.22	.83	-.19	.22	-.87	.38
Non- Lung	000	.	.	.	000	.	.	.

An additional model was developed that examined the distress of insomnia and the distress of fatigue at baseline. This model supported an association between the dimensions of distress of fatigue and distress of insomnia at baseline ($\beta = .37$, SE = .04, $t = 10.07$, $p < .01$, not in tables). Refer to Table 10 for results of the regression analysis for

the distress of insomnia and fatigue model with all covariates added. This same model was run with all covariates. This model demonstrated that there remains an association between distress of fatigue and distress of insomnia at baseline when all covariates are included ($\beta = .34$, SE = .04, $t = 9.18$, $p < .01$). Age was the only covariate that was significant in this model ($\beta = -.04$, SE = .01, $t = -3.71$, $p < .01$). See Table 10.

Distress of insomnia and the distress of fatigue at 10 weeks were also examined. This model supported an association between the two variables ($\beta = .33$, SE = .03, $t = 9.89$, $p < .01$, not found in tables). The covariates were added to this model to demonstrate that there remained an association between the dimensions of distress of fatigue and distress of insomnia at 10 weeks ($\beta = .33$, SE = .03, $t = 9.82$, $p < .01$). However, unique to this question, no covariates had a significant association with distress of insomnia at 10 weeks. Younger age was associated with a higher distress of insomnia at baseline over and above the distress of fatigue at baseline; however, age did not influence distress of insomnia over and above the effect of fatigue at 10 weeks. Refer to Table 10.

Research Question 4

Using categories of response to fatigue management (none / mild, non-response, partial response and full response) established in the literature, determine how changes in the dimensions of frequency, intensity, and distress of pain and insomnia are predicted by categories of response to the management of fatigue between baseline and 10 weeks? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions?

Table 10

Regression Analyses for Relating Distress of Insomnia to Distress of Fatigue and Other Covariates at Baseline and 10 Weeks

	Baseline				10-Weeks			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Fatigue Distress	.34	.04	9.18	< .01	.33	.03	9.82	< .01
Age	-.04	.01	-3.71	< .01	-.02	.01	-1.75	.08
Comorbids	.14	.08	1.75	.08	.10	.07	1.44	.15
Sex								
Male	.05	.25	.19	.85	.09	.21	.43	.67
Female	000	.	.	.	000	.	.	.
Stage								
Early	.30	.32	.94	.35	-.03	.26	-.12	.90
Late	000	.	.	.	000	.	.	.
Cancer								
Lung	-.31	.28	-1.08	.28	-.24	.25	-.95	.35
Non- Lung	000	.	.	.	000	.	.	.

Fatigue intensity levels (range 0-10) were converted from continuous to categorical variables to facilitate comparison with fatigue response categories (Mendoza, Wang, Cleeland, Morrissey, Johnson, Wendt, et al., 1999; Miaskowski, et al., in press). Theoretically continuous variables provide greater power for statistical tests. However, power was of less concern with a sample size of 671 versus clinical relevance for analyses of data for this question. The measurement of intensity of fatigue on a scale of 0-10 is common in clinical practice. Guyatt, Norman, Juniper, and Griffith (2002) suggest that a reduction in symptom severity that ranges from 33% to 50% is clinically significant.

However, clinical interpretation of changes in intensity levels between measurement periods indicate that the 0-10 fatigue scale is not necessarily considered an interval level

scale by practitioners. As an example, if a patient reports their fatigue intensity at a 9 at baseline and a 6 at 10 weeks one would say that the patient experienced a 33% improvement in fatigue intensity; however, clinically this patient is still experiencing a severe level of fatigue that requires intervention. I doubt that a practitioner would accept a 6 for fatigue intensity as being acceptable, it is an improvement, however, the symptom remains unresolved. On the contrary, a patient experiencing a fatigue intensity level of 3 at baseline and a 2 at 10 weeks likewise represents a 33% reduction in fatigue intensity. However, this 33% reduction in intensity level for fatigue has a completely different clinical interpretation then the prior example. Thus, when using a 0-10 scale to measure fatigue intensity both percent change and absolute value change values are not always clinically meaningful.

Given et al. (in press) used data from 339 patients in this current studies database to examine symptom response categories. It was noted by Given et al. that as intensity (severity) of symptoms increased, interference (distress) level of the symptom did not linearly increase. Differences in the associations between severity and distress were noted to appear on the 0-10 scales between 1 and 2, and 4 and 5. Thus, the establishment of cut points to create clinically meaningful fatigue categories.

The fatigue intensity categories for this current study were 0 = none, 1 = mild fatigue, 2-4 moderate fatigue, 5-10 severe fatigue. Response categories for the management of fatigue were determined by comparing the baseline fatigue intensity category with the 10 week fatigue intensity category. Response categories for the management of fatigue are as follows: None/mild = patient stays within the same none or mild fatigue intensity category at the baseline measurement as well as the 10 week measurement. Non-

responder = a patient who stays within the same category (excluding the none or the mild category) from the baseline measure of fatigue to the 10 week measurement, (i.e., severe at baseline and severe at 10 weeks). Partial responder = a patient who goes from severe to the moderate level of fatigue between baseline and 10 weeks. Full responder = a patient who goes to the none or mild category of fatigue from moderate or severe between baseline and 10 weeks (Given et al., in press; Paul, Zelman, Smith, & Miaskowski, 2005). Refer to Table 11 for a frequency table of fatigue management groups.

Table 11

Frequency and % of Fatigue Management Group Membership

Management of Fatigue	Frequency	Percent
None / mild	47	8.8
Non-responder	300	56.3
Partial responder	79	14.8
Full responder	107	20.1

Generalized linear regression model analysis was conducted with frequency of pain at 10 weeks as the dependent variable and the management of fatigue category and pain at baseline as covariates. This model supported an association between the dimensions of frequency of pain at baseline and frequency of pain at 10 weeks when management of fatigue categories are included in the model ($\beta = .43$, $SE = .04$, $t = 10.61$, $p < .01$). The only fatigue management category with a significant effect was the non-responders ($\beta = .93$, $SE = .28$, $t = 3.34$, $p = .01$). Non-responders had significantly higher frequency of pain at 10 weeks compared to full responders. See Table 12.

A generalized linear regression model was also conducted for frequency of pain at 10 weeks, the management of fatigue category, pain at baseline, cancer stage, site and sex,

age, and co-morbids. This model supported the association between frequency of pain at baseline and 10 weeks ($\beta = .41$, SE = .04, $t = 9.91$, $p < .01$). Other significant effects were, the non-responder fatigue management category ($\beta = 1.07$, SE = .28, $t = 3.78$, $p < .01$) and co-morbid conditions ($\beta = .15$, SE = .08, $t = 1.95$, $p = .05$). Therefore, non-responders (as compared to full responders) and patients with a greater number of co-morbid conditions had significantly higher frequency of pain at 10 weeks, see Table 12.

Generalized linear model regression analysis was conducted with intensity of pain at 10 weeks as the dependent variable, management of fatigue category, and intensity of pain at baseline as the covariates. This model supported an association between the variables ($\beta = .31$, SE = .04, $t = 8.70$, $p < .01$). Two fatigue management categories had significant effects; the non-responders ($\beta = .97$, SE = .25, $t = 3.88$, $p < .01$) and the partial responders ($\beta = .75$, SE = .33, $t = 2.29$, $p = .02$). Non-responders and partial responders had significantly higher intensity levels of pain at 10 weeks compared to full responders.

Model analysis was conducted with the same variables plus all covariates. This model supported an association between intensity of pain at baseline and 10 weeks ($\beta = .29$, SE = .04, $t = 7.96$, $p < .01$). Two fatigue management categories had significant effects; the non-responders ($\beta = 1.05$, SE = .25, $t = 4.18$, $p < .01$) and the partial responders ($\beta = .65$, SE = .33, $t = 1.95$, $p = .05$). Age ($\beta = -.03$, SE = .01, $t = -2.66$, $p = .01$) and number of co-morbid conditions also contributed to this model ($\beta = .23$, SE = .07, $t = 3.43$, $p < .01$). Non-responders and partial responders had significantly higher intensity of pain at 10 weeks compared to full responders. Younger patients and patients with greater numbers of co-morbid conditions experienced higher intensity levels of pain at 10 weeks. Refer to Table 12.

