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Entitled
SYMPTOM SEVERITY AND IMPORTANCE IN METASTATIC BREAST CANCER PATIENTS: AN EXAMINATION OF COGNITIVE COMPLAINTS AND RELATED SYMPTOMS

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ABSTRACT

Tometich, Danielle B. M.S., Purdue University, August 2016. Symptom Severity and Importance in Metastatic Breast Cancer Survivors: An Examination of Cognitive Complaints and Related Symptoms. Major Professor: Catherine Mosher.

Cognitive changes associated with cancer and its treatment have been well documented. However, the majority of research on cognitive symptoms in cancer has been conducted with early-stage breast cancer patients or survivors in remission. Little is known about cognitive symptoms in patients with late-stage or metastatic cancers. To address this gap in the literature, this study examines cognitive and related symptoms among metastatic breast cancer patients enrolled in a parent study of perceptions of symptom importance and interference. Eighty metastatic breast cancer patients were recruited from the Indiana University Simon Cancer Center to participate in this cross-sectional telephone interview study. The interview consisted of self-report measures, including measures of symptom severity, distress, and the importance of seeing improvement in specific symptoms post-treatment. I hypothesized that cognitive complaints would cluster with fatigue, sleep disturbance, depressive symptoms, anxiety, and pain. This hypothesis was tested using cluster analysis and was partially supported. Cognitive complaints were found to cluster with fatigue, sleep disturbance, depressive symptoms, and anxiety, but not pain. In addition, the extent to which ratings of symptom importance for cognitive symptoms
differed from those of other symptoms (i.e., pain, fatigue, sleep problems, depressive symptoms, anxiety, nausea, lymphedema, hot flashes, and neuropathy) was explored using ANOVA and Tukey’s HSD tests. Cognitive complaints were rated as significantly more important than anxiety, depressive symptoms, neuropathy, swelling, nausea, and hot flashes. Importance ratings for cognitive complaints, pain, fatigue, and sleep problems were not significantly different. Developing patient-centered treatment approaches that take into account symptom clustering and patients’ treatment priorities may increase treatment adherence and optimize healthcare quality.
CHAPTER 1. INTRODUCTION

1.1 Introduction

Cognitive changes have been associated with cancer and its treatment in early-stage breast cancer patients (Ahles, Schagen, & Vardy, 2012; Hurria, Somlo, & Ahles, 2007; Ono et al., 2015), but a paucity of research has examined cognitive changes in patients with metastatic cancers. Cognitive difficulties are typically viewed as a survivorship issue affecting functional capacity (Hede, 2008; Von Ah, 2015). The majority of research in this area has been conducted with early-stage breast cancer patients and survivors in remission due to their large numbers and high likelihood of long-term survival (Ahles, Schagen, et al., 2012; Newman, 2009; Von Ah, 2015). It is estimated that 2.9 million women were living with a breast cancer diagnosis of any stage in the United States in 2012 (Howlader et al., 2015), and 17-75% of breast cancer survivors have some degree of cognitive dysfunction (Ahles, Root, & Ryan, 2012; Von Ah, 2015).

Survivorship issues, including cognitive changes, are becoming increasingly relevant for patients with late-stage disease as recent advances in treatment have increased longevity (Mayer, 2010; Reed, Simmonds, Haviland, & Corner, 2012). After a diagnosis of metastatic breast cancer, survival can range from a few months to more than five years, and the median survival time is approximately three years (Smerage et al., 2014). Between 2005-2011, 5-year survival rates for metastatic breast cancer were
estimated to be 25.9% (Howlader et al., 2015). Thus, metastatic breast cancer patients may live for years with cognitive impairment which affects their daily activities and quality of life, but little is known regarding their cognitive symptoms. This study begins to address this gap by examining cognitive symptoms’ relationship to other symptoms in this population. In addition, patient ratings of the importance of seeing improvement in cognitive symptoms following symptom-focused treatment were compared to those for other common symptoms.

First, I will discuss the evidence for a relationship between cancer and its treatment and cognitive symptoms and current theoretical models of this relationship. Next, I will describe the available literature on cognitive symptoms in metastatic breast cancer patients. Finally, I will provide a rationale for characterizing symptom clusters and patient perceptions of symptom importance in cancer patients. Following this review, I will present my hypotheses, study methods, and results and discuss the implications and limitations of my findings.

1.2 Cognitive Symptoms in Cancer

**History, terminology, and definitions.** Medical and psychological scientists have known about the association between chemotherapy treatments for cancer and cognitive impairment for more than 40 years (Silberfarb, 1983; Weiss, Walker, & Wiernik, 1974). The first reviews exploring the neurotoxic effects of chemotherapy were published in the 1970s, and they acknowledged neurological symptoms such as somnolence and encephalopathy in cancer patients with primary central nervous system (CNS) disease or CNS metastases (Pochedly, 1977; Weiss et al., 1974). Shortly thereafter, reviews described the possibility of CNS toxicities due to cancer treatment in
patients without CNS disease (Allen, 1978; Silberfarb, 1983). The colloquial terms “chemobrain” and “chemofog” were coined in the 1990s to describe the cognitive symptoms that appeared to be related to chemotherapy (Ahles, Schagen, et al., 2012). It later became apparent that numerous factors besides chemotherapy can contribute to cognitive symptoms; thus, the terms “chemobrain” and “chemofog” have been replaced with “cancer- or cancer treatment-associated cognitive change” (Hurria et al., 2007).

The terminology for describing cancer patients’ cognitive performance on neuropsychological tests is also controversial. The term “cognitive impairment” is often used in cross-sectional studies comparing patients treated with chemotherapy to non-chemotherapy controls, and the term “cognitive decline” is used in longitudinal studies of chemotherapy-treated patients (Ono et al., 2015). Ahles and colleagues (2008) question whether it is appropriate to label cognitive problems in cancer patients as “impairment” when they are typically subtle and often within the normal range. Instead, these researchers describe the cognitive deficits found in a subset of their study participants as “lower than expected cognitive performance” (Ahles et al., 2008, p. 144).

Currently, little consensus exists regarding the definition of cognitive impairment/decline in cancer populations, and clinically significant cognitive impairment/decline has no established cut-off point or statistical convention (Ono et al., 2015). Ahles and colleagues (2008) define “lower than expected cognitive performance” as two neurocognitive domains that are 1.5 standard deviations below the mean of published norms or one domain that is 2 standard deviations below the mean. Cognitive decline in longitudinal studies has often been defined as a 1 to 2 standard deviation decrease in scores on one or more cognitive domains from pre- to post-chemotherapy
(Hurria et al., 2006; Ono et al., 2015; Shilling, Jenkins, Morris, Deutsch, & Bloomfield, 2005; A. Stewart et al., 2008; Vearncombe et al., 2009). Cognitive impairment in some cross-sectional studies has been defined as 2 standard deviations below the mean performance of a healthy comparison group or published norm (de Ruiter et al., 2011; Deprez et al., 2011; Donovan et al., 2005; Ono et al., 2015; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Schagen et al., 1999; Schilder et al., 2009). Cognitive impairment has also been classified by degrees from mild (1 standard deviation below the norm) to moderate impairment (2 standard deviations below the norm) (Hermelink et al., 2007; Ono et al., 2015).

Evidence suggests that, in general, breast cancer patients treated with chemotherapy have worse performance on objective cognitive tests than control groups, but impairment is not consistently found in specific neurocognitive domains (Jim et al., 2012; Ono et al., 2015). A recent meta-analysis examined cross-sectional and prospective longitudinal studies of cognitive functioning among non-metastatic breast cancer patients treated with adjuvant chemotherapy (Ono et al., 2015). Analyses of cross-sectional data revealed statistically significant cognitive impairment in five of the eight examined neurocognitive domains: processing speed ($d = -0.25$), executive function ($d = -0.19$), attention ($d = -0.16$), motor function ($d = -0.16$), and short-term memory ($d = -0.15$). Effect sizes were non-significant for the domains of language, long-term memory, and visuospatial function (Ono et al., 2015). These results are partially consistent with those of prior meta-analyses (see Table 1). Two of the four prior meta-analyses found significant deficits in executive function (Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005; A. Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006),
one found a significant deficit in processing speed (Jansen et al., 2005), and another
found significant deficits in motor speed, and short-term memory (A. Stewart et al.,
2006). However, three of the four prior meta-analyses also found significant deficits in
language (Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jim et al., 2012; A. Stewart
et al., 2006), two found significant deficits in spatial function (Falleti et al., 2005; Jim et
al., 2012), and one found significant deficits in long-term memory (A. Stewart et al.,
2006).

Findings are also inconsistent with respect to moderators of cognitive
performance in breast cancer patients post-chemotherapy. An earlier meta-analysis of
cross-sectional studies found that age and time since chemotherapy treatment moderated
the magnitude of cognitive impairment post-treatment (Falleti et al., 2005), whereas more
recent meta-analyses did not replicate these findings (Jim et al., 2012; Ono et al., 2015).
Instead, the type of control group and level of education were significant moderators (Jim
et al., 2012; Ono et al., 2015). Specifically, in cross-sectional studies, breast cancer
patients who had received chemotherapy had significant cognitive impairment when
compared to healthy controls, but not when compared to breast cancer patients without a
history of chemotherapy treatment (Ono et al., 2015). In addition, breast cancer patients
with fewer years of education showed a greater degree of cognitive impairment (Ono et
al., 2015). Age was also a significant moderator of cognitive change in a meta-analysis
of prospective longitudinal studies, with older age being associated with greater cognitive
decline post-chemotherapy (Ono et al., 2015).

Another key finding from prospective longitudinal studies is that breast cancer
patients show improved cognitive function in certain domains from pre- to post-
chemotherapy (Falleti et al., 2005; Ono et al., 2015; Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). One meta-analysis of these studies found that long-term memory significantly improved following chemotherapy ($d = 0.41$); however, other cognitive domains did not significantly change, with effect sizes ranging from $d = -0.29$ for visuospatial function to $d = 0.26$ for language (Ono et al., 2015). Conversely, an older prospective longitudinal study of breast cancer patients found improved attention ($d = 1.09$), executive function ($d = 0.39$), memory ($d = 0.36$), spatial ability ($d = 0.31$), and motor function ($d = 0.11$) post-chemotherapy (Falleti et al., 2005; Wefel et al., 2004).

Researchers have proposed multiple explanations for breast cancer patients’ improved cognitive function from pre- to post-chemotherapy. One explanation focuses on psychological factors (e.g., anxiety, depressive symptoms) associated with a cancer diagnosis and impending treatment that may affect cognitive performance; specifically, performance is expected to improve after chemotherapy as patients psychologically adjust to their medical situation (Falleti et al., 2005; Ono et al., 2015). Thus, pre-treatment assessments of cognitive functioning may not provide an accurate estimate of premorbid functioning, complicating examination of post-chemotherapy changes in cognition. This theory is supported by findings that greater pretreatment worry in breast cancer patients is associated with altered brain activation on an fMRI, worse objective performance in verbal working memory, and subjective cognitive dysfunction (Berman et al., 2014). Alternatively, improvement in cognitive performance from pre- to post-chemotherapy may be due to practice effects, although this is less likely because studies regularly control for practice effects with alternative test forms or statistical controls (Falleti et al., 2005; Ono et al., 2015). Lastly, meta-analyses of cognitive impairment in
breast cancer patients treated with adjuvant chemotherapy have not separately analyzed results from recognition and recall tests (Falleti et al., 2005; Jansen et al., 2005; Jim et al., 2012; Ono et al., 2015; A. Stewart et al., 2006). Recognition memory tests are not sensitive to subtle cognitive deficits (Welsh, Butters, Hughes, Mohs, & Heyman, 1992); thus, collapsing recall and recognition memory performance into one cognitive domain may be underestimating memory deficits and limit researchers’ ability to draw accurate conclusions from the data (F.W. Unverzagt, personal communication, March 17, 2015).

**Models of cognitive symptoms in cancer.** Cognitive impairment in cancer patients is most commonly associated with adjuvant chemotherapy treatments for breast cancer (Bender et al., 2006; Schagen et al., 1999; van Dam et al., 1998), but it has also been associated with endocrine or hormone therapy for breast cancer (Jenkins, Shilling, Fallowfield, Howell, & Hutton, 2004; Zwart, Terra, Linn, & Schagen, 2015) and radiation therapy for primary CNS cancer or CNS metastases (Dietrich, Monje, Wefel, & Meyers, 2008). Furthermore, some studies have found cognitive impairment in breast cancer patients after surgery, but before any hormone, radiation, or chemotherapy treatment (Ahles et al., 2008; Berman et al., 2014). This suggests that surgery, the disease, or psychological reactions to the disease may be sufficient precipitants of cognitive sequelae. To date, no systematic review has been conducted to compare the cognitive effects of different cancer treatments. Sufficient data are not available for this analysis because many cancer patients receive multiple treatment types, some of which are concurrently administered (Hurria et al., 2007).

A number of models have been proposed to characterize the multiple, interactive factors that may result in cognitive symptoms in cancer patients (Ahles, Root, et al.,
One conceptual model of cognitive dysfunction in cancer is analogous to the interaction between soil, seed, and pesticides (Figure 1). The soil represents host factors (e.g., genetics, cognitive reserve), the seed, disease-related factors (e.g., cytokines, tumor genetic mutations), and the pesticides, treatment-related factors (e.g., chemotherapy, radiation, hormonal therapy) (Meyers & Perry, 2008). As soil, seed, and pesticides all contribute to the health of a plant, so do host, disease, and treatment factors all contribute to the cognitive health of a cancer patient.