Table 12

Result of Regression Analysis for Frequency, Intensity, & Distress of Pain and Fatigue Management Category at 10 Weeks

	Frequency				Intensity				Distress			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Model with Pain at Baseline and Response to Fatigue Management (Ft Mng) at 10 weeks												
Pain	.43	.04	10.61	< .01	.31	.04	8.70	< .01	.22	.04	5.98	< .01
Ft Mng												
None-None	-.46	.43	-1.05	.29	-.35	.39	-.89	.37	-.31	.40	-.78	.44
Non-Resp	.93	.28	3.34	< .01	.97	.25	3.88	< .01	.94	.26	3.68	< .01
Part-Resp	.37	.37	1.02	.31	.75	.33	2.30	.02	.55	.34	1.62	.11
Full-Resp	000	.	.	.	000	.	.	.	000	.	.	.
Model with Pain at Baseline and Response to Fatigue Management (Ft Mng) at 10 weeks and all Covariates												
Pain	.41	.04	9.91	< .01	.29	.04	7.96	< .01	.20	.04	5.35	< .01
Ft Mng												
None-None	-.34	.44	-.77	.44	-.31	.39	-.79	.41	-.21	.40	-.53	.60
Non-Resp	1.07	.28	3.78	< .01	1.05	.25	4.18	< .01	1.07	.26	4.10	< .01
Part-Resp	.44	.37	1.18	.24	.65	.33	1.95	.05	.51	.34	1.50	.13
Full-Resp	000	.	.	.	000	.	.	.	000	.	.	.
Age	-.01	.01	-.76	.45	-.03	.01	-2.66	.01	-.03	.01	-2.89	< .01
Comorbids	.15	.08	1.95	.05	.23	.07	3.43	< .01	.17	.07	2.44	.02
Sex - Male	-.17	.24	-.68	.50	-.14	.22	-.65	.52	-.20	.23	-.87	.39
Female	000	.	.	.	000	.	.	.	000	.	.	.
Stage - Early	-.01	.29	-.02	.99	-.28	.26	-.95	.34	-.18	.27	-.68	.50
Late	000	.	.	.	000	.	.	.	000	.	.	.
Cancer - Lung	-.09	.29	-.31	.76	-.07	.26	-.25	.80	.13	.27	.49	.635
Non- Lung	000	.	.	.	000	.	.	.	000	.	.	.

Generalized linear model regression analysis was conducted with distress of pain at 10 weeks as the dependent variable, management of fatigue category, and distress of pain at baseline as the covariates. This model supported an association between these variables ($\beta = .22$, SE = .04, $t = 5.98$, $p < .01$). One fatigue management category contributed, the non-responders ($\beta = .94$, SE = .26, $t = 3.67$, $p < .01$). This same model was repeated with all covariates added. The association between the dimensions of distress of pain at baseline and 10 weeks remained present ($\beta = .20$, SE = .04, $t = 5.35$, $p < .01$). Again, one fatigue management category had a significant effect, the non-responders ($\beta = 1.07$, SE = .26, $t = 4.10$, $p < .01$), age ($\beta = -.03$, SE = .01, $t = -2.89$, $p < .01$) and number of co-morbid conditions ($\beta = .17$, SE = .07, $t = 2.44$, $p = .02$). Non-responders had significantly higher distress of pain at 10 weeks compared to full responders. Younger patients and patients with greater numbers of co-morbid conditions experienced higher distress of pain at 10 weeks. See Table 12.

General linear model regression analysis was conducted with frequency of insomnia at 10 weeks as the dependent variable, fatigue management categories, and frequency of insomnia at baseline as covariates. This model supported an association between the dimensions of frequency of insomnia at baseline and the frequency of insomnia at 10 weeks ($\beta = .21$, SE = .04, $t = 5.59$, $p < .01$). One fatigue management category had a significant effect, the non-responders ($\beta = 1.19$, SE = .26, $t = 4.64$, $p < .01$). This same model was run with all covariates added. This model continued to support an association between the dimensions of frequency of insomnia at baseline and 10 weeks ($\beta = .19$, SE = .04, $t = 5.00$, $p < .01$). The non-responder fatigue management category continued to have a significant effect ($\beta = 1.28$, SE = .26, $t = 4.88$, $p < .01$). Thus, the non-responders

had significantly higher frequency of insomnia at 10 weeks compared to full-responders. Refer to Table 13.

General linear model regression analysis was conducted with intensity of insomnia at 10 weeks as the dependent variable, fatigue management categories, and intensity of insomnia at baseline as covariates. This model supported an association between the variables ($\beta = .16$, SE = .04, $t = 4.48$, $p < .01$). Two fatigue management categories also had a significant effect; the non-responders ($\beta = 1.67$, SE = .29, $t = 5.72$, $p < .01$) and the partial responders ($\beta = 1.27$, SE = .39, $t = 3.30$, $p = .01$). This same model with all covariates added supported the association between the dimensions of intensity of insomnia at baseline and 10 weeks ($\beta = .14$, SE = .04, $t = 3.75$, $p < .01$). Two fatigue management categories continued to have a significant effect; the non-responders ($\beta = 1.79$, SE = .30, $t = 6.02$, $p < .01$) and the partial responders ($\beta = 1.31$, SE = .39, $t = 3.35$, $p = .01$). No additional covariates contributed to the model. Non-responders and partial responders had significantly higher intensity of pain at 10 weeks compared to full responders. Refer to Table 13.

General linear model regression analysis was conducted with the distress of insomnia at 10 weeks as the dependent variable, fatigue management categories, and the distress of insomnia at baseline as covariates. This model supported an association between the dimensions of distress of insomnia at baseline and the distress of insomnia at 10 weeks ($\beta = .17$, SE = .03, $t = 5.13$, $p < .01$). Two fatigue management categories had a significant effect; the non-responders ($\beta = 1.22$, SE = .25, $t = 4.89$, $p < .01$) and the partial responders ($\beta = .91$, SE = .33, $t = 2.77$, $p = .01$). This same model was run with all covariates. This model continued to support the association between the dimensions of

distress of insomnia at baseline and 10 weeks ($\beta = .16$, SE = .04, $t = 4.53$, $p < .01$). The same two fatigue management categories continued to contribute; the non-responders ($\beta = 1.32$, SE = .25, $t = 5.18$, $p < .01$) and the partial responders ($\beta = .90$, SE = .34, $t = 2.68$, $p = .01$). No additional covariates contributed to the model. Thus, non-responders and partial responders had significantly higher intensity of pain at 10 weeks compared to full responders. Refer to Table 13.

Power

Following data analysis post hoc power analysis was performed for each research question. The observed effect size was determined for the essential parameters tested in the models. The magnitude of the effect size and the sample size were considered in calculating statistical power. In power calculations for regression the effect size of .02 is considered small; effect sizes below .01 represent extremely small effects with no practical interpretation. Table 14 lists the variables with eta squared values of .01 or greater and the corresponding values of statistical power to detect the effects of these variables on the outcomes. Power was considered adequate ($\geq .80$) for the statistical tests completed for this study.

Table 13

Result of Regression Analysis for Frequency, Intensity, & Distress of Insomnia and Fatigue Management Category 10 Weeks

	Frequency				Intensity				Distress			
Parameter	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value	Est.	St. Error	T	P-value
Model with Insomnia at Baseline and Response to Fatigue Management (Ft Mng) at 10 weeks												
Insomnia	.21	.04	5.59	< .01	.16	.04	4.48	< .01	.17	.03	5.13	< .01
Ft Mng												
None-None	-.13	.40	-.31	.76	-.08	.46	-.16	.87	.02	.39	.05	.96
Non-Resp	1.19	.26	4.64	< .01	1.67	.29	5.72	< .01	1.22	.25	4.89	< .01
Part-Resp	.59	.34	1.74	.08	1.27	.40	3.29	.001	.91	.33	2.77	.01
Full-Resp	000	.	.	.	000	.	.	.	000	.	.	.
Model with Insomnia at Baseline and Response to Fatigue Management (Ft Mng) at 10 weeks and all Covariates												
Insomnia	.19	.04	5.00	< .01	.14	.04	3.75	< .01	.16	.04	4.53	< .01
Ft Mng	-.06	.41	-.14	.38	.03	.46	.07	.94	.09	.40	.22	.83
None-None												
Non-Resp	1.28	.26	4.88	< .01	1.79	.30	6.02	< .01	1.32	.25	5.18	< .01
Part-Resp	.61	.35	1.78	.08	1.31	.39	3.35	< .01	.90	.34	2.68	.01
Full-Resp	000	.	.	.	000	.	.	.	000	.	.	.
Age	-.01	.01	-.61	.55	-.02	.01	-1.77	.08	-.01	.01	-1.49	.14
Comorbids	-.00	.07	.01	1.00	.08	.08	1.00	.32	.13	.07	1.93	.06
Sex – Male	-.20	.27	-.74	.46	.01	.26	.03	.97	.13	.22	.59	.56
Female	000	.	.	.	000	.	.	.	000	.	.	.
Stage – Early	.17	.27	.61	.54	.39	.31	1.25	.21	-.06	.26	-.24	.81
Late	000	.	.	.	000	.	.	.	000	.	.	.
Cancer - Lung	-.20	.27	-.74	.46	-.01	.30	-.05	.96	-.04	.26	-.15	.89
Non-Lung	000	.	.	.	000	.	.	.	000	.	.	.

Table 14

Power to Detect Effects of Covariates in the Models for Pain or Insomnia & Fatigue Frequency, Intensity & Distress at Baseline & 10 Weeks

Parameter	Frequency				Intensity				Distress			
	Baseline		10 weeks		Baseline		10 weeks		Baseline		10 weeks	
	Partial Eta Squared	Obs. Power	Partial Eta Squared	Obs. Power	Partial Eta Squared	Obs. Power	Partial Eta Squared	Obs. Power	Partial Eta Squared	Obs. Power	Partial Eta Squared	Obs. Power
Model with Pain												
Pain	.12	1.00	.08	1.00	.15	1.00	.11	1.00	.17	1.00	.16	1.00
Model with Pain Plus all Covariates												
Pain	.10	1.00	.09	1.00	.12	1.00	.11	1.00	.14	1.00	.15	1.00
Age	.02	.97	.01	.68	.02	.96	.02	.95	.02	.96	.02	.89
Comorbids	.01	.84	.02	.84	.01	.78	.03	.95	.03	.99	.01	.66
Model with Insomnia												
Insomnia	.04	1.00	.08	1.00	.08	1.00	.15	1.00	.13	1.00	.16	1.00
Model with Insomnia Plus all Covariates												
Insomnia	.03	.99	.09	1.00	.07	1.00	.16	1.00	.11	1.00	.16	1.00
Age	.03	.99	.01	.34	.02	.92	.01	.51	.02	.96	.02	.89
Comorbids	.01	.77	.00	.06	.00	.27	.00	.06	.01	.42	.01	.42

Discussion

Despite a recent trend to begin to examine multiple co-occurring symptoms and/or symptom clusters in oncology nursing (Barsevick et al., 2006; Dodd et al., 2001b; Gift et al., 2003; Kim et al., 2005; Parker et al., 2005), the majority of research to date has focused on individual symptoms (Dodd et al., 2001a). In addition, the dimensions of frequency, intensity and distress of symptoms are typically measured, researched and intervened upon as they relate to individual symptoms. No randomized clinical trials (RCT's) containing a nursing intervention was identified that associated the dimensions of the frequency, intensity, and distress of one symptom with these same dimensions for additional symptoms that are co-occurring. No studies were found that examined the effect of a change in dimension of one symptom being able to predict a change in the dimensions of other co-occurring symptoms.

This study examined the dimensions of frequency, intensity and distress for fatigue, pain and insomnia. All dimensions for fatigue were associated with all of the dimensions for pain and insomnia at baseline as well as 10 weeks into the trial. Although the influence of a behavioral cognitive nursing intervention on the management of fatigue as associated with the other symptoms of pain and insomnia was also of interest, the exact effect of the intervention was not able to be determined in this study. Recall that study group (nurse versus non-nurse intervention) and study membership (study number one or study number 2) were adjusted for in each regression equation. In addition, all subjects, regardless of group or study membership were included. This study did find that the management of fatigue categories was able to differentiate non-responders from full-responders with respect to pain and insomnia experiences. This study also found that

21% of the participants in this study were full-responders for fatigue management. Although this finding supports that some patients experienced decreased severity of fatigue at 10 weeks versus baseline, due to the regression analysis as well as study design we can not determine that this effect was due to fatigue intervention or which intervention or group attributed to this finding.

Pain and Fatigue

Numerous studies have been conducted that support an association between frequency of pain and frequency of fatigue at baseline of chemotherapy (Cooley et al., 2003; Dodd et al., 2001b; Gaston-Johansson et al., 1999; Given et al., 2001; Hickok et al., 1996). The association between frequency of pain and frequency of fatigue at baseline for chemotherapy patients was validated in this current study. The addition of covariates such as age, sex, site and stage of cancer and number of co-morbid conditions at baseline and 10 weeks did not influence this association.

Hickok et al. (1996) noted that over time, by the sixth week of radiation therapy (RT) treatment, less then half of their 50 lung cancer patient's still reporting fatigue reported pain. Eleven patients completed chemotherapy immediately prior to the start of radiation, of these patients 54% (n=6) were fatigued throughout RT. Seven patients received Interferon concurrently with RT, 100% (n=7) of the Interferon patients reported fatigue during RT. Fifty-four percent (n=11)Likewise, Cooley et al. (2003) noted that three months into therapy only 61% of their 117 lung cancer patients continued to report fatigue and 33% reported pain. Despite these findings, this study found that 90.3% of all patients (n=671) reported fatigue at baseline and 50.5% of all patients reported pain at baseline. At 10 weeks, 75% of all patients continued to report fatigue and 40.1%

continued to report pain. This current study supported an association between frequency of fatigue and pain that was not only present at baseline, however, remained statistically significant at 10 weeks as well.

Age

Given et al. (2001) found that age was not associated with the frequency of fatigue or pain in their sample of 841 solid tumor and NHL chemotherapy patients. On the contrary, Tishelman et al. (2005) found in their sample of 400 lung cancer patients that age (being younger) negatively influenced the frequency of fatigue in their study. In this study age did influence the frequency of pain at both baseline and 10 weeks. The lower one's age at baseline or 10 weeks the greater the frequency of pain over and above the effect of fatigue at baseline or 10 weeks.

Sarna (1993) and Given et al. (2001) both noted that age did not correlate with symptom distress and frequency in their studies with lung cancer and solid tumor / NHL patients. However, Bower et al. (2000), Degner & Sloan (1995), and Tishelman et al. (2005) did find that age (being younger) negatively influenced fatigue levels throughout their studies. This current study found that the younger one's age at baseline and/or 10 weeks the greater the influence over and above the effect of fatigue on the frequency, intensity and distress of pain. Thus, all dimensions (frequency, intensity and distress) of pain were affected by age (younger) and the number of co-morbid conditions (higher number) at baseline and 10 weeks.