Host factors are generally present prior to cancer treatment and include age, genetics, cognitive reserve, and psychological factors. Older age is associated with greater cognitive decline in prospective longitudinal studies of breast cancer patients treated with chemotherapy (Bender et al., 2006; Collins, Mackenzie, Stewart, Bielajew, & Verma, 2009; Debess, Riis, Engebjerg, & Ewertz, 2010; Falleti et al., 2005; Hermelink et al., 2007; Hurria et al., 2006; Jansen, Cooper, Dodd, & Miaskowski, 2011; Jenkins et al., 2006; Ono et al., 2015; Shilling et al., 2005; A. Stewart et al., 2008; Vearncombe et al., 2009; Wefel et al., 2004). Genetic factors related to cognitive decline in aging and cancer include apolipoprotein E (APOE) and catechol-o-methyl transferase (COMT) (Ahles, Root, et al., 2012; Ahles et al., 2003; Harris & Deary, 2011; Small et al., 2011). Genetic and environmental variables (e.g., education, occupation) contribute to cognitive reserve, or the capacity for cognitive function (Ahles et al., 2010; Stern, 2002). People with lower levels of cognitive reserve are at higher risk for neurodegenerative diseases such as Alzheimer’s disease (Ahles et al., 2010; Whalley, Deary, Appleton, & Starr, 2004) and are more susceptible to poorer cognitive outcomes after exposure to
neurotoxins compared to those with higher levels of cognitive reserve (Ahles et al., 2010; Bleecker, Ford, Celio, Vaughan, & Lindgren, 2007). Age, cognitive reserve, and receipt of chemotherapy were found to have an interactive effect on cognitive functioning in non-metastatic breast cancer patients; specifically, older patients who had lower levels of cognitive reserve and had been exposed to chemotherapy were impaired on processing speed compared to other groups (e.g., younger patients, patients with higher levels of cognitive reserve, patients not exposed to chemotherapy, healthy controls) (Ahles et al., 2010). Processing speed was the only examined outcome because previous research has found it to be sensitive to the effects of cancer treatment (Ahles et al., 2010; Correa & Ahles, 2008).

The host factors of anxiety, depression, fatigue, and sleep disturbance have been inconsistently associated with cognitive symptoms in cancer patients (Ahles & Saykin, 2001, 2002; Ono et al., 2015; Schagen, Muller, Boogerd, & van Dam, 2002; Valentine & Meyers, 2001; Vearncombe et al., 2009). These factors are more often related to subjective cognitive complaints than objective cognitive impairment (Jim et al., 2012; Ono et al., 2015; van Dam et al., 1998). These four constructs are frequently characterized as “psychological factors” in research on cognitive difficulties in cancer and are either statistically or methodologically controlled (Ahles, Root, et al., 2012; Hurria et al., 2007; Ono et al., 2015). Other researchers argue that they are also symptoms of cancer and its treatment (Miaskowski, Dodd, & Lee, 2004).

Disease-related factors possibly involved in cognitive change in cancer patients include genetic mutations and DNA damage, neurotoxic cytokines, and disease stage (Ahles, Root, et al., 2012; Meyers & Perry, 2008). Even prior to chemotherapy, it is
estimated that 20-30% of non-metastatic breast cancer patients have some degree of
cognitive impairment compared to age- and education-adjusted norms, and this does not
appear to be due to depressive symptoms, anxiety, fatigue, or surgery (Ahles, Root, et al.,
2012; Ahles et al., 2008). Ahles and colleagues (2012) have presented two non-mutually
exclusive hypotheses for direct effects of disease-related factors on cognitive symptoms
in cancer: 1) there may be common risk factors for breast cancer and age-related
cognitive decline; and 2) the biology of cancer affects cognitive performance. Both of
these hypotheses have correlational support. Genetic mutations preventing repair of
damaged DNA have been associated with increased risk for developing breast cancer,
and deficient DNA repair has also been associated with neurodegenerative disorders such

Regarding the second hypothesis, one way that the biology of cancer can impact
cognition is through an inflammatory response that activates neurotoxic cytokines (Ahles,
Root, et al., 2012; Ahles & Saykin, 2007). Cytokine dysregulation has been associated
with neurodegenerative disorders, cognitive disorders, fatigue, and depression (Ahles &
Saykin, 2007). Recent findings show a significant relationship between elevated
cytokine levels and poorer cognitive performance in breast cancer patients prior to
treatment after controlling for other factors related to cognitive decline, such as age,
education, and mood (Patel et al., 2015).

Cancer stage is another disease-related factor that may contribute to cognitive
impairment. One study found that prior to chemotherapy, breast cancer patients with
invasive disease were more likely than breast cancer patients with noninvasive disease to
have decrements in cognitive performance compared to published norms, and these
patient groups did not differ on depressive symptoms, anxiety, or fatigue (Ahles et al., 2008). Unfortunately, disease stage is often confounded with treatment type in prospective longitudinal studies examining cognitive changes in cancer, which limits the conclusions that may be drawn (McDonald, Conroy, Ahles, West, & Saykin, 2010).

Treatment-related factors that may contribute to cognitive changes in cancer patients include chemotherapy, endocrine or hormone therapy, and radiation therapy. Evidence suggests that chemotherapy may cause changes in brain structure for at least a subgroup of cancer patients (Ahles, Root, et al., 2012; Hurria et al., 2007; Ono et al., 2015; A. Stewart et al., 2006). For example, imaging studies with breast cancer patients showed decreased grey matter in frontal, temporal, and cerebellar regions and the right thalamus at one month post-chemotherapy, whereas non-chemotherapy treated patients only showed decreased grey matter in cerebellar regions and healthy controls showed no significant structural changes (McDonald et al., 2010). These structural changes have not been associated with objective cognitive impairment, although chemotherapy-treated patients showed a non-significant decline in high-load working memory performance from baseline to one month post-chemotherapy along with compensatory hyperactivation in frontal cortices on fMRI (McDonald, Conroy, Ahles, West, & Saykin, 2012). Chemotherapy-treated patients showed only partial recovery of grey matter density at 1-year follow-up (McDonald et al., 2010). The mechanism by which chemotherapy affects cognition is still unknown (Ahles, Root, et al., 2012), although there are several theories. Animal models suggest that chemotherapy agents that cross the blood-brain barrier can reduce blood flow to the brain, cause DNA and white matter damage, inhibit the growth
of neurons in the hippocampus, and decrease activation in the hypothalamic-pituitary-adrenal (HPA) axis (Ahles, Root, et al., 2012; Seigers & Fardell, 2011).

Knowledge of the effects of hormonal and radiation therapy on cognition in cancer patients has been growing in recent years. Regarding hormonal therapy, results of several randomized trials suggest that tamoxifen is associated with cognitive impairment in breast cancer patients, whereas aromatase inhibitors (e.g., exemestane, anastrozole) are not (Zwart et al., 2015). Although radiation therapy to the brain and spinal cord has long been associated with cognitive and neurological symptoms in cancer patients (Crossen, Garwood, Glatstein, & Neuwelt, 1994; Dietrich et al., 2008; Keime-Guibert, Napolitano, & Delattre, 1998; Perry & Schmidt, 2006), emerging evidence suggests non-CNS radiation therapy is also associated with objective and subjective cognitive change in patients with several cancer types (Geinitz et al., 2001; Janaki et al., 2010; Jim et al., 2009; Kohli et al., 2007; Marchand et al., 2010; Noal et al., 2011; Phillips et al., 2012; Quesnel, Savard, & Ivers, 2009; Schagen et al., 2008; Shibayama et al., 2014). However, the evidence is inconsistent: one study found no relationship between radiation therapy and cognitive complaints (Browall et al., 2008), a few showed rapid reductions in cognitive complaints after treatment (Geinitz et al., 2001; Janaki et al., 2010; Marchand et al., 2010), and others found objective and subjective cognitive symptoms lasting months to years after treatment (Jim et al., 2009; Kohli et al., 2007; Noal et al., 2011; Phillips et al., 2012; Quesnel et al., 2009; Schagen et al., 2008; Shibayama et al., 2014). Methodological differences may explain some of the inconsistent findings (Shibayama et al., 2014). Some studies only assessed subjective cognitive complaints (Browall et al., 2008; Geinitz et al., 2001; Janaki et al., 2010; Kohli et al., 2007; Marchand et al., 2010),
whereas others also measured objective cognitive performance (Jim et al., 2009; Noal et al., 2011; Phillips et al., 2012; Quesnel et al., 2009; Schagen et al., 2008; Shibayama et al., 2014). Control groups also differed (Shibayama et al., 2014); some studies only used healthy comparison groups (Jim et al., 2009; Phillips et al., 2012; Quesnel et al., 2009), and several did not include a comparison group (Browall et al., 2008; Geinitz et al., 2001; Janaki et al., 2010; Marchand et al., 2010; Noal et al., 2011). Shibayama and colleagues (2014) explored a possible mechanism for the effect of non-CNS radiation therapy on cognition in early-stage breast cancer patients. Specifically, elevated levels of proinflammatory cytokine IL-6 were found to significantly mediate the relationship between receipt of radiation treatment and worse cognitive performance.

While some models describe potential contributors to cognitive symptoms in cancer patients, other models describe the trajectory of cognitive changes. The phase shift hypothesis assumes stable decrements in cognition in cancer patients compared to healthy individuals without a cancer history, such that cognitive dysfunction in cancer patients parallels normal aging (Figure 2) (Ahles, Root, et al., 2012; Mandelblatt et al., 2013). Conversely, the accelerated aging hypothesis suggests that the slope of cognitive decline over time is steeper for cancer patients compared to healthy individuals without a cancer history (Figure 2) (Ahles, Root, et al., 2012; Mandelblatt et al., 2013). Further longitudinal research is needed to determine which hypothesis is correct, or if both are correct, but for different patient populations. For example, it is possible that younger patients with greater cognitive reserve show a phase shift pattern, whereas older patients with less cognitive reserve show accelerated aging (Ahles, 2012).
Ahles and colleagues (2012) hypothesize that aging and cancer affect cognition in two ways: 1) the initial impact of cancer treatments has a domino effect on several biological systems that results in progressive cognitive decline with aging, or 2) a treatment might not result in enough initial biological damage to affect cognition immediately, but there may be a delayed effect with increasing age. These patterns are supported by evidence from a longitudinal study of non-metastatic breast cancer patients treated with chemotherapy (Wefel, Saleeba, Buzdar, & Meyers, 2010). The following patterns of cognitive functioning were found: 1) cognitive decline immediately post-treatment and continued decline one year post-treatment; 2) cognitive decline immediately post-treatment and stable cognitive functioning at one year; and 3) no cognitive decline immediately post-treatment and new cognitive decline at one year post-treatment (Ahles, Root, et al., 2012; Wefel et al., 2010). Clinical, mood, and demographic variables did not significantly differentiate patients with acute or late cognitive decline, but there were non-significant trends suggesting that older age and baseline cognitive impairment may be risk factors for acute and late decline (Wefel et al., 2010). The authors suggested that diminished cognitive reserve pre-treatment may contribute to late cognitive decline or prevent recovery from acute impairment.

To summarize, evidence suggests that host, disease, and treatment factors are directly and indirectly associated with cognitive impairment in cancer patients (Ahles, Root, et al., 2012; Ahles & Saykin, 2007; Ahles et al., 2003; Berman et al., 2014; Conroy et al., 2013; McDonald et al., 2010; Meyers & Perry, 2008; Ono et al., 2015; Patel et al., 2015; Zwart et al., 2015). However, a number of gaps in this literature remain, especially with respect to the impact of psychological factors and disease variables on cognition.
The model of trajectories of aging and cognitive decline in cancer is theoretically sound and has support from one longitudinal study (Ahles, Root, et al., 2012; Mandelblatt et al., 2013; Wefel et al., 2010). Taken together, models of cognition in cancer inform research and treatment by suggesting testable pathways by which various factors may impact cognition within the broader context of aging (Ahles, Root, et al., 2012; Mandelblatt et al., 2013; Meyers & Perry, 2008).

**Cognitive complaints in cancer.** Although substantial evidence supports cognitive change associated with cancer and its treatment (Ahles, Root, et al., 2012; Hurria et al., 2007; Ono et al., 2015; Von Ah, 2015), the relationship between objective and subjective cognitive impairment in cancer patients is less clear. Objective cognitive impairment as measured by neuropsychological tests is often found to have little to no correlation with subjective cognitive impairment or cognitive complaints (Ahles & Saykin, 2002; Hurria et al., 2007; Schagen et al., 2002; Schagen et al., 1999). One explanation for this finding is that brief neuropsychological tests commonly used in research are not sufficiently sensitive to detect the subtle cognitive deficits associated with cancer and its treatment (Hurria et al., 2007). An fMRI neuroimaging study found support for this hypothesis; during a working memory task, breast cancer patients did not show objective impairment compared to controls, yet they had hyperactivation of brain areas associated with executive function (McDonald et al., 2012). These findings suggest that the brains of breast cancer patients engage in compensatory processes (McDonald et al., 2012); thus, patients may find tasks to be more effortful while showing little to no objective impairment. Some researchers have concluded that cognitive complaints represent subtle changes in cognitive function that should be a focus of research and
clinical efforts (Pullens, De Vries, Van Warmerdam, Van De Wal, & Roukema, 2013; Von Ah & Tallman, 2015).