To further explore this effect of age and fatigue, separate generalized linear regression models were run with frequency, intensity, and distress of fatigue at baseline and again at 10 weeks as the dependent variable, study name, group and age as covariates. Age was

noted to not statistically contribute to the models for: frequency of fatigue at baseline (β = -.01, SE = .01, t = -1.18, p = .24) and 10 weeks (β = .02, SE = .01, t = 1.62, p = .11), 10 week intensity of fatigue (β = .01, SE = .01, t = .72, p = .48), and 10 week distress of fatigue (β = .01, SE = .01, t = .16, p = .87). Only the intensity of fatigue at baseline (β = -.02, SE = .01, t = -2.50, p = .01) and the distress of fatigue at baseline (β = -.03, SE = .01, t = -2.73, p = .01) demonstrated statistically significant negative associations in the fatigue and age models.

Generalized linear regression models were also run with frequency, intensity and distress of fatigue at baseline as the dependent variable and age, sex, site and stage of cancer, number of co-morbid conditions and 10 week frequency, intensity or distress of fatigue as covariates. When the dimensions of fatigue were studied with all covariates, age was a statistically significant explanatory variable within each dimension; dependent variable frequency of fatigue (β = -.03, SE = .01, t = -2.46, p = .01), intensity of fatigue (β = -.04, SE = .01, t = -3.45, p < .01), and distress (β = -.04, SE = .01, t = -3.04, p < .01). It appears that younger age does have an effect on 10 week fatigue for all dimensions over and above all baseline fatigue for all dimensions when the covariates of sex, site and stage of cancer, number of co-morbid conditions are considered. When fatigue is removed from the regression model the effects of age did not change much, suggesting the age effect persists without fatigue in the model. Thus, the effect of age noted in this study in not simply due to the fact that fatigue and age appear together in the models. The effect of age is unique to the dimensions of pain at baseline and 10 weeks regardless of the association that fatigue and age have with each other. This current study supported that younger age over and above the effect of fatigue at baseline influences frequency of

fatigue at baseline as well as frequency, intensity, and distress of fatigue at 10 weeks for chemotherapy patients.

The oncology literature offers numerous studies supporting physiological and psychological rationale for advancing age to have a negative effect on fatigue and/or pain (Balducci & Extermann, 2000; Balducci & Yates, 2000; Lipschitz, 1995; Salive, Cornoni-Huntly, Guralnik, Phillips, Wallace, Ostfeld, et al., 1992). However, little rationale is available to support the findings of this study and others for younger age influencing fatigue and/or pain. It is proposed that younger patents may have increased demands for personal and rest time versus their older counterparts such as caring for children and/or others, employment, and household responsibilities. Discrepancies between the types of symptoms that are reported or seen as burdensome may exist between younger and older patients (Demaria & Cohen, 1987; Krech, Davis, Walsh, & Curtis, 1992). Younger chemotherapy patients may receive greater doses of chemotherapy based on the perception that the elderly may be more susceptible to chemotherapy toxicities (Lyman, Dale, Crawford, 2003; Samet, Hunt, Key, Humble, & Goodwin, 1986; Zelenetz, Reider, & Delgado, 2000). Thus, younger patients may ultimately experience greater symptoms related to receiving greater doses of chemotherapy. Chemotherapy dose was not available at the time of analysis for this dataset to evaluate this further.

Researchers have supported that younger patients may be more likely to participate in research then older patients (Hutchins, Unger, Crowley, Coltman, & Albain, 1999). However, age was normally distributed in this sample. Refer to Figure 3. The mean age

was 57.6 years (SD 11.79), range 25-90, and skewness was -.009. Thus, bias is not expected.

The effect of age was also statistically significant (with a negative association) for all dimensions of insomnia with the exception of frequency of insomnia at 10 weeks and distress of insomnia at 10 weeks. No covariates influenced the models for frequency of fatigue and frequency of insomnia at 10 weeks. Thus, no covariates, including age or number of co-morbid conditions affected frequency of insomnia at 10 weeks over and above the effect of frequency of fatigue. These findings for the effect of age in this study, as well as in the literature, provide support for future research in this area. In addition, rationale for the effect of younger age on the influence of the dimensions of frequency, intensity, and distress for fatigue, pain and insomnia is in need of further exploration.

Co-morbid Conditions

The number of co-morbid conditions also influenced the outcome of pain in this study. An increased number of co-morbid conditions had an effect on frequency, intensity and distress of pain at baseline and 10 weeks over and above the effect of frequency, intensity and distress of baseline fatigue. This finding validates the work of numerous researchers who have reported correlations between number of co-morbid conditions and frequency, intensity, and/or distress for pain and fatigue (Bower et al., 2000; Given et al., 2001; Kurtz et al., 1993; Sarna, 1993). Similar to findings in this study, Kurtz et al. (1993), noted strong correlations between co-morbidity and age and the symptoms of pain, fatigue, insomnia, and nausea. Kurtz et al. (1993) found that the strongest correlations

between number of co-morbid conditions and symptoms were with patients of younger (age < 60) ages.

The number of co-morbid conditions was significant in the models for pain and fatigue in this study, validating the work of Given et al. (2001). Given et al. (2001) noted that patients who reported 3 or more co-morbid conditions were more likely then their counterparts reporting less then 3 symptoms to experience both pain and fatigue concurrently during chemotherapy. However, in this current study the number of co-morbid conditions did not influence the frequency, intensity or distress of insomnia to the extent that it did pain. The number of co-morbid conditions only produced an effect on frequency of insomnia over and above the effect of frequency of fatigue at baseline.

The frequency of insomnia and fatigue at baseline was the only dimension / time period for insomnia that demonstrated an effect for co-morbid conditions. A source of support for this finding is from the work of Gift et al. (2003). Gift et al. (2003) found in their sample of 112 lung cancer patients that the severity score for the cluster of symptoms that included: fatigue, weakness, weight loss, appetite loss, nausea, vomiting, and altered taste, declined over time from diagnosis to six months later. Based on these findings, one may propose that the frequency of insomnia will decrease over time. Recall that the mean frequency for insomnia at baseline was 3.07 (SD = 2.74) and the mean frequency for insomnia at 10 weeks was 1.62 (SD = 2.41) in this study. Over time (from baseline to 10 weeks) as the frequency of insomnia decreases, the co-morbid conditions may loose their influence over and above the effect of fatigue frequency. These differences in effect of number of co-morbid conditions on fatigue and pain versus fatigue and insomnia require further investigation in future studies.

Insomnia and Fatigue

Numerous studies have been conducted that support an association between insomnia and fatigue during chemotherapy (Ancoli-Israel, Liu, Marler, Parker, Jones, Sadler et al., 2006; Bower et al., 2000; Cooley et al., 2003; Curt et al., 2000; Degner & Sloan, 1995; Wang et al., 2002). This study validated these findings with support that all of the dimensions (frequency, intensity, and distress) of fatigue and insomnia were associated, regardless of the addition of covariates such as age, sex, site and stage of cancer and number of co-morbid conditions at baseline and 10 weeks. This finding is in contrast to Dodd et al. (2001b) who found only a weak negative correlation between fatigue and sleep insufficiency ($r = -.013$) in their solid tumor chemotherapy patients.

As noted with the variables of fatigue and pain above, the younger one's age is at baseline the greater the influence over and above the effect of fatigue on the frequency, intensity, and distress of insomnia. At baseline, younger age was associated with greater levels of frequency, intensity and distress of insomnia. However, at the 10 week point in time age had an effect over and above fatigue only for the outcome of intensity of insomnia. Frequency and distress of fatigue and insomnia were not influenced by age at 10 weeks. Thus, differing findings related to the variable of age between baseline and 10 weeks were noted for insomnia, these findings suggest an opportunity for future research.

Lung Cancer

Differing from the findings for pain and fatigue, the site of cancer demonstrated a significant association with the frequency of insomnia and frequency of fatigue at baseline. This study found that patients that had a diagnosis of lung cancer experienced a significantly lower frequency of insomnia at baseline compared to patients who did not

have lung cancer, over and above the influence of fatigue at baseline, age, and number of co-morbid conditions. However, numerous studies claim that a diagnosis of lung cancer results in greater frequency of symptoms versus other cancer diagnosis (Cooley, 2002; Cooley et al., 2003; Degner & Sloan, 1995; Gift et al., 2003; Montazeri, Gillis, & McEwen, 1998). Sarna and Brecht, 1997 and Degner and Sloan, 1995 both found that fatigue and insomnia were the most distressing symptoms reported by lung cancer patients. Other researchers have noted that 30-50% of patients with lung cancer experience insomnia (Davidson, MacLean, Brundage, & Schulze, 2002; Rumble, Keefe, Edinger, Porter & Garst, 2005; Savard & Morin, 2001; Tishelman et al., 2000). Rumble et al. (2005) noted in their study of 32 early stage lung cancer patients that "early in their course of therapy" lung cancer patients face emotional distress related to the diagnosis, possible surgery and/or hospitalizations, sleep disturbing medications and lung cancer symptoms such as pain or dyspnea that cause sleep disruption.

Due to these unique findings for lung cancer in this study the data was further explored to determine if differences existed between lung cancer and non-lung cancer patients. An argument may be posed that a greater number of the non-lung cancer patients had late stage disease, thus, why they may experience greater insomnia at baseline over the lung cancer patients. However, crosstab analysis for lung and non-lung with early and late stage revealed that 9.29% (13) of the lung cancer patients in this study had early stage disease versus 15.81% (83) of the non-lung cancer patients. In addition, 90.71% (127) experienced late stage lung cancer versus 84.19% (442) non-lung cancer patients with late stage disease. These differences were statistically significant ($\chi^2 = 3.81$, $df = 1$, $p = .05$) and do not support the argument that group differences for stage of

disease may have influenced the findings for insomnia; non-lung cancer patients in this sample were more likely to have early disease then their lung cancer counterparts.

T-tests were also conducted to examine the differences between the groups (lung versus non-lung) for means of frequency of insomnia at baseline. Lung cancer patients' insomnia frequency mean value was 2.68 versus non-lung cancer patients' mean of 3.17. These mean values were not statistically significantly different ($t = -1.89$, $df = 669$, $p = .06$). This non-significant difference in mean frequency of insomnia values as well as the fact that the variable of non-lung cancer was not significantly associated with any other regression models in this study for all dimensions of pain and insomnia at baseline and 10 weeks encourages one to further explore in future research this finding.

The Dimension of Distress and Insomnia

As noted previously, age and co-morbid conditions appear to influence fatigue, pain, and insomnia for the dimensions of frequency and intensity at both baseline assessment and 10 weeks. However, when examining the dimension of distress, age and co-morbid conditions only influenced fatigue and pain at baseline and 10 weeks; age was the only covariate that influenced distress of insomnia over and above the effect of fatigue at baseline. The number of co-morbid conditions did not affect distress of insomnia over and above baseline fatigue, and age and number of co-morbid conditions did not influence distress for insomnia over and above fatigue at 10 weeks.

Distress examines how disturbing or bothersome a symptom is perceived to be. Many researchers have suggested that the concept of distress is fundamentally different from frequency and/or intensity (Borjeson, Hursti, Tishelman, Peterson, & Steineck, G., 2002; Lough, Lindsey, Shinn, & Stotts, 1987; Tishelman, Degner, & Mueller, B., 2000;

Tishelman et al., 2005). Frequency and intensity reflect an incidence rate and severity ranking, versus, distress depicts " . . . meanings that the illness holds for an individual and that these meanings are relative to one's life" (Tishelman et al., 2005, p. 2014). This view of the dimension of distress from a meaning perspective differentiates distress from the dimensions of frequency and intensity that may be considered a direct reflection of the disease (Tishelman et al., 2005). It may be possible that age and co-morbid conditions influence one's meaning associated with pain more so then insomnia. Recall that age and number of co-morbid conditions influenced insomnia over and above fatigue only at baseline and not at 10 weeks. This may be indicative that a change takes place in what influences insomnia over time for patients receiving chemotherapy.

Summary of Findings for Research Questions 1-3

Prior to beginning a discussion of research question 4 a summary of research questions 1-3 will be provided. Research Question 1 asked: At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *frequency* of fatigue and frequency of pain, as well as frequency of fatigue and frequency of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Associations were found between frequency of fatigue and frequency of pain as well as frequency of fatigue and frequency of insomnia at baseline and 10 weeks for adults receiving chemotherapy. These associations of frequency of fatigue and frequency of pain were influenced by age and number of co-morbid conditions at baseline and 10 weeks. The association between frequency of fatigue and frequency of insomnia was influenced by age, number of co-morbid conditions, and the diagnosis of non-lung cancer at baseline.

However, no covariates influenced the association of frequency of fatigue and frequency of insomnia at 10 weeks.

Research Question 2 asked: At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *intensity* of fatigue and intensity of pain, as well as intensity of fatigue and intensity of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Associations were found between intensity of fatigue and intensity of pain as well as intensity of fatigue and intensity of insomnia at baseline and 10 weeks for adults receiving chemotherapy. These associations of intensity of fatigue and intensity of pain were influenced by age and number of co-morbid conditions at baseline and 10 weeks. The association between intensity of fatigue and intensity of insomnia was influenced only by age at baseline and 10 weeks. No additional covariates, including number of co-morbid conditions, influenced the association of intensity of fatigue and intensity of insomnia at baseline or 10 weeks.

Research Question 3 asked: At baseline observation, prior to entry into a clinical trial, and at 10 weeks is there an association between the dimension of *distress* of fatigue and distress of pain, as well as distress of fatigue and distress of insomnia for adults receiving chemotherapy? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions? Associations were found between distress of fatigue and distress of pain as well as distress of fatigue and distress of insomnia at baseline and 10 weeks for adults receiving chemotherapy. These associations of distress of fatigue and distress of pain were influenced by age and number of co-morbid conditions at baseline and 10 weeks. The association between distress of fatigue and distress of insomnia was

influenced only by age at baseline. No additional covariates influenced the association of distress of fatigue and distress of insomnia at baseline. No covariates, including age or number of co-morbid conditions influenced the association of distress of fatigue and distress of insomnia at 10 weeks.

Findings for Research Question 4

Research Question 4 asked: Using categories of response to fatigue management (none / mild, non-response, partial response and full response) established in the literature, determine how changes in the dimensions of frequency, intensity, and distress of pain and insomnia are predicted by categories of response to the management of fatigue between baseline and 10 weeks. Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions?

Frequency of Pain

This study found that there is an association between the dimensions of frequency of pain at 10 weeks and management of fatigue categories after adjusting for frequency of pain at baseline. The only fatigue management category that produced statistically significant findings was the non-responders. Therefore, non-responders (patients who stay within the same category [excluding the "none" or "mild" category] from the baseline measure to the 10 week measure) when compared to full responders (patients who go to the none or mild category of fatigue from moderate or severe between baseline and 10 weeks) experience significantly increased frequency of pain at 10 weeks.

The number of co-morbid conditions was significant in the regression model. Thus, at 10 weeks the number of co-morbid conditions influenced frequency of pain over and above the effect of fatigue management. Unlike findings for research questions 1-3, age

was not found to affect pain at 10 weeks when taking into account fatigue management categories.

Intensity of Pain

An association also existed between the dimensions of intensity of pain at 10 weeks and intensity of pain at baseline when management of fatigue categories was studied. Two fatigue management categories produced statistically significant findings for the dimension of intensity and pain, the non-responders and the partial responders. Therefore, non-responders and partial responders (a patient who goes from severe to the moderate level of fatigue between baseline and 10 weeks) when compared to full responders experience significantly increased intensity of pain at 10 weeks.

The association between intensity of pain and the effect of the fatigue management categories was influenced by the number of co-morbid conditions and the age. Thus, at 10 weeks the number of co-morbid conditions as well as younger age influenced intensity of pain at 10 weeks over and above the effect of fatigue management.