An alternative explanation for the small to non-existent correlation between subjective and objective cognitive impairment is that cognitive complaints are more indicative of psychological distress than cognitive dysfunction (Jansen, 2013; Jenkins et al., 2006; Kibiger, Kirsh, Wall, & Passik, 2003; Poppelreuter et al., 2004; Pullens, De Vries, & Roukema, 2010; Shilling & Jenkins, 2007; Von Ah & Tallman, 2015). Multiple studies have found a significant, moderate to strong positive relationship between depressive symptoms and cognitive complaints (Cimprich, So, Ronis, & Trask, 2005; Jenkins et al., 2006; Pullens et al., 2013; Shilling & Jenkins, 2007; Weis, Poppelreuter, & Bartsch, 2009). Some researchers have suggested that depressive symptoms are more likely to impair cognitive functioning in everyday life than during controlled neuropsychological testing; thus, cancer patients with depressive symptoms may report difficulty performing routine tasks while still performing normally on objective tests (Shilling & Jenkins, 2007; Weis et al., 2009). Others argue that although psychological factors may directly increase cognitive complaints, they may also contribute to subtle deficits in cognitive function that may not be detectable with objective tests (Jean-Pierre, Johnson-Greene, & Burish, 2014). Indeed, depression has been associated with structural and functional changes in brain regions responsible for attention and memory (Bird & Burgess, 2008; Jean-Pierre et al., 2014; Milne, MacQueen, & Hall, 2012; Sievers et al., 2012). Depression has also been associated with proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha (Schiepers, Wichers, & Maes,
2005), which have been related to objective and subjective cognitive symptoms in cancer patients (Ganz et al., 2013; Seruga, Zhang, Bernstein, & Tannock, 2008).

Subjective cognitive function may also be influenced by patients’ expectations. One study found that breast cancer patients who were primed with a letter explaining cognitive changes associated with cancer and its treatment were more likely to report cognitive complaints during an interview about their symptoms compared to those who did not receive the letter (Schagen, Das, & van Dam, 2009). The priming effect was present for both patients who had and had not been previously treated with chemotherapy, although it was stronger for patients with no prior chemotherapy treatment (Schagen et al., 2009). This discrepant priming effect may be explained by ceiling effects for the chemotherapy-treated patients. That is, chemotherapy-naïve patients may be more vulnerable to priming because they are unable to draw upon personal experience with effects of chemotherapy (Schagen et al., 2009). The same group of researchers later conducted a similar priming study that produced comparable expectancy effects with respect to cognitive complaints and objective test performance; however, the effects were stronger for chemotherapy-treated patients than chemotherapy-naïve patients (Schagen, Das, & Vermeulen, 2012). Prior knowledge of the possible effect of chemotherapy on cognition may be important for priming to take place; only about half of patients in the first study had pre-study knowledge of the relationship between chemotherapy and cognition, whereas the majority of the patients in the second study had that knowledge (Schagen et al., 2012). The researchers concluded that providing information about cognitive symptoms to patients treated with chemotherapy induces a stereotype threat which can affect both objective and subjective cognitive outcomes (Schagen et al., 2012).
Although cognitive complaints have been variously characterized as subtle cognitive deficits, psychological distress, and expectancy effects, assessment of these complaints uniquely informs our understanding of patients' experiences. Some researchers argue that perceived cognitive impairment is as important to assess as objective impairment due to its association with patients’ functional status and quality of life (Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Shilling & Jenkins, 2007). Greater cognitive complaints are associated with greater depressive symptoms, anxiety, and fatigue and poorer quality of life in cancer patients (Hutchinson et al., 2012; Pullens et al., 2010). Continued assessment of patients’ self-reported cognitive symptoms is warranted to understand symptom experiences from the patients’ perspective (Pullens et al., 2010) and inform patient-centered treatment approaches.

### 1.3 Cognitive Symptoms in Metastatic Breast Cancer

Although most research on cognitive symptoms has focused on early-stage breast cancer patients, a few studies have documented self-reported cognitive symptoms in metastatic breast cancer patients (Aranda et al., 2005; Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Mayer, 2010; Mayer & Grober, 2006). One study found that cognitive dysfunction was only reported by 8% of 105 metastatic breast cancer patients on the 2-item cognitive subscale of the EORTC QLQ-30 (Aranda et al., 2005). Conversely, another survey of metastatic breast cancer patients found that 60% of 618 patients reported cognitive problems on an author-constructed item (Mayer, 2010). Differences in findings across studies may reflect differential measurement of cognitive symptoms and sample characteristics: the first study consisted of patients from four urban hospitals in Australia (61% response rate) (Aranda et al., 2005), whereas the second study
was an online survey of patients from 13 countries (unknown response rate) (Mayer, 2010; Mayer & Grober, 2006). Given limitations of the research to date, the prevalence of cognitive symptoms in metastatic breast cancer patients is unclear.

Another study found that one cognitive symptom (i.e., loss of concentration) tended to cluster with fatigue, increased weakness, and mood problems in metastatic breast cancer patients; however, the analysis was limited to symptoms related to menopause (Bender et al., 2005). This symptom cluster has also been found in early-stage breast cancer patients and patients with other common cancers (Ahles & Saykin, 2002; Fan, Filipczak, & Chow, 2007; Ono et al., 2015). To my knowledge, further studies have not documented objective or subjective cognitive symptoms or symptom clusters in metastatic breast cancer patients. Standardized assessment of cognitive and other symptoms would contribute to our understanding of the symptom experience of this population.

1.4 Symptom Clusters

Research on symptom clusters in cancer and non-cancer populations is limited by a lack of consensus regarding their conceptual or methodological definition (Dong, Butow, Costa, Lovell, & Agar, 2014). A symptom cluster was originally defined by Dodd and colleagues (2001) as “three or more concurrent symptoms” that are related in some way (Dodd, Miaskowski, & Paul, 2001). A more recent definition is that two or more symptoms form a cluster if they predictably occur together in a stable group and are more strongly associated with each other than with symptoms in separate clusters (Aktas, Walsh, & Rybicki, 2010; Dong et al., 2014; Fan et al., 2007; Kim, McGuire, Tulman, & Barsevick, 2005). However, a recent systematic review of the symptom cluster literature
on patients with advanced cancer found clusters to be generally unstable both longitudinally and methodologically (Dong et al., 2014). It is also challenging to replicate clusters across studies due to a lack of consensus regarding appropriate assessment tools, symptom domains, and statistical methodologies (Aktas et al., 2010; Dong et al., 2014). For example, a systematic review found that several studies of advanced cancer patients used author-developed symptom checklists with unknown psychometric properties, and other studies with this population did not comprehensively assess common symptoms (Dong et al., 2014). Additionally, studies using different approaches to statistically derive symptom clusters within the same data set found poor stability of clusters between statistical methods (Dong et al., 2014). However, clusters derived with principal component analysis (PCA) and hierarchical cluster analysis (HCA) were more strongly correlated than clusters derived with exploratory factor analysis (EFA) (Chen et al., 2013; Chen et al., 2012; Dong et al., 2014; Khan et al., 2013).

Despite methodological and conceptual challenges, symptom clusters are especially important to examine in cancer patients for several reasons. First, when multiple symptoms occur together in cancer patients, they often have a compounding effect which may impair functional status and decrease quality of life (Cleeland, 2007; Cleeland et al., 2003; Dodd, Cho, Cooper, & Miaskowski, 2010; Dodd et al., 2001; Kurzrock, 2001; Valentine & Meyers, 2001). Second, on average, cancer patients concurrently experience 11-13 symptoms (Chang, Hwang, Feuerman, & Kasimis, 2000; Fan et al., 2007; Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Coyle, et al., 1994); thus, assessing and treating one symptom at a time is unlikely to have a large impact on patients’ distress or quality of life (Miaskowski et al., 2004).
Furthermore, identifying symptom clusters informs research and treatment by pointing to common mechanisms—both biological and psychological—that may underlie various symptoms (Kim, Barsevick, Fang, & Miaskowski, 2012; Miaskowski et al., 2004). For example, in cancer patients with various disease sites, pain has been shown to cluster with cognitive problems (Fan et al., 2007). Although this relationship may be explained by analgesic medication use, an alternative explanation is that pain demands attention, resulting in cognitive deficits when limited attentional resources are focused on pain (Eccleston & Crombez, 1999; Grisart & Van der Linden, 2001; Moriarty, McGuire, & Finn, 2011).

Recently, researchers have suggested that cognitive symptoms, pain, fatigue, sleep problems, anxiety, and depressive symptoms form a psychoneurological symptom cluster with several interacting psychological and biological mechanisms (Kim et al., 2012; Starkweather et al., 2013; Wood & Weymann, 2013). Inflammation is an example of a possible biological mechanism underlying the psychoneurological symptom cluster (Dong et al., 2014). Elevated proinflammatory cytokines have been associated with greater overall symptom severity in lung cancer patients (Wang et al., 2010) and fatigue and cognitive dysfunction in breast cancer patients prior to chemotherapy (Patel et al., 2015). Whether inflammation is a cause or an outcome of symptom burden is currently unclear, but it appears to be one of many interactive factors influencing symptom outcomes (Dong et al., 2014; Kim et al., 2012). Another common biological mechanism that may interact with factors such as inflammation is HPA axis dysregulation (Kim et al., 2012). Animal models suggest that some chemotherapy treatments lead to HPA axis dysregulation (Seigers & Fardell, 2011), and stress associated with having cancer may
also be associated with this outcome (Kim et al., 2012). Even after completing treatment, breast cancer survivors with chronic fatigue have shown dysregulation of HPA axis responsiveness with significantly blunted cortisol response to laboratory stressors (Bower, Ganz, & Aziz, 2005). HPA axis dysregulation has also been found to be significantly associated with more sleep disturbance, pain, and depressive symptoms among metastatic breast cancer patients (Koopman et al., 2002). Exploring symptoms clusters in metastatic breast cancer patients may inform future research regarding common mechanisms of these symptoms such as stress, inflammation, and HPA axis dysregulation.

1.5 Patient Perceptions of Symptom Importance

Research on symptoms in cancer patients has largely focused on symptom severity, frequency, and distress. Assessing patients’ perceptions of symptom importance—how important it is for them to see improvement in a symptom after it is treated—would also inform patient-centered treatment approaches. The goals of patient-centered treatment are to enhance communication and collaboration between patients and clinicians and respect patients’ autonomy (Epstein, Fiscella, Lesser, & Stange, 2010). Some evidence suggests that patient-centered treatment improves quality of care, health outcomes, and patient satisfaction while reducing financial costs of health care (Epstein et al., 2010; Epstein et al., 2005; Fiscella et al., 2004; Little et al., 2001; Mallinger, Griggs, & Shields, 2005; Mead & Bower, 2002; Rao, Anderson, Inui, & Frankel, 2007; Safran et al., 2006; M. Stewart et al., 2000). However, a patient-centered approach has not been adopted in symptom research with cancer patients; studies have not examined patients’ perceptions of the importance of reducing specific symptoms.
Perceptions of symptom importance have been examined in research on patients with chronic pain conditions. This research found subgroups of patients who had differential perceptions of the importance of improving specific symptoms; some patients focused on pain as the most important symptom, whereas others equally valued improvement in various symptoms (M. E. Robinson et al., 2005; Yi, Kim, Ha, & Lim, 2014; Zeppieri et al., 2012). Evidence suggests that patients with chronic pain who rate all symptoms as highly important have increased depressive and anxiety symptoms (Yi et al., 2014; Zeppieri et al., 2012). One study of patients with Parkinson’s disease found that they either rated all or none of their symptoms as highly important (Nisenzon et al., 2011). Although disease and treatment factors were unrelated to symptom importance ratings, low importance ratings were associated with more formal education (Nisenzon et al., 2011).

Treating symptoms such as pain, fatigue, and sleep disturbance may be a greater priority for advanced cancer patients than maintaining their cognitive functioning. For example, treating pain with narcotics often results in temporary cognitive impairment (Bruera, Macmillan, Hanson, & MacDonald, 1989), and some advanced cancer patients may consider pain treatment to be a higher priority than maintaining optimal cognitive function. Yet other patients, especially those with cognitively demanding jobs, may find cognitive deficits to be more distressing than other symptoms. Many metastatic breast cancer patients are living for years with this disease and have high levels of functioning (Mayer, 2010; Reed et al., 2012). Despite this population’s increased longevity and functional capacity, their cognitive symptoms have received scarce research attention. Understanding cognitive symptoms in the context of metastatic breast cancer patients’
symptom treatment priorities informs patient-centered care for this highly burdened and prevalent, yet understudied population.

1.6 The Present Study

To address gaps in our understanding of metastatic breast cancer patients’ cognitive symptoms, the present study has two specific aims:

Aim 1: Examine the extent to which cognitive complaints cluster with other common symptoms (i.e., fatigue, sleep disturbance, depressive symptoms, anxiety, pain, hot flashes, lymphedema, neuropathy, and nausea) in metastatic breast cancer patients.

Hypothesis 1: Cognitive complaints will cluster with fatigue, sleep disturbance, depressive symptoms, anxiety, and pain in metastatic breast cancer patients.

This hypothesis is illustrated in Figure 3 and is based on limited evidence from two studies suggesting that fatigue, sleep disturbance, and mood disturbance are associated with cognitive complaints in metastatic breast cancer patients (Aranda et al., 2005; Bender et al., 2005). One of these studies did not perform a cluster analysis on reported symptoms (Aranda et al., 2005). In the study that included a cluster analysis of symptoms, only single-item measures of menopausal symptoms were analyzed (Bender et al., 2005). In the current study, multi-item symptom assessments developed by the NIH and validated in cancer populations were used in order to provide a more reliable estimate of cognitive and other symptoms in metastatic breast cancer patients.

This hypothesis is also based on research suggesting that pain tends to cluster with cognitive problems in other cancer populations (Fan et al., 2007). It is estimated that 70-90% of patients with advanced cancer have chronic pain (Irvin, Muss, & Mayer, 2011; Portenoy & Lesage, 1999). Although the prevalence of chronic pain in metastatic...
breast cancer patients is unknown, it is estimated that 44-64% of breast cancer patients at any stage (excluding survivors with no evidence of disease) have chronic pain (Van den Beuken-van Everdingen et al., 2007). Thus, it is important to examine whether pain tends to cluster with cognitive complaints in metastatic breast cancer patients.

Finally, this hypothesis is based on theory and empirical research suggesting that a psychoneurological symptom cluster may have common biological and psychological mechanisms (Kim et al., 2012; Miaskowski et al., 2004). Elevated proinflammatory cytokines may be one biological mechanism underlying symptom clusters, as they have been associated with greater overall symptom severity in lung cancer patients (Dong et al., 2014; Wang et al., 2010) and fatigue and cognitive dysfunction in breast cancer patients prior to chemotherapy (Patel et al., 2015). HPA axis dysregulation is another possible common mechanism underlying symptoms such as cognitive symptoms, sleep problems, fatigue, pain, anxiety, and depressive symptoms (Bower et al., 2005; Kim et al., 2012; Koopman et al., 2002; Seigers & Fardell, 2011).

Exploratory Aim: To compare metastatic breast cancer patient ratings of symptom importance for cognitive symptoms to those of other symptoms (i.e., pain, fatigue, sleep disturbance, depression, anxiety, nausea, lymphedema, hot flashes, and neuropathy).

This aim is exploratory due to the absence of prior research and theorizing on cancer patient ratings of symptom importance.
CHAPTER 2. METHOD

This study examines a portion of the data from a Walther-funded study on metastatic breast cancer patients’ perceptions of symptom importance and interference. The Indiana University Institutional Review Board and IU Simon Cancer Center Scientific Review Committee approved all study procedures. This study complies with the Health Insurance Portability and Accountability Act (HIPAA).

2.1 Participants

Eighty metastatic breast cancer patients were recruited from the IU Simon Cancer Center to participate in a telephone survey. Eligible participants met the following inclusion criteria: female, diagnosis of stage IV breast cancer, at least 18 years old, able to speak and read English, and no evidence of cognitive impairment that may limit their capacity to give informed consent or participate in the study. This degree of cognitive impairment was based on investigator judgment or exceeding a clinical cutpoint (i.e., 3 or more errors) on a validated cognitive screening measure (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002).

2.2 Procedure

IU Simon Cancer Center medical records were screened to identify patients with stage IV breast cancer, and their treating oncologists were contacted to verify eligibility
for the current study. Eligible patients were then mailed an introductory letter signed by
the PI and the patient’s oncologist along with consent and HIPAA authorization forms.
The letter included an option to call or email the research assistant to decline further
contact. Within approximately 1 to 2 weeks after the mailing, the research assistant
called patients who had not opted-out to describe the study, answer any questions,
administer a brief cognitive screening assessment (Callahan et al., 2002), and obtain
verbal informed consent. Patients who declined study participation were asked to
provide their reason for study refusal as well as age and race to assess for possible
selection biases. If the patient verbally consented to participate, a 45-minute telephone
assessment was scheduled. The assessment was administered by a trained research
assistant and included questions regarding demographic information, medical history, and
symptom severity and importance. A subsample of 25 participants with one or more
symptoms of at least moderate severity (i.e., sleep problems, pain, anxiety, sadness, or
fatigue) were invited to participate in a separate qualitative phone interview, but the
qualitative data were not analyzed in the present study. Participants received a $40
Target gift card for the first assessment, and those who participated in the qualitative
interview received an additional $50 Target gift card, for a possible total of $90 in gift
cards.

2.3 Measures

The following sections describe measures analyzed in the current study and time
points for data collection.

Brief screening measure for probable dementia. The cognitive screener was a
6-item assessment of global cognitive functioning. The 6 items were taken from the
Mini-Mental State Examination, a commonly used and validated measure (Cockrell & Folstein, 2002). Three items assess orientation to time, which increase the measure’s specificity for assessing probable dementia (Callahan et al., 2002). The other 3 items assess short-term word recall, which increase the measure’s sensitivity because deficits in short-term word recall are highly indicative of cognitive impairment (Callahan et al., 2002). Patients were ineligible if they missed 3 or more items on this measure, as this suggested that they lacked the capacity to provide consent and accurate responses to study questions. A cutoff score of 3 or more errors has been shown to have 88.7% sensitivity and 88.0% specificity for a diagnosis of dementia (Callahan et al., 2002). Although including this screener limited the range of cognitive abilities of study participants, mild to moderate cognitive symptoms that were not confounded with a diagnosis of dementia were the focus of this study.

Demographics. Participants were asked to report their marital status, race, ethnicity, education, income, and employment status. Age was assessed via medical record review.

Medical information. The following information was collected from the medical record after informed consent: diagnosis date and cancer treatment history (i.e. surgeries, chemotherapy, radiation, hormone therapy, targeted therapy, bisphosphonates, and other treatment).

Medical comorbidities. A self-report measure of 9 medical conditions was used to assess the presence of comorbid conditions that were diagnosed or treated within the last 3 years (Kroenke et al., 2009). This measure has been used in NIH-funded research
with cancer patients (Kroenke et al., 2009). Reliability and validity of this measure have not been established, as this is a checklist rather than a scale (Kroenke et al., 2009).

**Cognitive complaints.** General cognitive concerns were assessed with a 4-item Patient Reported Outcomes Information System (PROMIS) measure (Cella et al., 2010). Patients were asked to rate the frequency of their cognitive complaints (e.g., “My thinking has been slow…”) over the past 7 days on a scale from 1 (*never*) to 5 (*very often*).

The development of PROMIS measures was funded by the NIH to create a standardized way to reliably assess patient-reported health outcomes (Cella et al., 2010; Cella et al., 2007). Standardized T scores with a mean of 50 and a standard deviation of 10 can be used to compare scores to population norms. Cancer patients were involved in focus groups to develop items for PROMIS measures (Garcia et al., 2007), and several publications have demonstrated the PROMIS measures’ reliability and validity in cancer populations with early to late-stage disease (Baum, Basen-Engquist, Swartz, Parker, & Carmack, 2014; Stachler, Schultz, Nerenz, & Yaremchuk, 2014; Wagner et al., 2015; Yost, Eton, Garcia, & Cella, 2011). Initial development of PROMIS short-forms showed excellent internal consistency reliability of each of the symptom measures and strong correlations between short forms and item banks ($r > .96$) (Cella et al., 2010). PROMIS items also have good convergent validity, as evidenced by moderate to strong correlations between these items and similar legacy measures ($r$ ranges from .69 to .96) (Cella et al., 2010).

**Other physical and psychological symptoms.** Nine additional physical and psychological symptoms were selected for assessment in the current study due to their
high prevalence in metastatic breast cancer patients (Aranda et al., 2005; Bender et al., 2005; Carpenter et al., 1998; Given et al., 2008; Grabsch et al., 2006; Holmes et al., 1991; Ozaslan & Kuru, 2004; Palesh et al., 2007). PROMIS measures (Cella et al., 2010) were used to assess some of these symptoms. Specifically, 4-item PROMIS measures were used to assess four of these symptoms during the past week, including depressive symptoms and anxiety on a scale from 1 (never) to 5 (always), fatigue on a scale from 1 (not at all) to 5 (very much), and sleep disturbance with the first item (i.e., “My sleep quality was…”) rated on a scale from 1 (very poor) to 5 (very good) and subsequent items rated on a scale from 1 (not at all) to 5 (very much). A 3-item PROMIS measure was used to assess pain intensity over the past week on a scale from 1 (no pain) to 5 (very severe).

No PROMIS measures have been developed to assess nausea, hot flashes, lymphedema, or neuropathy. Thus, these symptoms were assessed with other validated measures. Items from the Memorial Symptom Assessment Scale (MSAS) (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Kiyasu, et al., 1994) were used to measure nausea, peripheral neuropathy, and lymphedema. Patients were asked to indicate whether they had experienced the symptom in the past week, and those who answered yes were asked to rate the frequency of the symptom over the past week on a scale from 1 (rarely) to 4 (almost constantly). In addition, patients reported usual symptom severity over the past week on a scale from 1 (slight) to 4 (very severe) and the extent to which the symptom was distressing on a scale from 0 (not at all) to 4 (very much). Lymphedema symptom assessment does not include a question about frequency because it is not relevant for this symptom (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar,
Kiyasu, et al., 1994). In research with cancer patients, the MSAS had moderate to high internal consistency for physical symptom assessment (Cronbach’s α ranges from 0.58 to 0.88) and showed evidence of convergent and discriminant validity (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Kiyasu, et al., 1994). For example, it was highly correlated with other measures of clinical status and quality of life (e.g., r ranges from -0.52 to -0.75 for MSAS physical symptoms and the Functional Living Index-Cancer) (Portenoy, Thaler, Kornblith, Lepore, Friedlander-Klar, Kiyasu, et al., 1994).

The MSAS does not include an assessment of hot flashes; thus, this symptom was assessed with a brief measure developed to assess hot flashes in breast cancer patients treated with hormone therapy (Carpenter et al., 1998). Similar to the MSAS, patients were first asked to indicate whether they had experienced hot flashes, and those who answered yes were asked to rate their severity on a scale from 0 (not at all) to 4 (extremely) and the extent to which they were bothersome on a scale from 0 (not at all bothered) to 10 (extremely bothered). Unlike the MSAS, patients were asked if they have experienced hot flashes over the past two weeks rather than one week. This time period is similar to that of prior research (Brambilla, Mckinlay, & Johannes, 1994; Carpenter et al., 1998; Hemminki, Topo, & Kangas, 1995). Hot flashes tend to be periodic (Kronenberg, 1990); thus, limiting the assessment time period to one week may significantly decrease the sensitivity of the measure.

**Perceptions of symptom importance.** Patient perceptions of symptom importance were assessed with the Patient Centered Outcomes Questionnaire (PCOQ) (Robinson et al., 2005), which was modified to include the symptoms described above. The modified PCOQ consists of four sections, whereas the original PCOQ had five
sections. We omitted the section on desired level of symptom severity because ideal outcomes were likely to be “none” for the majority of patients. This section was omitted in another study using a modified version of the PCOQ with a different medical population (Nisenzon et al., 2011). In the first section of the modified PCOQ in the current study, patients were asked to report their usual level of symptom severity over the past week on a scale of 0 (none) to 10 (worst imaginable) for each of the 10 symptoms (i.e. pain, fatigue, anxiety, sadness, numbness/tingling in hands/feet, swelling of arms or legs, nausea, hot flashes, sleep problems, attention/thinking/memory problems). In the second section, patients were asked to report for each symptom the level of symptom severity that they would consider a treatment success on a scale of 0 (none) to 10 (worst imaginable). In the third section, patients were asked to report for each symptom their expected symptom severity following treatment of the symptom on a scale of 0 (none) to 10 (worst imaginable). In the fourth and final section, patients were asked to rate the importance of experiencing improvement in each of their symptoms on a scale of 0 (not at all important) to 10 (most important). Because an aim of this study was to compare metastatic breast cancer patient ratings of symptom importance for cognitive symptoms to those of other symptoms, analysis of this measure focused exclusively on the fourth section.

The PCOQ was originally developed for patients with chronic pain, and the original version showed adequate test-retest reliability over a 48 hour period (values ranging from 0.84 to 0.90) and good convergent validity with other standardized measures of pain, emotional distress, and disability (r values ranging from 0.52 to 0.75) (Brown et al., 2008).
2.4 Data Analysis

Data were analyzed with SPSS (IBM SPSS Statistics for Windows, Version 23.0; Armonk, NY, USA) and R (R Foundation for Statistical Computing, Version 3.2.3; Vienna, Austria) statistical software. Minimal missing data were expected; thus, listwise deletion would have been employed (i.e., all cases with missing data would be excluded from analyses). However, none of the data were missing. To examine symptoms on the same metric, scores for all measures of symptom severity (i.e., PROMIS measures, MSAS subscales, and the hot flashes assessment) were converted to z scores. Data were then examined for possible outliers, and Winsorization transformation was employed in order to reduce the influence of any extreme values by modifying scores to equate to z-scores with an absolute value of 3.0 (i.e., to 3 standard deviations of the mean) (Tukey, 1962). The assumption of normality was examined by computing skewness and kurtosis indices, which should be less than the absolute values of 3.0 and 8.0, respectively (Kline, 2011). If the assumption of normality was violated, the appropriate variable transformation (i.e., log or square root) would have been employed based on the characteristics of the violation, and sensitivity analyses would have been performed to determine differential effects of data transformations. Frequencies, means, and standard deviations were computed to characterize patient demographics, medical information, and symptom levels (i.e. cognitive complaints, hot flashes, nausea, lymphedema, neuropathy, depression, anxiety, sleep disturbance, fatigue, and pain) as well as ratings of symptom importance for each of the 10 symptoms. Chronbach’s alphas were computed for multi-item assessments.
To test the hypothesis that cognitive complaints would cluster with fatigue, sleep disturbance, depressive symptoms, and anxiety, an agglomerative hierarchical cluster analysis was performed on the z scores for the 10 symptoms. This provided subgroups of co-occurring symptoms, allowing me to determine which symptoms tended to cluster with cognitive complaints. Squared Euclidian distances were used in the proximities matrix, and weighted average linkage was used as the clustering method (Everitt, Landau, & Leese, 2001; McQuitty, 1966). This cluster analysis method is frequently used in symptom cluster research with cancer patients (Bender et al., 2005; Dodd et al., 2010; Glaus et al., 2006; Miaskowski et al., 2006; Ridner, 2005). There is no reason to expect similar subgroup sizes; thus, this clustering method is preferable to Ward’s method—another commonly used cluster analysis method—which forms spherical clusters, forcing the clusters to have similar sizes (Everitt et al., 2001). Because cluster analysis is an exploratory method of examining multivariate relationships, no formal power analysis based on sample size is feasible (Everitt et al., 2001; Kozachik, 2006).