Distress of Pain

An association also existed between the dimensions of distress of pain at 10 weeks and distress of pain at baseline with the consideration of management of fatigue categories. Only one fatigue management category, the non-responders, produced a statistically significant finding for the dimension of distress and pain. Therefore, non-responders when compared to full responders experience significantly increased frequency of pain at 10 weeks.

The association between distress of pain and the effect of the fatigue management categories was also influenced by the number of co-morbid conditions and age. Thus, at

10 weeks the number of co-morbid conditions as well as younger age influenced distress of pain at 10 weeks over and above the effect of fatigue management.

Frequency of Insomnia

This study also found that when fatigue categories are examined there is an association between the dimensions of frequency of insomnia at 10 weeks and frequency of insomnia at baseline. Similar to the findings noted for frequency of pain, the only fatigue management category that produced statistically significant findings was the non-responders. Non-responders when compared to full responders experience significantly increased frequency of insomnia at 10 weeks. Unlike pain, the association between frequency of insomnia and the effect of the fatigue management categories was not influenced by any of the covariates (age, sex, site and stage of cancer, and number of co-morbid conditions). Thus, the number of co-morbid conditions or age did not influence frequency of insomnia at 10 weeks over and above the effect of fatigue management.

Intensity of Insomnia

An association also existed between the dimensions of intensity of insomnia at 10 weeks and intensity of insomnia at baseline when management of fatigue categories was considered. Again, similar to the findings for intensity of pain, two fatigue management categories produced statistically significant findings for the dimension of intensity of insomnia, the non-responders and the partial responders. Non-responders and partial responders when compared to full responders experience significantly increased intensity of insomnia at 10 weeks. As noted with the dimension of frequency of insomnia, the association between intensity of insomnia and the effect of the fatigue management categories was also not influenced by any of the covariates.

Distress of Insomnia

An association also existed between the dimensions of distress of insomnia at 10 weeks and distress of insomnia at baseline when management of fatigue categories was involved. As found with intensity of insomnia, two fatigue management categories produced statistically significant findings for the dimension of distress and insomnia; the non-responders and the partial responders. Non-responders and partial responders when compared to full responders experience a significantly increased distress of insomnia at 10 weeks. As noted with the dimensions of frequency and intensity of insomnia, the association between distress of insomnia and the effect of the fatigue management categories were not influenced by any of the covariates.

Summary of Findings for Research Question 4

To summarize, Research Question 4 asked: Using categories of response to fatigue management (none / mild, non-response, partial response and full response) established in the literature, determine how changes in the dimensions of frequency, intensity, and distress of pain and insomnia are predicted by categories of response to the management of fatigue between baseline and 10 weeks? Is this association influenced by; age, site and stage of cancer, sex, and co-morbid conditions?

Frequency, intensity and distress of pain can be predicted by category of response to fatigue management. Non-responders when compared to full responders experience increased frequency, intensity and distress of pain at 10 weeks. In addition, partial responders as well as non-responders when compared to full responders experience increased intensity of pain at 10 weeks. These associations are influenced by an increased number of co-morbid conditions. Age also influenced the associations between

partial and non-responders with full responders, however, only for pain intensity and distress at 10 weeks.

Frequency, intensity and distress of insomnia can also be predicted by category of response to fatigue management. Non-responders when compared to full responders experience increased frequency, intensity and distress of insomnia at 10 weeks. In addition, partial responders as well as non-responders when compared to full responders experience increased intensity and distress of insomnia at 10 weeks. These associations were not influenced by age, number of co-morbid conditions, sex, cancer site or stage.

In this study with no standard care control group and with study group membership controlled for we can conclude that the fatigue management categories provide an appropriate means of measuring the broad effectiveness of the cognitive behavioral intervention. This analysis was not designed to compare the different interventions. However, overall the intervention components of both studies (ATSM or NASM) appear to have demonstrated some success for fatigue management reflected by the counts and percents for the response to fatigue management categories cited above.

One hundred and seven patients (20.08%) were considered full responders for fatigue management, an additional 79 (14.82%) were partial responders. Mean fatigue scores fell from baseline to 10 weeks for frequency (4.70 [SD= 2.49] to 3.68 [SD=2.85]), intensity (4.71 [SD= 2.69] to 3.22 [SD=2.67]), and distress (4.18 [SD= 3.06] to 2.52 [SD=2.78]). This finding supports past work by Given et al. (2001) that found in their cognitive behavioral intervention study with a standard of care control group (n= 841) that fewer patients in the experimental group reported pain and fatigue at 20 weeks versus the control group. Similarly, Savard, Sinard, Ivers, & Morin, (2005) were able to

demonstrate that a cognitive behavioral nursing intervention positively impacted breast cancer patient responses to insomnia.

Study Limitations

Although intervention evaluation was not proposed for this study it did examine response to fatigue management. It is assumed that patients in the partial response and full response fatigue management categories did benefit from one of the interventions in the two studies that made up this dataset. A lack of ability to differentiate which intervention was received as well as the lack of a control group in this study limits the ability to advise practice and research on strategies that contribute to fatigue management. Sikorskii et al. (in press) also point out that lack of a control group provides difficulty in comparing symptom dimension changes over baseline. Reduction in symptom frequency, intensity, and/or distress over baseline may be attributed to response shift or regression to the mean, however, response shift would be expected to occur in both groups and would not bias the analyses of between group differences (Sikorskii et al., in press).

Samples differed due to the fact that all patients experienced interviews and only some patients experienced intervention contacts (Skorskii et al., in press). Only patients randomized to the nursing behavioral cognitive intervention arms of both studies could have received interventions for fatigue, pain, and/or insomnia that were beyond the scope of the toolkit. In addition, this study did not separate patients receiving interventions for fatigue, pain and insomnia from patients who did not receive such intervention. All symptom assessment in this dataset was self-report, per the patient's perception, no

comparisons were made with practitioner assessment via the intervention recorded data or medical record audit.

This study was conducted as a secondary data analysis. Stage of disease was established a priori to be a categorical variable as early (TNM 1 or 2) and late (TNM 3 or 4). Stage III and IV cancer patients have very different clinical presentation and typically receive very different chemotherapy regimens. Stage IV patients for all diagnosis will have metastatic disease; the extent of their disease will also vary greatly and effect symptoms in different ways. This sample also contained only 10% non-Caucasian, although reflective of the geography used for recruiting, this provides a limitation for generalizability to minority populations. Some authors have reported that minorities may be more likely then Caucasians to present with later stages of disease and also may have difficulty accessing cancer care centers (Benjamin, Reddy, & Brawley, 2003; Gadgeel & Kalemkerian, 2003). Practitioners will need to be aware of these limitations and future studies will need to address the limitations cited above. Additional implications for clinical practice and future studies will follow.

Implications for Clinical Practice

Data from this study provides several implications for clinical practice. It is due to the multiple nature of symptoms that people seek health care (Cleeland et al., 2000; Rutledge & McGuire, 2003). Three of the most common co-occurring symptoms for patients experiencing chemotherapy are fatigue, pain and insomnia. Patients will experience varying degrees of differing dimensions (frequency, intensity, and distress) of each symptom over time. As noted in this current study, each dimension depicts a separate assessment area that is uniquely associated with fatigue, pain, and/or insomnia.

Frequency is assessed to quantify the presence of the symptom, intensity to note the severity, and distress to represent how bothersome the symptom is to the patient. This study also supported the association of these dimensions over time (baseline to 10 weeks).

In the ideal world of clinical practice the nurse would have adequate time and sophisticated computerized documentation systems that would allow for thorough assessments and documentation of all three dimensions for all symptoms. Unfortunately, this is not the case, the question then becomes: If you have limited time and resources and the patient presents with fatigue, pain and insomnia, what dimension of pain and insomnia assessment is absolutely necessary?