To test the exploratory aim, a within-factors ANOVA was performed to compare patient ratings of the importance of symptom improvement for cognitive symptoms to those of nine other symptoms (i.e., pain, fatigue, sleep disturbance, depression, anxiety, nausea, lymphedema, hot flashes, and neuropathy). Planned simple contrasts were then performed to compare importance ratings between all symptom pairs while preventing alpha inflation. We estimated the statistical power to detect a difference between importance ratings with the G*Power statistical power analysis program (Faul, Erdfelder, Lang, & Buchner, 2007). A sensitivity power analysis for a within-factors ANOVA was performed. With a sample size of 80 and an alpha of 0.05, we had 80% power to detect a
small effect size \( (f = 0.10) \). Prior research using the PCOQ has not compared the
importance ratings for different symptoms; thus, we do not have an empirical basis for
estimating the effect size.
CHAPTER 3. RESULTS

3.1 Preliminary Analyses

Descriptive statistics. Participant characteristics are shown in Table 2. On average, participants were 55.5 years of age ($SD = 11.26$), had 15.03 years of education ($SD = 2.42$), and were 3.93 years from their stage IV breast cancer diagnosis ($SD = 3.64$). The majority of participants were Caucasian (91.3%), married or partnered (66.3%), and earning an annual household income of $51,000 or higher (55.1%). Regarding cancer treatment history, the majority of participants had received chemotherapy (86.3%), hormonal therapy (85.0%), radiation (65.0%), and a mastectomy (66.3%). The most prevalent medical comorbidities reported by participants were hypertension (32.5%) and arthritis (25.0%). There was an 87% acceptance rate for study participation (83 patients consented to participate out of 95 contacted by phone), and a 96% completion rate for those who consented to participate (see Figure 4).

Following Winsorization transformation of four outliers in the main study variables to 3 standard deviations of the mean, their means, standard deviations, and ranges were examined (see Table 4). All values were within the ranges expected for the measures. Cronbach’s alphas for symptom assessments also were examined (see Table 4). Internal consistency reliability was good for PROMIS-measured symptoms ($\alpha = 0.83$ to 0.95) and MSAS-measured symptoms ($\alpha = 0.89$ to 0.95), and adequate for the
hot flashes assessment (α = 0.75). The limited information regarding metastatic breast
cancer patients’ symptom experiences precludes comparisons of the current mean
symptom levels of nausea, neuropathy, swelling, and hot flashes to prior literature. Total
scores for symptoms measured with PROMIS instruments (i.e., pain, fatigue, sleep
problems, cognitive problems, anxiety, and depressive symptoms) were uploaded to the
scoring service on the PROMIS assessment center website (www.assessmentcenter.net),
and T-scores were derived for each symptom. The scoring service returned spreadsheets
for each symptom with each participant’s calibrated T-scores. These T-scores were
calibrated to the cancer sample when available (i.e., anxiety, cognitive concerns,
depressive symptoms, and fatigue). For measures of pain and sleep disturbance, data
from a cancer sample were unavailable; thus, T-scores were calibrated to the wave 1
general population sample.

The cancer calibration sample consisted of 1,754 participants that completed
PROMIS measures on a web-based polling platform and self-reported a cancer diagnosis
(Cella et al., 2010). The cancer stage of participants in the cancer population sample has
not been reported. The wave 1 general population sample consisted of 21,133
participants (including clinical samples such as those who reported cancer) who were
52% female with a mean age of 50 years, and this sample has been shown to be
representative of the general U.S. population (Cella et al., 2010; Liu et al., 2010). The
means and standard deviations for the current sample’s calibrated T-scores for PROMIS
symptom measures are reported in Table 5. Mean calibrated T-scores for all PROMIS
symptom measures were within one standard deviation of 50 (i.e., the average for the
respective calibration sample). Additionally, unpublished results from a study of 634
metastatic breast cancer patients showed average T-scores for PROMIS measures of pain, fatigue, sleep disturbance, anxiety, depressive symptoms, and cognitive function within 1 standard deviation of those reported in the current sample (R. Jensen, personal communication, April 8, 2016). Regarding symptom importance ratings, there are no prior reports in cancer patients to serve as a comparison.

**Tests of assumptions of cluster analysis and ANOVA.** None of the data were missing. Data were screened for outliers (i.e., z-scores +/- 3), and Winsorization transformation was employed on four outliers to reduce the influence of these extreme values while still representing the sample distribution (Tukey, 1962) (see Table 3). After Winsorization, the normality of symptom ratings and symptom importance ratings was examined with skewness and kurtosis indices (see Table 4). Skewness and kurtosis indices were all less than the absolute values of 3.0 and 8.0 respectively; therefore, the data were normally distributed (Kline, 2011). The assumption of sphericity for a repeated-measures ANOVA on ratings of the importance of the ten symptoms was examined with Mauchly’s test of sphericity. Mauchly’s test was significant ($W = 0.06$, $\chi^2(44, N = 80) = 213.75, p < 0.05$); therefore, the assumption of sphericity for a repeated-measures ANOVA was violated. In other words, the variances of the differences between symptom importance ratings were not equal. This violation is common when there are more than three repeated measures, and patients rated the importance of ten symptoms. When the assumption of sphericity is violated, the $F$-ratio should be interpreted with caution, and the appropriate correction to the degrees of freedom should be employed (Warner, 2013). The Greenhouse-Geisser correction to degrees of freedom was appropriate because $\varepsilon < 0.75$ (Girden, 1992).
3.2 Analyses for Aim 1

To examine symptoms that co-occurred with cognitive complaints in metastatic breast cancer patients, a hierarchical agglomerative cluster analysis was performed with squared Euclidean distance and weighted average linkage. Results of this cluster analysis are shown in Figures 5 and 6. The number of clusters may be determined by examining the dendrogram (see Figure 5) and determining the “best cut” at the height of the dendrogram below which the changes in fusion levels are smaller relative to the changes above the cut (Everitt et al., 2001). The best cut for the current cluster analysis is approximately at a height of 115 on the dendrogram (see Figure 6). Findings partially supported my hypothesis that cognitive symptoms would cluster with fatigue, sleep problems, anxiety, depressive symptoms, and pain. Specifically, cognitive symptoms clustered with all of these symptoms except for pain. Another cluster consisted of pain, neuropathy, and nausea. Hot flashes and swelling failed to cluster with other symptoms.

There were three outlying symptom scores that were Winsorized prior to the cluster analysis. A sensitivity analysis was performed such that another hierarchical agglomerative cluster analysis with squared Euclidean distance and weighted average linkage was conducted with the non-Winsorized values. Results of this cluster analysis are shown in Figures 7 and 8. Without reducing the influence of extreme values for swelling, anxiety, and depressive symptoms, the cluster of symptoms co-occurring with cognitive complaints did not change. However, swelling clustered with pain, neuropathy, and nausea. Hot flashes again failed to cluster with other symptoms.
3.3 Analyses for Aim 2

To assess differences between importance ratings for the ten examined symptoms, a repeated-measures ANOVA was performed. Because the assumption of sphericity was violated, the Greenhouse-Geisser correction to the degrees of freedom was employed. Results of the repeated-measures ANOVA are shown in Table 6. Symptom importance ratings were significantly different among the ten symptoms, $F(5.8, 457.97) = 13.77, p < 0.001$; the corresponding effect size for this difference was an $\eta^2$ of 0.15. It is noteworthy that after the Greenhouse-Geisser correction was applied to the degrees of freedom for $F$, the obtained $F$ remained statistically significant.

Planned simple contrasts were conducted to compare mean symptom importance for cognitive symptoms (i.e., thinking problems) to each of the nine other symptoms (see Table 7 and Figure 9). The importance of cognitive symptoms was significantly greater than anxiety ($MD = 1.11, p < 0.05$), depressive symptoms (i.e., sadness) ($MD = 1.33, p < 0.05$), neuropathy ($MD = 1.98, p < 0.05$), swelling ($MD = 2.76, p < 0.05$), nausea ($MD = 1.44, p < 0.05$), and hot flashes ($MD = 2.28, p < 0.05$). There were no significant differences in importance for cognitive symptoms, pain, fatigue, and sleep problems.

There was one outlying symptom importance value that was Winsorized prior to the repeated-measures ANOVA and planned contrasts. A sensitivity analysis was performed with the non-Winsorized value, and the results did not change.
CHAPTER 4. DISCUSSION

Broadly, the purpose of this study was to characterize metastatic breast cancer patients’ symptom experiences and treatment priorities with respect to cognitive and other symptoms. Because recent advances in treatment have resulted in increased longevity for metastatic breast cancer patients, these patients may live for years with cognitive problems affecting their quality of life and functional capacity. However, little research has examined cognitive symptoms in metastatic breast cancer patients and their co-occurrence with other common symptoms. Additionally, symptom importance, or the degree to which symptoms are viewed as treatment priorities, has not been examined in any cancer population. Understanding metastatic breast cancer patients’ symptom experiences and treatment priorities is a crucial step in developing patient-centered approaches to symptom management. Such approaches may improve the quality and cost of care as well as patients’ adherence to treatment recommendations.

4.1 Symptom Cluster Findings

The first aim of the study was to examine the extent to which cognitive complaints cluster with other common symptoms (i.e., fatigue, sleep disturbance, depressive symptoms, anxiety, pain, hot flashes, lymphedema, neuropathy, and nausea) in metastatic breast cancer patients. I hypothesized that cognitive complaints would cluster with fatigue, sleep disturbance, depressive symptoms, anxiety, and pain. This hypothesis
was informed by limited evidence from prior studies of metastatic breast cancer patients’ symptom experiences (Aranda et al., 2005; Bender et al., 2005), the finding that pain tends to cluster with cognitive complaints in people with other cancer types (Fan et al., 2007), and theoretical and empirical support for common psychological and biological mechanisms underlying a psychoneurological symptom cluster (Bower et al., 2005; Dong et al., 2014; Kim et al., 2012; Koopman et al., 2002; Miaskowski et al., 2004; Patel et al., 2015; Seigers & Fardell, 2011; Wang et al., 2010). Findings from the current study partially supported my hypothesis. Cognitive complaints were found to cluster with fatigue, sleep disturbance, depressive symptoms, and anxiety. A separate symptom cluster consisted of pain, neuropathy, and nausea. Hot flashes and swelling failed to cluster.

The symptom clusters found in the current study are partially consistent with findings from the symptom cluster literature with various cancer populations (Bender et al., 2005; Bruera, 2013; Chen et al., 2013; Fan et al., 2007; Jiménez et al., 2011). To my knowledge, only one prior study has examined cognitive symptoms and symptom clusters in metastatic breast cancer patients, and findings indicated that loss of concentration clustered with anxiety, depressive symptoms, fatigue, and decreased physical strength (Bender et al., 2005). Sleep disturbance was also assessed in this prior study, but failed to cluster. When examining the symptom cluster literature on advanced cancer patients, anxiety and depressive symptoms appear to be the most consistently obtained symptom cluster (Bender et al., 2005; Bruera, 2013; Cheung, Le, & Zimmermann, 2009; Edward Chow, Fan, Hadi, & Filipczak, 2007; E Chow et al., 2008; Dong et al., 2014; Fan et al., 2007; Hird et al., 2010; Jiménez et al., 2011; Kirkova, Aktas, Walsh, Rybicki, & Davis,
Occasionally, anxiety and depressive symptoms have also been found to cluster with other symptoms such as sleep problems (Jiménez et al., 2011; Walsh & Rybicki, 2006) and fatigue (Chen et al., 2013) in advanced cancer patients. Regarding cognitive symptoms, memory difficulties have been found to cluster with pain, fatigue, sleep problems, sadness, and neuropathy in several studies examining the validity of the M.D. Anderson Symptom Inventory among medically and ethnically diverse cancer patients (Cleeland et al., 2000; Fan et al., 2007; Okuyama et al., 2003; Wang et al., 2006; Wang et al., 2004). In addition, a study of non-metastatic breast cancer patients receiving chemotherapy or radiation found a psychoneurological symptom cluster consisting of cognitive symptoms, depressed mood, fatigue, insomnia, and pain (Kim, Barsevick, Tulman, & McDermott, 2008).

Recently, biological and psychological mechanisms underlying the psychoneurological symptom cluster in non-metastatic breast cancer patients have been explored. These mechanisms include oxidative stress, telomere shortening, DNA damage, proinflammatory cytokines, HPA axis dysfunction, and perceived stress (Kim et al., 2012; Starkweather et al., 2013; Wood & Weymann, 2013). Oxidative stress and telomere shortening—two factors involved in DNA damage—have been shown to be associated with cancer and chemotherapy treatment (Calado & Young, 2012), memory impairments and decreased grey matter density in breast cancer survivors (Conroy et al., 2013), muscle weakness and fatigue in patients with various cancer types (Gilliam & St. Clair, 2011), and major depressive disorder in non-cancer populations (Wolkowitz et al., 2011). Elevated proinflammatory cytokines have been associated with fatigue and cognitive symptoms in breast cancer patients (Patel et al., 2015), greater symptom burden
in lung cancer patients (Wang et al., 2010), and depressive symptoms in patients with various cancer types (Dunn et al., 2013). HPA axis dysregulation has also been found to be significantly associated with chronic fatigue in breast cancer survivors (Bower et al., 2005), and more sleep disturbance, pain, and depressive symptoms in metastatic breast cancer patients (Koopman et al., 2002). Chronic perceived stress associated with the diagnosis and management of cancer has been correlated with increased proinflammatory cytokines, HPA axis dysregulation, fatigue, sleep disturbance, and pain in patients with metastatic breast cancer and other cancer types (Bower et al., 2009; Koopman et al., 2002).

In the present study, the cluster of symptoms including cognitive complaints (i.e., cognitive complaints, fatigue, sleep problems, anxiety, and depressive symptoms) seems to be consistent with a psychoneurological symptom cluster. Pain may not have clustered with the other psychoneurological symptoms due to differences in measurement, as pain was assessed with a 3-item PROMIS measure and the other symptoms in the psychoneurological symptom cluster were assessed with 4-item PROMIS measures. Instead, pain clustered with symptoms that were assessed with 3-item MSAS measures. However, differences in variance between pain and the symptoms assessed with the 4-item PROMIS measures were small (i.e., 3-13 for pain, 4-20 for fatigue, sleep problems, and cognitive problems, and 4-16 for anxiety and depressive symptoms) and MSAS assessments had smaller ranges (i.e., 0-3 for nausea and 0-3.67 for neuropathy). Also, z scores were computed for each of the symptom scores prior to the cluster analysis in order to place the symptom scores on the same metric.
Alternatively, pain may have clustered with neuropathy instead of the other psychoneurological symptoms because participants may have been experiencing neuropathic pain. In non-metastatic breast cancer patients treated with certain chemotherapies (i.e., taxanes), the numbness and tingling sensations of neuropathy predict later development of neuropathic pain (Reyes-Gibby, Morrow, Buzdar, & Shete, 2009). The progression of neuropathy to neuropathic pain increases with multiple lines of chemotherapy (Swain & Arezzo, 2008), and some metastatic breast cancer patients in our sample may have received multiple lines of chemotherapy. In addition, nausea may have clustered with neuropathy and pain because it is also a common side effect of chemotherapies (Hesketh 2008). However, taxane chemotherapies that are often associated with neuropathy are less emetogenic than other types of chemotherapies (Ghersi et al., 2015). Future research may benefit from exploring relationships between symptom clusters and types of ongoing chemotherapy treatments as well as other ongoing treatments among metastatic breast cancer patients. In addition, assessing pain types (e.g., neuropathic pain) would extend the current findings.

With the exception of sleep problems, the symptoms that clustered with cognitive complaints are consistent with findings from the only other published study to conduct a cluster analysis on symptoms in metastatic breast cancer patients (Bender et al., 2005). Findings from the symptom cluster literature are often slightly inconsistent; for instance, symptom clusters derived with different statistical methodologies—even from the same sample—are found to be unstable (Dong et al., 2014). Because cluster analysis is a data-driven exploratory statistical approach, current findings of symptoms clusters may be specific to this sample and should be replicated in future research. Differences in
measurement can also contribute to differential findings across studies. Most symptoms in the current study were assessed with validated measures, while single-item measures of menopausal symptoms were used in the prior study of symptom clusters in metastatic breast cancer patients (Bender et al., 2005).

4.2 Symptom Importance Findings

Whereas findings from the first aim provide information about co-occurring symptoms, findings from the second aim increase our understanding of metastatic breast cancer patients’ treatment priorities. Specifically, the second aim was to compare patient ratings of symptom importance for cognitive symptoms to those of other symptoms (i.e., pain, fatigue, sleep disturbance, depression, anxiety, nausea, lymphedema, hot flashes, and neuropathy). There was no empirical or theoretical basis for a hypothesis; therefore, this aim was exploratory. Patients were found to rate cognitive symptoms as significantly more important than anxiety, depressive symptoms, neuropathy, swelling, nausea, and hot flashes. Importance ratings for cognitive symptoms, pain, fatigue, and sleep problems were not significantly different.

The current study was the first to statistically compare ratings of symptom importance for different symptoms in any medical population. Rather than comparing importance ratings, prior research on symptom importance in certain medical populations (i.e., patients with chronic pain and Parkinson’s disease) has found subgroups of patients based on their ratings of symptom importance (Nisenzon et al., 2011; M. E. Robinson et al., 2005). These subgroups typically consist of patients who rate all symptoms as high, moderate, or low in importance. In patients with chronic pain, researchers have also found subgroups of patients who consider pain to be most important (M. E. Robinson et
al., 2005). Thus, significant differences in symptom importance ratings in the current study converge with chronic pain research indicating that some symptoms are considered more important than others.

Several factors may explain the current findings regarding ratings of symptom importance. First, metastatic breast cancer patients may have been more comfortable giving a higher importance rating to cognitive symptoms than anxiety and depressive symptoms because emotional disturbances among cancer patients may be stigmatizing (Holland, 2002; Holland, Kelly, & Weinberger, 2010; Knowles, Chew-Graham, Adeyemi, Coupe, & Coventry, 2015). There are several lines of evidence pointing to stigma associated with emotional disturbances, including cancer patients’ underuse of psychosocial support services (Abbott et al., 2013); one study found that only 14% of a heterogeneous sample of cancer patients reported using psychosocial support services over a period of 6 months, and this sample was moderately distressed on average (McDowell, Occhipinti, Ferguson, & Chambers, 2011). Additionally, many cancer patients endorse barriers to support services use that may be related to stigma, such as discomfort with seeking counseling and the belief that counseling may be more upsetting than helpful (Eakin & Strycker, 2001).

Second, some of the current differences in symptom importance ratings mirrored differences in symptom severity; specifically, usual levels of cognitive complaints, pain, fatigue, and sleep problems appeared to be higher in severity than neuropathy, swelling, nausea, and hot flashes. The mean severity ratings for cognitive complaints, pain, fatigue, and sleep problems fell within 40% of the total possible range, while those for neuropathy, hot flashes, nausea, and swelling were lower and fell within 15-30% of the
total possible range. However, the clinical significance of this numerical difference is unclear.

Third, high importance ratings for pain, sleep disturbance, and fatigue as well as cognitive symptoms may reflect the distressing quality of these symptoms. Pain, sleep disturbance, and fatigue have been found to be highly prevalent and distressing symptoms among patients with various advanced cancers (Butt, Wagner, et al., 2008; Reilly et al., 2013). In addition, when cancer patients in two studies ranked symptoms according to the importance of monitoring them, fatigue was consistently ranked as most important, and pain was among the top 5-6 most important (Butt, Rosenbloom, et al., 2008; Cella et al., 2011; Reeve et al., 2014). Sleep disturbance and cognitive problems were only examined in one of these studies. Of 533 advanced cancer patients who ranked 11 symptoms on the importance of monitoring them, 48% ranked fatigue as most important (ranked 1st), 16% ranked insomnia as most important (ranked 5th), 11% ranked pain as most important (ranked 6th), and only 3% ranked cognitive problems as most important (ranked 11th) (Cella et al., 2011; Reeve et al., 2014). Further research is needed to determine the degree to which cognitive symptoms are considered a clinical priority among advanced cancer patients.

Fourth, the symptoms rated as equally important in this study (i.e., cognitive symptoms, pain, fatigue, and sleep problems) may be difficult to distinguish from one another at times. There may be common biological and psychological mechanisms involved in these symptoms such as oxidative stress, telomere shortening, DNA damage, proinflammatory cytokines, HPA axis dysfunction, and perceived stress (Kim et al., 2012; Starkweather et al., 2013; Wood & Weymann, 2013). These symptoms have also
been found to exacerbate each other and have a compounding effect on health and quality-of-life outcomes in cancer populations (Cleeland, 2007; Dodd et al., 2010; Husain, Myers, Selby, Thomson, & Chow, 2011; Miaskowski et al., 2006). Although statistically significant differences in importance ratings were obtained in the present sample, it is unclear whether these are clinically meaningful differences. Mean importance ratings for cognitive symptoms, pain, fatigue, and sleep problems ranged from 7.23 to 7.96, whereas mean importance ratings for anxiety and depressive symptoms ranged from 6.36 to 6.58 and those for neuropathy, swelling, and hot flashes ranged from 4.93 to 5.71. There is currently no established standard for a clinically meaningful difference in symptom importance; therefore, the present findings are difficult to interpret. Future research may determine clinically meaningful differences by examining levels of symptom importance that predict patient-centered care outcomes such as adherence to treatment recommendations. Furthermore, mixed-methods designs may examine differences between patient’s ratings and rankings of symptom importance and elucidate patients’ decision-making processes for determining symptom importance.

4.3 Synthesis of Findings for Symptom Clusters and Importance

Overall, findings suggest that assessing symptom clusters and symptom importance provides a more comprehensive picture of symptom experiences. Interestingly, cognitive symptoms were found to cluster with anxiety, depressive symptoms, sleep disturbance, and fatigue, but cognitive symptoms were rated as significantly more important than anxiety and depressive symptoms. Therefore, the co-occurrence of symptoms in metastatic breast cancer patients does not necessarily indicate that these symptoms are perceived as equally important to treat. It is possible that
focusing treatment on physical symptoms is more palatable to some cancer patients compared to psychological symptoms because of stigma associated with anxiety and depressive symptoms (Holland, 2002; Holland et al., 2010). Alternatively, physical symptoms may be more noticeable than psychological symptoms for patients with less insight into their psychological state. Again, differences in importance ratings across symptoms should be cautiously interpreted until further studies explore the degree to which these differences are clinically meaningful.

4.4 Research and Clinical Implications

The current findings regarding symptom clusters and importance have a number of implications for future research and clinical practice. Theoretically, patient ratings of symptom importance inform patient-centered care by providing information about patients’ treatment priorities (Zeppieri et al., 2012). There is some evidence that patient-centered care improves the quality and cost of care as well as patients’ adherence to treatment recommendations, although findings are mixed (Rathert, Wyrwich, & Boren, 2013; J. H. Robinson, Callister, Berry, & Dearing, 2008). Increased adherence to treatment recommendations in patient-centered care may be due in part to focusing on the patients’ priorities. As an example, motivational interviewing is an effective behavioral intervention for improving treatment adherence which has a focus on patients’ priorities. A central component of motivational interviewing is assisting patients in generating motivation to change based on their own values—what is important to them (Rollnick & Miller, 1995). This approach from motivational interviewing may be applied to future symptom management interventions. Such interventions may assist patients in generating motivation to adhere to treatment recommendations by tailoring those
recommendations to target symptoms rated as most important. Furthermore, future research may compare adherence between patients assigned to symptom management interventions that are tailored or untailored to symptoms rated as highly important.

Another potential direction for future research is testing treatments targeting one or more symptoms that cluster with other symptoms and are rated as highly important. Symptoms in a cluster may exacerbate one another (Cleeland, 2007; Dodd et al., 2010; Husain et al., 2011; Miaskowski et al., 2006; Starkweather et al., 2013); therefore, treatment focused on one symptom rated as highly important may still provide patients some relief from the other symptoms in the cluster and enhance adherence. For example, Cognitive Behavioral Therapy for Insomnia (CBT-I) is an evidence-based treatment for insomnia (Okajima, Komada, & Inoue, 2011). If CBT-I can be used to alleviate sleep disturbance in metastatic breast cancer patients, a symptom rated as highly important, the effect of sleep disturbance on other symptoms in the cluster—including anxiety and depressive symptoms—may dissipate. However, when a sample of cancer patients has heterogeneous treatment priorities, these individual differences may lessen the effects of one treatment approach—such as CBT-I—on adherence to treatment recommendations and severity of related symptoms. Therefore, single-subject designs or micro-randomized trials may provide an avenue for tailoring treatment to patients’ priorities while still maintaining experimental control.

4.5 Limitations, Strengths, and Future Directions

Limitations of the current study should be noted. With the exception of medical record data (i.e., age, diagnosis date, and cancer treatment history), all measures were self-report. Self-reported data are vulnerable to biases including a desire to comply with
study expectations, social desirability, or an inability to accurately remember symptoms and their severity. Inaccurate recall may have been a particular issue for this study because participants with cognitive complaints may have had more difficulty remembering the severity of their symptoms over the last one or two weeks. However, many of these symptoms (e.g., pain) are inherently subjective experiences with self-report as the primary method of assessment.

Another limitation is the use of multiple brief symptom assessments. Although the measures have shown adequate reliability and validity, they may not fully capture the complexity of symptom constructs. The use of multiple assessments resulting in a 45-minute interview may also be overly burdensome for some patients with metastatic cancer. However, interviews of this length have been performed successfully in prior research with metastatic breast cancer patients (Mosher & DuHamel, 2012). Furthermore, the length of the interview in the current study seemed to be feasible considering the high consent and completion rates (see Figure 4).