This study found that frequency, intensity and distress of pain when associated with fatigue, were all influenced by younger age and number of co-morbid conditions at both baseline and 10 weeks. Associations existed over time between each dimension of pain and fatigue at baseline and 10 weeks. In addition, when examining fatigue response categories, the non-responders were noted to be different from the full-responders for all pain and fatigue dimensions at 10 weeks. Thus, similar findings were noted for all dimensions of pain and fatigue. It may not be necessary to assess each dimension for pain when being assessed with fatigue at baseline or 10 weeks.

Naturally, the next question is what dimension should you assess for pain if you only have the time to assess one? As stated above all findings for pain and fatigue were similar. However, when examining fatigue management categories, the regression model that included the intensity dimension of pain was the only model that was able to support non-responders as well as partial responders in demonstrating increased fatigue as

compared to full responders. In addition, t-tests of the differences among adjusted means (adjusted for other variables in the model) were conducted with intensity of pain as the dependent variable. With intensity of pain as the dependent variable it was noted that the non-response fatigue management category is different from the none / mild category and the full responder category. The none / mild category was also noted to be different from the partial response category. Thus, the intensity of pain dimension assessment is as likely as any other dimension to be influenced by age and co-morbid conditions, demonstrates an association between baseline and 10 weeks, and demonstrates differences within the fatigue management categories. Based on the above findings, the intensity dimension is the dimension to focus the pain assessment on if time and resources do not allow for a complete assessment of all dimensions.

The findings for insomnia were not as consistent. Associations did exist between each dimension of insomnia and fatigue at baseline and 10 weeks. However, frequency, intensity and distress of insomnia, when associated with fatigue, were not all influenced by younger age and number of co-morbid conditions at either baseline or 10 weeks. For example, age and co-morbids did influence frequency of insomnia over and above the effect of fatigue at baseline. The lung cancer group also demonstrated a negative association in the frequency of insomnia model at baseline; this effect was not noted for any other dimension or for pain. No covariates influenced the frequency of insomnia at 10 weeks. No covariates influence any dimension of insomnia in the fatigue management category models. Models that included fatigue management categories for both the dimensions of intensity and distress demonstrated differences between non responders and partial responders when compared to full responders. Due to these differences noted

in the dimensions of insomnia it is not possible to prioritize a specific dimension to assess.

Knowing that associations exist between these dimensions and between the symptoms of fatigue, pain and insomnia, clinical interventions must be targeted toward the appropriate dimensions of each symptom. Interventions must also accommodate the co-occurrence of symptoms such as fatigue and pain and/or insomnia. Due to the associations noted in this study between fatigue and pain and fatigue and insomnia it is essential to treat both symptoms concurrently.

Interventions for symptoms must also occur over time. As noted in the Yates et al, 2005 and the Anderson et al, 2006 studies behavioral cognitive nursing interventions may loose their effect over time. Both of these studies demonstrated a need for booster intervention sessions when addressing the symptoms of fatigue or pain. Cancer treatments are given over time, some symptoms may be most severe immediately following chemotherapy (such as vomiting) others may increase, stay the same or decrease as time goes by. Interventions must be provided over time and stepped to meet the changing needs of the patient. Assessment must continue over time as well do to the "wax and wane" effect of symptoms. Symptoms thought to be under control with a past intervention may re-appear at a later time during or even after treatment. Some symptoms, such as fatigue, may persist well after chemotherapy is completed. Continuous follow up and monitoring of symptoms over time for the chemotherapy patient is essential.

As noted in this study, the use of fatigue management categories may be an appropriate technique to evaluate the effectiveness of interventions aimed toward single

or multiple symptoms. Intensity of fatigue is typically measured on a scale of 0-10. A reduction in symptom intensity that ranges from 33% to 50% is considered clinically significant (Guyatt et al. 2002). However, when using a 0-10 scale to measure fatigue intensity both percent change and absolute value change values are not always clinically meaningful. The relationship between the intensity of a symptom and distress of a symptom is not linear across the scale (Given et al., in press). Differences in the associations between intensity and distress appear on the 0-10 scales between 1 and 2 and 4 and 5. Therefore, the use of cut points (0 = none, 1 = mild fatigue, 2-4 moderate fatigue, 5-10 severe fatigue) within the 0-10 intensity of fatigue scale may produce a more clinically meaningful fatigue assessment. It is also important to note that thorough assessment and documentation are required to be able to retrospectively calculate fatigue management categories that can be used for quality assurance monitoring and/or research purposes.

In order to provide appropriate assessment and intervention it is also essential to be aware of the covariates that influence fatigue, pain, and insomnia. For all dimensions of pain and insomnia, with the exception of 10 week frequency of insomnia and 10 week distress of insomnia, younger age enhanced the dimension of the outcome of pain or insomnia over and above the effect of fatigue. An increased number of co-morbid conditions also enhanced the frequency, intensity and distress of pain at both baseline and 10 weeks over and above the effect of fatigue. Therefore, practitioners need to be aware that chemotherapy patients who are younger in age and those with co-morbid conditions may be considered at greater risk of experiencing enhanced frequency, intensity and distress of fatigue with pain and/or insomnia.

Implications for Research

As cited above, this current study noted a significant affect for younger age on the dimensions of pain and insomnia over and above the effect of fatigue with the exception of 10 week frequency and distress of insomnia. The negative influence of younger age on symptom frequency, intensity and distress is just beginning to appear in the literature (Bower et al., 2000; Tishelman et al., 2005). Future research as to the biological, physiological, and psychological rationale for this phenomena is required. Likewise, various assumptions made regarding ageing and increased symptom frequency, intensity and distress of symptoms associated with chemotherapy are now challenged. Age as a risk factor for increased frequency, intensity and distress of fatigue, pain, and insomnia when these symptoms co-occur in chemotherapy patients should be examined in future research studies.

The number of co-morbid conditions also influenced all dimensions of pain over and above the effect of fatigue at baseline and 10 weeks as well as frequency of insomnia at baseline over and above the effect of fatigue at baseline. Due to the fact that age and number of co-morbid conditions influenced fatigue and insomnia over and above fatigue only at baseline and not at 10 weeks may be reason to believe that a change takes place in what influences the association between fatigue and insomnia over time. Time plays a key role in symptom presentation as well as management for patients receiving multiple cycles of chemotherapy. This unique finding that co-morbid conditions effect pain but not insomnia and the role that time may play in this scenario requires future research. Additional research related to specific co-morbid conditions (i.e., diabetes, high blood

pressure) as well as their clinical history (onset, duration, management, etc.) that are most likely to result in increased fatigue, pain and or insomnia is also needed.

This current study found that cancer site was not significant in any of the regression models examining fatigue with pain and insomnia with the exception of the non-lung cancer category effecting frequency of insomnia at baseline over and above the effect of fatigue. This unique effect for patients without a diagnosis of lung cancer as compared to those who have lung cancer on insomnia and not pain, as well as at baseline and not 10-weeks is contradictory to the majority of published research on lung cancer and the symptoms of fatigue, pain, and insomnia (Cooley et al., 2003; DeMaria & Cohen, 1987; Given et al., 2001; Hickok et al., 1996; Kurtz et al., 2000). Thus, continued research on the differences noted with a lung cancer diagnosis (as well as stage and treatment specifics) on pain versus insomnia when they co-occur with fatigue is needed.

Recall that this effect for non-lung cancer in this study was also only noted at baseline for frequency of insomnia. Based on this finding, the effect of time on the symptom of insomnia for the lung cancer chemotherapy patient is of interest for future research. An appropriate research question to examine time and insomnia would include baseline and multiple measures of various dimensions (frequency, intensity and distress) during therapy and following the conclusion of chemotherapy. As noted from this study, covariates such as age, number of co-morbid conditions would need to be controlled. In addition, from the literature, factors such as surgery, anxiety level, quality of life, depression, stage, medications, and presence of pain would need to be controlled for to examine insomnia in the lung cancer versus non-lung cancer patients (Cooley et al., 2002; Rumble et al., 2005).

This study also demonstrated that frequency, intensity and distress of pain and insomnia can be predicted by categories of response to fatigue management. This provides an important validation of the appropriateness of the use of fatigue management categories in clinical research for this area of study that is in its' infancy (Given et al., in press; Mendoza et al., 1999; Miaskowski et al., in press). Although this study was not designed to evaluate the effectiveness of individual cognitive behavioral interventions, significant differences were noted between the non-responders and full-responders for each dimension (frequency, intensity and distress) of pain and insomnia at 10 weeks. Thus, non-responders experienced significantly increased frequency, intensity and distress for both pain and insomnia at 10 weeks when compared to the full responders. This current study does support the appropriateness of the use of fatigue management categories as a new research technique. Future studies should be directed toward use of these categories to compare interventions against each other in randomized clinical trials. The implementation of randomized control studies using stepped interventions over time that address solo as well as multiple co-occurring symptoms will be needed to advance research as well as clinical practice.

Conclusion

The purpose of this study was to examine the dimensions of frequency, intensity, and distress of the co-occurring symptoms of fatigue, pain and insomnia as they occur at two different data collection points in two randomized clinical trials of a cognitive behavioral intervention. This study did support that at baseline as well as 10 weeks there is an association between the dimensions of frequency, intensity and distress of fatigue and the same dimensions for pain and insomnia.

In addition, categories of response to fatigue management were capable of predicting changes in the dimensions of frequency, intensity, and distress of pain and insomnia at 10 weeks. For all dimensions of pain and insomnia, with the exception of 10 week frequency of insomnia and 10 week distress of insomnia, younger age enhanced the dimension of the outcome of pain or insomnia over and above the effect of fatigue. An increased number of co-morbid conditions also enhanced the frequency, intensity and distress of pain at both baseline and 10 weeks over and above the effect of fatigue. However, an increased number of co-morbid conditions only influenced the frequency dimensions of insomnia at baseline over and above the effect of fatigue at baseline.

Further studies to examine relationships between covariates such as age and number of co-morbid conditions that influence fatigue combined with pain and/or insomnia over time are recommended. The influence of time on the dimensions of frequency, intensity, and distress for co-occurring symptoms associated with chemotherapy is strongly encouraged. The Adapted SEM (see Figure 2) may be used in the future to guide intervention research examining multiple co-occurring symptoms over time. The use of fatigue management categories as a means of evaluating the effect of cognitive behavioral interventions with co-occurring symptoms was also supported in this research. Other researchers are encouraged to examine these variables cited above as a part of RCT intervention studies for symptom cluster research.

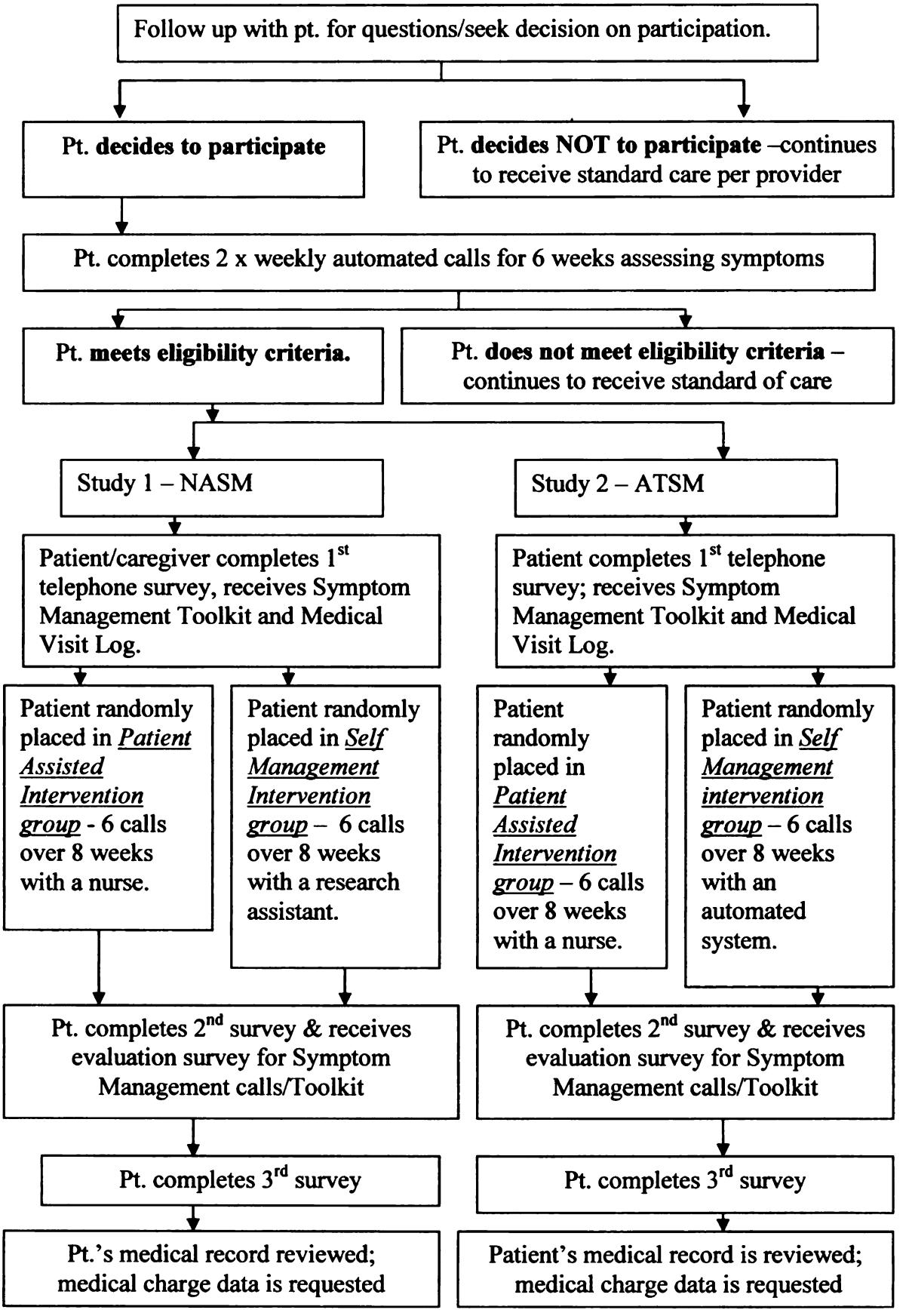
An immediate next step for this research project is to continue to use the fatigue management categories to determine if differences exist in the effectiveness of the various cognitive behavioral interventions noted within the study. Future research with this dataset will continue to evaluate the influence of time and all dimensions of symptom

presentation to continue to advance this evolving field of study of co-occurring symptoms in oncology practice.

APPENDIX A

Study Schema

(See next page)


Follow up with pt. for questions/seek decision on participation.
Pt. decides to participate
Pt. decides NOT to participate –continues to receive standard care per provider
Pt. completes 2 x weekly automated calls for 6 weeks assessing symptoms
Pt. meets eligibility criteria.
Pt. does not meet eligibility criteria – continues to receive standard of care
Study 1 – NASM
Study 2 – ATSM
Patient/caregiver completes 1st telephone survey, receives Symptom Management Toolkit and Medical Visit Log.
Patient completes 1st telephone survey; receives Symptom Management Toolkit and Medical Visit Log.
Patient randomly placed in Patient Assisted Intervention group - 6 calls over 8 weeks with a nurse.
Patient randomly placed in Self Management Intervention group – 6 calls over 8 weeks with a research assistant.
Patient randomly placed in Patient Assisted Intervention group – 6 calls over 8 weeks with a nurse.
Patient randomly placed in Self Management intervention group – 6 calls over 8 weeks with an automated system.
Pt. completes 2nd survey & receives evaluation survey for Symptom Management calls/Toolkit
Pt. completes 2nd survey & receives evaluation survey for Symptom Management calls/Toolkit
Pt. completes 3rd survey
Pt. completes 3rd survey
Pt.'s medical record reviewed; medical charge data is requested
Patient's medical record is reviewed; medical charge data is requested

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