Our sample was primarily Caucasian and only included women recruited from one academic cancer center in the Midwest; thus our findings may not generalize to men with the same disease, ethnic minorities, or patients in other geographical or institutional settings. Also, participants in our study had attained some college education on average ($M = 15.02$ years of education), although a wide range of education was reported (11-20 years). Regarding socio-economic status, one-fifth of the sample reported the lowest (i.e., $0-$30,999 per year) and highest (i.e., $100,000 +$) income levels, and the most common income category was middle class ($51,000 - $99,999). Therefore, although
this sample had a range of education and income levels, our findings may not generalize to patients of lower socioeconomic status.

Another potential limitation is the use of cluster analysis, a data driven, exploratory analytical approach; therefore, findings warrant replication. However, an exploratory approach was appropriate considering the paucity of research on symptom clusters in metastatic breast cancer patients. The analytic approach was also strengthened by using weighted average linkage as the clustering method rather than Ward’s method; Ward’s method forces clusters to be similar sizes and is sensitive to outliers (McQuitty, 1966; Miaskowski et al., 2006).

The cross-sectional nature of our study precludes examining change in symptom clusters or patient ratings of symptom importance, both of which may be temporally unstable. Furthermore, although we collected information on cancer treatments, unexamined factors such as contact with a physician or adherence to medications may also be related to symptom clusters and importance.

Despite limitations, the current study also has several strengths. The study sample consisted of metastatic breast cancer patients, a population which has received scarce research attention despite their high symptom burden and increased longevity. Additionally, the majority of self-report measures have demonstrated good validity and reliability. There was also a considerably high response rate, as 87% (83/95) of patients contacted by phone consented to participate, and 96% (80/83) of consenting participants completed the assessment.

Future research on symptom clusters and symptom importance in cancer populations may build upon the current findings. Longitudinal designs may track
symptom clusters and symptom importance to test the temporal stability of these constructs. Future designs may also include objective measurements of symptoms when possible (e.g., sleep disturbance) or supplement self-report measures with observer (e.g., physician, caregiver) ratings. Treatment priorities may also be assessed with other methods such as asking participants to rank order their symptoms by importance, and differences among such measurement methods may be explored. A mixed-methods approach to this research may provide quantitative information about symptoms rank-ordered by importance, and qualitative information about participants reasoning for those rankings. Finally, future research may benefit from assessing other disease and quality-of-life factors along with symptom clusters and importance to generate a model of factors influencing symptom relationships and patients’ treatment priorities. Such models may change at different points in the illness trajectory (e.g., diagnosis, treatment, end of life).
CHAPTER 5. CONCLUSION

Many breast cancer patients experience cognitive symptoms related to cancer and its treatment, but our current understanding of cognitive symptoms in metastatic breast cancer patients is limited. The present study addresses gaps in our understanding of symptoms co-occurring with cognitive complaints in this population and the patient-rated importance of cognitive complaints as compared to other symptoms. In this sample, cognitive complaints clustered with anxiety, depressive symptoms, sleep problems, and fatigue. Additionally, cognitive symptoms were rated as significantly more important than anxiety, depressive symptoms, neuropathy, swelling, nausea, and hot flashes, and importance ratings did not differ among cognitive symptoms, pain, fatigue, and sleep problems. Although pain did not cluster with cognitive symptoms, fatigue, and sleep problems, it was still rated as equally important. Although anxiety and depressive symptoms clustered with cognitive symptoms, fatigue, and sleep problems, they were both rated as significantly less important. However, the differences in importance ratings were small. Future research may provide a more comprehensive understanding of symptom experiences and treatment priorities by using alternative and mixed methods to assess treatment priorities, exploring how symptom clusters and symptom importance may change over time, and developing a model of symptom experiences with other important outcomes such as patient adherence to interventions. Developing patient-
centered approaches to symptom management based on symptom severity and treatment priorities has the potential to impact patients’ quality of life as well as improve health care quality and patients’ adherence to treatment recommendations.
REFERENCES


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Appendix A  Measures

Cognitive Screening for Patients

I would like to ask you some questions that ask you to use your memory. I am going to name three objects. Please wait until I say all three words, then repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. Please repeat these words for me: APPLE—TABLE—PENNY. (Interviewer may repeat words 3 times if necessary but repetition not scored.)

Did patient correctly repeat all three words?  Yes  No  Incorrect  Correct

1. What year is this?  0  1
2. What month is this?  0  1
3. What day of the week?  0  1
What were the three objects I asked you to remember?
4. Apple =  0  1
5. Table =  0  1
6. Penny =  0  1
Demographic Information

1. What race or ethnicity do you consider yourself to be?
   
   1 = non-Hispanic White
   
   2 = African American/Black
   
   3 = Asian
   
   4 = Hispanic
   
   5 = Native Hawaiian or other Pacific Islander
   
   6 = American Indian/Alaskan Native
   
   7 = Other

2. What was the last grade you completed in school?

3. What is your marital status?
   
   1 = Married
   
   2 = Living with partner
   
   3 = Separated
   
   4 = Single
   
   5 = Divorced
   
   6 = Widowed
4. Thinking about your yearly household income, before taxes, is it $21,000 or higher?

   1 = $0 - $10,999

   if no, Is it $11,000 or higher? 2 = $11,000 - $20,999

   if yes, Is it $31,000 or higher? 3 = $21,000 - $30,999

   if yes, Is it $41,000 or higher? 4 = $31,000 - $50,999

   if yes, Is it $51,000 or higher? 5 = $50,000 - $99,999

   if yes, Is it $100,000 or more? 6 = $100,000 +

5. What is your current employment status?

   1 = Employed full-time

   2 = Employed part-time

   3 = Student

   4 = Homemaker

   5 = Retired

   6 = Unemployed, looking for paid work

   7 = Unemployed due to disability

   8 = Other
Information Collected from Medical Record

(1) Age: _____

(2) Date(s) of Breast Cancer Diagnosis and Disease Stage at Diagnosis:

a. ____/____/_____; Disease Stage (circle one): 0 1 2 3 4
b. ____/____/_____; Disease Stage (circle one): 0 1 2 3 4
c. ____/____/_____; Disease Stage (circle one): 0 1 2 3 4

Treatments for Breast Cancer (check all that have been received): 1 = yes, 0 = no

☐ Mastectomy
☐ Lumpectomy
☐ Surgery to remove metastases
☐ Bilateral oophorectomy
☐ Other surgery (specify): ______________
☐ Chemotherapy
☐ Radiation
   Did the patient receive radiation to the brain? ___yes ___no
☐ Targeted therapy (e.g., trastuzumab, bevacizumab)
☐ Hormonal therapy (e.g., Tamoxifen)
☐ Bisphosphonates
☐ Other (please specify): ______________________________
Medical Conditions

I am going to read you a list of chronic health problems that some people have. Please tell me if a doctor or another health care worker has diagnosed you with or treated you for one of the following medical problems in the past 3 years.

<table>
<thead>
<tr>
<th>No = 0</th>
<th>Yes = 1</th>
<th>Don’t know or refused to answer = 99</th>
</tr>
</thead>
</table>

1. In the past 3 years, have you been diagnosed or treated for asthma, emphysema, or chronic bronchitis
2. In the past 3 years, have you been diagnosed or treated for high blood pressure or hypertension
3. High blood sugar or diabetes
4. Arthritis or rheumatism (inflammation of the joints)
5. Angina, heart failure, or other types of heart disease
6. Stroke, seizures, Parkinson’s disease, or another neurological condition
7. Liver disease
8. Kidney or renal disease
9. Cancer other than breast cancer or skin cancer

if Yes [List types: ________________________________]
**PROMIS Applied Cognition – General Concerns**

In the past 7 days…

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely (Once)</th>
<th>Sometimes (Two or three times)</th>
<th>Often (About once a day)</th>
<th>Very Often (Several times a day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My thinking has been slow…</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2. It has seemed like my brain was not working as well as usual…</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3. I have had to work harder than usual to keep track of what I was doing…</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4. I have had trouble shifting back and forth between different activities that require thinking…</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
**PROMIS Emotional Distress – Depression**

In the past 7 days…

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I felt worthless…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. I felt helpless…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. I felt depressed…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. I felt hopeless…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**PROMIS Emotional Distress – Anxiety**

In the past 7 days…

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I felt fearful…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. I found it hard to focus on anything other than my anxiety…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
3. My worries overwhelmed me…

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. I felt uneasy…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**PROMIS Fatigue**

During the past 7 days…

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I feel fatigued…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. I have trouble starting things because I am tired…</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

In the past 7 days…

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. How run-down did</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
PROMIS Sleep Disturbance

In the past 7 days…

1. My sleep quality was…
   Very poor = 1    Poor = 2    Fair = 3    Good = 4    Very Good = 5

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. My sleep was refreshing…</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. I had a problem with my sleep…</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. I had difficulty falling asleep…</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
PROMIS Pain Intensity

In the past 7 days...

<table>
<thead>
<tr>
<th>Question</th>
<th>No pain</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How intense was your pain at its worst?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. How intense was your average pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. What is your level of pain right now?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
MSAS Selected items and Carpenter et al. (1998)

1. Have you had **nausea** in the past week?
   
   No = 0, skip to question 2. Yes = 1
   
   how often did you have it?
   
   Rarely = 1 Occasionally = 2 Frequently = 3 Almost constantly = 4
   
   how severe was it usually?
   
   Slight = 1 Moderate = 2 Severe = 3 Very Severe = 4
   
   how much did it distress or bother you?
   
   Not at all = 0 A little bit = 1 Somewhat = 2 Quite a bit = 3 Very much = 4

2. Have you had **numbness/tingling in your hands/feet** in the past week?
   
   No = 0, skip to question 3. Yes = 1
   
   how often did you have it?
   
   Rarely = 1 Occasionally = 2 Frequently = 3 Almost constantly = 4
   
   how severe was it usually?
   
   Slight = 1 Moderate = 2 Severe = 3 Very Severe = 4
   
   how much did it distress or bother you?
   
   Not at all = 0 A little bit = 1 Somewhat = 2 Quite a bit = 3 Very much = 4
3. Have you had swelling of arms or legs in the past week?
   No = 0, skip to question 4.       Yes = 1

   how severe was it usually?
   Slight = 1     Moderate = 2     Severe = 3     Very Severe = 4

   how much did it distress or bother you?
   Not at all = 0   A little bit = 1   Somewhat = 2   Quite a bit = 3   Very much = 4

4. Have you experienced hot flashes in the past 2 weeks?
   No = 0, skip to next measure.       Yes = 1

   how severe were they usually?
   Not at all = 0    Slightly = 1   Moderately = 2    Quite a bit = 3    Extremely = 4

   how much did the hot flashes bother you on a scale from 0 to 10, 0 being not at all bothered and 10 being extremely bothered?

   0  1  2  3  4  5  6  7  8  9  10
   Not at all bothered          Extremely bothered
PCOQ-Revised for metastatic breast cancer

Many people experience pain, fatigue (i.e. feeling tired), anxiety, and other symptoms as a result of their medical condition. We would like to understand how you have been impacted in each of these areas. We would also like to learn more about what you want your treatment to do for you.

First, we would like to know your **USUAL** levels of pain, fatigue, anxiety, and other symptoms.

On a scale of 0 (none) to 10 (worst imaginable) please indicate your **usual level** (during the past week) of…

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>_____</td>
</tr>
<tr>
<td>Swelling of arms or legs</td>
<td>_____</td>
</tr>
<tr>
<td>Fatigue (or tiredness)</td>
<td>_____</td>
</tr>
<tr>
<td>Nausea</td>
<td>_____</td>
</tr>
<tr>
<td>Anxiety</td>
<td>_____</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>_____</td>
</tr>
<tr>
<td>Sadness</td>
<td>_____</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>_____</td>
</tr>
<tr>
<td>Numbness/tingling in hands/feet</td>
<td>_____</td>
</tr>
<tr>
<td>Attention/thinking/memory problems</td>
<td>_____</td>
</tr>
</tbody>
</table>

Patients understandably want their treatment to result in desired or ideal outcomes. Unfortunately, available treatments do not always produce desired outcomes. Therefore, it is important for us to understand what treatment outcomes you would consider successful.

On a scale of 0 (none) to 10 (worst imaginable) please indicate the level each of these areas would have to be at for you to consider treatment **SUCCESSFUL**.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>_____</td>
</tr>
<tr>
<td>Swelling of arms or legs</td>
<td>_____</td>
</tr>
<tr>
<td>Fatigue (or tiredness)</td>
<td>_____</td>
</tr>
<tr>
<td>Nausea</td>
<td>_____</td>
</tr>
<tr>
<td>Anxiety</td>
<td>_____</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>_____</td>
</tr>
<tr>
<td>Sadness</td>
<td>_____</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>_____</td>
</tr>
<tr>
<td>Numbness/tingling in hands/feet</td>
<td>_____</td>
</tr>
<tr>
<td>Attention/thinking/memory problems</td>
<td>_____</td>
</tr>
</tbody>
</table>
Now, we would like to know what you **EXPECT** your treatment to do for you.

On a scale of 0 (none) to 10 (worst imaginable) please indicate the levels you expect following treatment.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Swelling of arms or legs</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

| Fatigue (or tiredness) | Nausea       | _____ |
|------------------------|--------------|

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Hot flashes</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sadness</th>
<th>Sleep problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Numbness/tingling in hands/feet</th>
<th>Attention/thinking/memory problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

Other (please specify)__________

Say, “Is there any other symptom that you have experienced? What level of this symptom do you expect following treatment?”

Finally, we would like to understand how **IMPORTANT** it is for you to see improvement in your pain, fatigue, anxiety, and other symptoms following treatment.

On a scale of 0 (not at all important) to 10 (most important) please indicate how important it is for you to see improvement in your…

<table>
<thead>
<tr>
<th>Pain</th>
<th>Swelling of arms or legs</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

| Fatigue (or tiredness) | Nausea       | _____ |
|------------------------|--------------|

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Hot flashes</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sadness</th>
<th>Sleep problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Numbness/tingling in hands/feet</th>
<th>Attention/thinking/memory problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>_____</td>
<td>____</td>
</tr>
</tbody>
</table>
Figure 1. Model of Interacting Factors Involved in Cognitive Change Associated with Cancer and Its Treatment.
Figure 3. Hypothesized Dendrogram of a Symptom Cluster Involving Cognitive Complaints in Metastatic Breast Cancer Patients.
Medical records screened to identify potentially eligible patients and treating physicians contacted to confirm potential eligibility

Potentially eligible patients mailed an introductory letter and consent form (N = 107)

Could not be reached by phone (N = 12)

1-2 weeks after mailing, RA contacted patients to describe study, administer cognitive screener, and obtain informed consent (N = 95)

Those with 3+ errors on cognitive screener were ineligible (N = 2)

Refused participation (N = 10)
Reason:
• Too busy (N = 5)
• Too ill (N = 3)
• Already participating in another study (N = 1)
• Too emotionally difficult (N = 1)

45-minute phone assessment scheduled for eligible, consenting patients (N = 83)

Unable to reach for interview (N = 3)

Completed phone assessment (N = 80)

Figure 4. Flow Chart of Study Procedures.
Figure 5. Cluster Dendrogram. One value each for swelling, anxiety, and depressive symptoms was Winsorized prior to this analysis.
Figure 6. Cluster Dendrogram with Clusters Boxed. One value each for swelling, anxiety, and depressive symptoms was Winsorized prior to this analysis.
Figure 7. Cluster Dendrogram using non-Winsorized Variables.
Figure 8. Cluster Dendrogram using non-Winsorized Variables with Clusters Boxed.
Figure 9. Bar Graph of Mean Symptom Importance Ratings with 95% Confidence Interval Error Bars. One value for fatigue importance was Winsorized prior to this analysis.
Table 1. Cognitive Domains found to be Impaired among Breast Cancer Survivors in Meta-Analyses. *Found to be a significant deficit. Findings in red text are inconsistent with findings in the most recent meta-analysis. N/A = domain not assessed in the meta-analysis.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Processing speed*</td>
<td>Processing speed</td>
<td>Processing speed</td>
<td>Processing speed*</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Executive function*</td>
<td>Executive function</td>
<td>Executive function*</td>
<td>Executive function*</td>
<td>Executive function</td>
<td></td>
</tr>
<tr>
<td>Attention*</td>
<td>Attention</td>
<td>Attention</td>
<td>Attention</td>
<td>Attention</td>
<td></td>
</tr>
<tr>
<td>Motor function*</td>
<td>Motor function</td>
<td>Motor function*</td>
<td>Motor function</td>
<td>Motor function</td>
<td></td>
</tr>
<tr>
<td>Short-term memory*</td>
<td>N/A</td>
<td>Short-term memory*</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Language</td>
<td>Language*</td>
<td>Language*</td>
<td>Language</td>
<td>Language*</td>
<td></td>
</tr>
<tr>
<td>Long-term memory</td>
<td>N/A</td>
<td>Long-term memory*</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>Visuospatial function*</td>
<td>Visuospatial function</td>
<td>Visuospatial function</td>
<td>Visuospatial function*</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Participant Characteristics ($N = 80$). SD = standard deviation.  aAfrican American/Black, Hispanic, and other.  bHistory of bladder cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55.5 (11.26)</td>
<td>32-80</td>
</tr>
<tr>
<td>Years of education</td>
<td>15.03 (2.42)</td>
<td>11-20</td>
</tr>
<tr>
<td>Years since the stage IV breast cancer diagnosis</td>
<td>3.93 (3.64)</td>
<td>.21-19.46</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>73 (91.3%)</td>
<td></td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>7 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Married or partnered, no. (%)</td>
<td>53 (66.3)</td>
<td></td>
</tr>
<tr>
<td>Employed, no. (%)</td>
<td>24 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Household Income, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$0 - $30,999</td>
<td>17 (21.8)</td>
<td></td>
</tr>
<tr>
<td>$31,000 - $50,999</td>
<td>18 (23.1)</td>
<td></td>
</tr>
<tr>
<td>$51,000 - $99,999</td>
<td>26 (33.3)</td>
<td></td>
</tr>
<tr>
<td>$100,000 +</td>
<td>17 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Cancer treatment history, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>69 (86.3)</td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>68 (85.0)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>53 (66.3)</td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>52 (65.0)</td>
<td></td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>36 (45.0)</td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>17 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (32.5)</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>20 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Asthma, emphysema, or chronic bronchitis</td>
<td>9 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Stroke or other neurological condition</td>
<td>3 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Kidney disease</td>
<td>2 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Other cancers $^{b}$</td>
<td>1 (1.3)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Winsorization of Main Study Variable Outliers.  

aMemorial Symptom Assessment Scale (MSAS) average score of symptom severity and distress.

bPROMIS measure total score.  cPatient-Centered Outcomes Questionnaire (PCOQ) symptom importance score.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Original</th>
<th>Winsorized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling (^a)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Anxiety (^b)</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Depressive symptoms (^c)</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue importance (^d)</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4. Descriptive Statistics and Normality Estimates for Main Study Variables. SD = standard deviation.

| Variable                  | Mean  | SD    | Range | Skewness | Kurtosis | Skewness | Kurtosis | Skewness | Kurtosis | Skewness | Kurtosis | Skewness | Kurtosis | Skewness | Kurtosis | Skewness | Kurtosis | Skewness | Kurtosis |
|---------------------------|-------|-------|-------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
| Nausea                    | 0.63  | 0.91  | 0 – 3.00 | 1.12    | -0.07    | 0.95     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Neuropathy                | 1.13  | 1.19  | 0 – 3.67 | 0.39    | -1.44    | 0.89     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Swelling                  | 0.46  | 0.87  | 0 – 3.00 | 1.65    | 1.28     | 0.91     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Hot flashes               | 1.64  | 1.92  | 0 – 7.00 | 0.75    | -0.66    | 0.75     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Pain                      | 6.60  | 2.65  | 3 – 13   | 0.26    | -0.76    | 0.83     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Fatigue                   | 11.39 | 4.31  | 4 – 20   | 0.20    | -0.97    | 0.92     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Sleep problems            | 11.10 | 3.90  | 4 – 20   | 0.48    | -0.43    | 0.84     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Cognitive problems        | 11.43 | 5.11  | 4 – 20   | 0.26    | -1.06    | 0.95     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Anxiety                   | 7.33  | 3.14  | 4 – 16   | 0.51    | -0.85    | 0.86     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Depressive symptoms       | 6.65  | 3.20  | 4 – 16   | 1.39    | 1.19     | 0.90     |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Pain importance           | 7.79  | 2.83  | 0 – 10   | -1.61   | 1.83     |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Fatigue importance        | 7.96  | 2.21  | 2 – 10   | -1.48   | 1.53     |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Anxiety importance        | 6.58  | 3.53  | 0 – 10   | -0.89   | -0.61    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Sadness importance        | 6.36  | 3.48  | 0 – 10   | -0.78   | -0.72    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Neuropathy importance     | 5.71  | 3.57  | 0 – 10   | -0.47   | -1.21    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Swelling importance       | 4.93  | 4.06  | 0 – 10   | -0.07   | -1.72    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Nausea importance         | 6.25  | 4.01  | 0 – 10   | -0.64   | -1.31    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Hot flashes importance    | 5.41  | 3.65  | 0 – 10   | -0.34   | -1.34    |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Sleep importance          | 7.23  | 3.04  | 0 – 10   | -1.11   | 0.07     |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
| Thinking problems         | 7.69  | 3.14  | 0 – 10   | -1.52   | 1.10     |          |          |          |          |          |          |          |          |          |          |          |          |          |          |
Table 5. T Score Means and Standard Deviations for PROMIS-Measured Symptoms.

Scores from the current sample were calibrated based on scores obtained in PROMIS calibration samples. The cancer calibration sample consisted of 1,754 participants that completed PROMIS measures on a web-based polling platform and self-reported a cancer diagnosis (Cella et al., 2010). The cancer stage of participants in the cancer population sample has not been reported. The wave 1 general population sample consisted of 21,133 participants (including clinical samples such as those who reported cancer) who were 52% female with a mean age of 50 years, and this sample has been shown to be representative of the general U.S. population (Cella et al., 2010; Liu et al., 2010). Mean T score of 50 and standard deviation of 10 reflect the mean and standard deviation obtained in calibration samples.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer calibration&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Wave 1 calibration&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Anxiety</td>
<td>51.27</td>
<td>8.82</td>
</tr>
<tr>
<td>Cognitive concerns</td>
<td>41.16</td>
<td>9.97</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>50.42</td>
<td>8.45</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55.39</td>
<td>9.73</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Repeated-Measures ANOVA on Symptom Importance Ratings for Symptoms Assessed with the Modified Patient-Centered Outcomes Questionnaire (PCOQ). \(^a\)df corrected with Greenhouse-Geisser \(\varepsilon\) for violation of sphericity assumption.

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df(^a)</th>
<th>MS</th>
<th>F</th>
<th>(\eta^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>801.75</td>
<td>5.80</td>
<td>138.30</td>
<td>13.77</td>
<td>0.15</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Error</td>
<td>4600.66</td>
<td>457.97</td>
<td>10.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Simple Contrasts Comparing the Importance of Thinking Problems to the Importance of Other Symptoms. SE = standard error. *p < 0.05.

<table>
<thead>
<tr>
<th>Symptom (I)</th>
<th>Symptom (J)</th>
<th>Mean Difference (I – J)</th>
<th>SE</th>
<th>p</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>problems</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bound</td>
</tr>
<tr>
<td>Pain</td>
<td>-0.10</td>
<td>0.41</td>
<td>.810</td>
<td>.810</td>
<td>-0.92</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.28</td>
<td>0.28</td>
<td>.328</td>
<td>.328</td>
<td>-0.83</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.11*</td>
<td>0.37</td>
<td>.004</td>
<td>.004</td>
<td>0.37</td>
</tr>
<tr>
<td>Sadness</td>
<td>1.33*</td>
<td>0.33</td>
<td>.000</td>
<td>.000</td>
<td>0.67</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>1.98*</td>
<td>0.43</td>
<td>.000</td>
<td>.000</td>
<td>1.12</td>
</tr>
<tr>
<td>Swelling</td>
<td>2.76*</td>
<td>0.46</td>
<td>.000</td>
<td>.000</td>
<td>1.84</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.44*</td>
<td>0.49</td>
<td>.005</td>
<td>.005</td>
<td>0.46</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>2.28*</td>
<td>0.36</td>
<td>.000</td>
<td>.000</td>
<td>1.57</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>0.46</td>
<td>0.26</td>
<td>.076</td>
<td>.076</td>
<td>-0.05</td>
</tr>
</tbody>
</table>
Appendix D  Syntax

R Syntax – For Cluster Analysis

install.packages("cluster")
library(cluster)
thesisdata = read.csv(file.choose(), header = TRUE)
#remove non-numeric column
thesisdata.use=thesisdata[, -c(1)]
thesisdata.use
#calculate the euclidean distance matrix
distance=dist(thesisdata.use, method="euclidean")
#calculate squared euclidean distance
d.sqeucl=distance^2
#run the cluster analysis
thesisdata.hclust=hclust(d.sqeucl, method="mcquitty")
#create dendrogram of cluster analysis
plot(thesisdata.hclust)
plot(thesisdata.hclust,labels=thesisdata$Symptom)
#cut the winsorized one at 110 and non-winsorized one at 120
rect.hclust(hclust(d.sqeucl, method="mcquitty"),h=110)
SPSS Syntax – For Repeated-Measures ANOVA

GLM PCOQ4pain PCOQ4fatig PCOQ4anx PCOQ4sad PCOQ4numb PCOQ4swell PCOQ4naus PCOQ4hotf PCOQ4sleep PCOQ4cog
/WSFACTOR=symptom 10 Polynomial
/MEASURE=importance
/METHOD=SSTYPE(3)
/EMMEANS=TABLES(symptom) COMPARE ADJ(LSD)
/PRINT=DESCRIPTIVE
/CRITERIA=ALPHA(.05)
/WSDESIGN=symptom.

DATASET ACTIVATE DataSet1.

GRAPH
/BAR(SIMPLE)=MEAN(PCOQ4pain) MEAN(PCOQ4fatig) MEAN(PCOQ4anx)
MEAN(PCOQ4sad) MEAN(PCOQ4numb) MEAN(PCOQ4swell)
  MEAN(PCOQ4naus) MEAN(PCOQ4hotf) MEAN(PCOQ4sleep) MEAN(PCOQ4cog)
/MISSING=LISTWISE
/INTERVAL CI(95.0).