CLASSES OF WOMEN EXPERIENCING SIMILAR SYMPTOM TRAJECTORIES WHILE RECEIVING CHEMOTHERAPY FOR BREAST CANCER

by

Meagan Sue Whisenant

A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

College of Nursing

The University of Utah

August 2016

The University of Utah Graduate School

STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Meagan Sue Whisenant**

has been approved by the following supervisory committee members:

Kathleen Mooney	, Chair	**05/02/2016** Date Approved
Susan L. Beck	, Member	**05/02/2016** Date Approved
Bob Wong	, Member	**05/02/2016** Date Approved
Sandra A. Mitchell	, Member	Date Approved
Leigh Neumayer	, Member	Date Approved

and by **Patricia Gonce Morton** , Chair/Dean of

the Department/College/School of **Nursing**

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

Breast cancer is characterized by significant disease-related and treatment-related symptoms. The objectives of this study were to identify classes of women experiencing similar symptom trajectories while undergoing chemotherapy for breast cancer and to determine if demographic, clinical, and symptom variables are associated with specific subgroups.

Through a secondary analysis, Latent Growth Mixture Modeling (LGMM) was used to examine potential subgroups of women experiencing similar symptom patterns. Daily symptom severity data for 10 symptoms reported by 166 women during cycles 2 and 3 were analyzed. The women's mean age was 53 and most were Caucasian with Stage II disease. Factors related to subgroup membership were explored for association with subgroups using independent-samples *t* tests, ANOVA, and chi-square analysis.

The multisymptom model did not reveal distinct subgroups of women with similar symptom profiles. A 3-class solution was found for fatigue and 2-class models were found for disturbed sleep, depressed mood, and anxiety.

Education was the only associated demographic factor with women with no college more likely to be in the moderate anxiety group (p=.03). Type of chemotherapy was the only associated clinical variable with women who received doxorubicin more likely to be in higher severity classes for fatigue (p=.01), depressed mood (p<.01), and anxiety (p=.04). More hours spent lying down was associated with membership in the higher fatigue (p=.02) and anxiety (p=.03) classes.

A variety of other symptoms were associated with worsening or higher severity symptom classes for each of the four symptoms in one or both treatment cycles. Higher overall symptoms in cycle 2 were associated with the higher severity subgroups for all four symptoms in cycle 3.

Limitations were found using LGMM with daily symptom data and caution is warranted in interpreting study results. Further research with longitudinal data, advanced statistical methods, and large samples is needed. Findings suggest symptoms are common and co-occur. Clinicians should be aware that symptoms at higher severity levels persist over cycles and require intensified management earlier to reduce continuing symptom burden.

This dissertation is dedicated to the women with breast cancer who shared their time and experiences.

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ACKNOWLEDGEMENTS

As I move towards completing my doctoral studies, I find myself reflecting on those who have supported me through this long journey. While there are many to thank, I feel it important to recognize those who have made significant sacrifices to allow me the time, resources, and energy needed to achieve my goals.

First, I wish to express thanks to my family, especially to my husband and my children for their consistent encouragement. Attending to my personal needs as a student has undoubtedly taken time and energy away from my family's need for a mother. My oldest, Colin, was just 3-years-old when I began my doctoral studies, and our family has grown to include his three siblings, Reed, Eleanor, and Margaret during my time as a student. I am grateful for the sacrifices they each have made, allowing their mother to work towards her dream of completing a PhD and hope that they will reflect back on this time knowing it was with their best interests in mind always. I am grateful for a partner in life, Clark, who provides perspective, encouragement, and expresses tireless faith in my abilities always. I also want to thank my parents, Allen and Patrice Peterson, who taught me the value of education and of finishing what you start, and Doug and Eleanor Whisenant for their unwavering support and encouragement.

Next, I wish to thank my committee members: Dr. Kathi Mooney (chair), Dr. Sandra Mitchell, Dr. Bob Wong, Dr. Susan Beck, and Dr. Leigh Neumayer for countless hours of mentoring, challenging my thinking, and providing support during the strenuous process of developing and working through a program of study that has been enriching,

fulfilling, and rewarding. I have felt connected and supported through my doctoral studies because of the efforts of so many staff and faculty at the University of Utah and have been honored to learn from the experiences of so many before me.

Finally, there are many friends and colleagues who have provided advice, encouragement, and attended to the physical needs of my family at varying times during this journey. Special thanks to the many mom-friends, who over the years have tended my children as their own, listened during moments of feeling overwhelmed, and provided perspective and laughter. To my cohort of fellow PhD students, who are now in varying stages of their careers and to the cohorts of distance oncology PhD students who adopted me as one of their own at times, I am grateful for your examples of dedication to your research interests and efforts and your friendship.

CHAPTER 1

INTRODUCTION

Statement of the Problem

Adequate symptom relief is an important goal for patients and clinicians during treatment for cancer (Kayl & Meyers, 2006). Not only are symptoms major contributors to decreased quality of life and ability to function and disease-related interference with employment, but they may also interrupt treatment and influence treatment effectiveness (Bradley, Neumark, Luo, & Schenk, 2007; Cleeland et al., 2003; Groenvold et al., 2007; Kayl & Meyers, 2006). Prompt evaluation and management of symptoms reduces use of emergency room and hospitalization, cost of treatment, and patient distress (Cleeland et al., 2000; Lee et al., 2004). In addition, prompt and effective prevention or treatment of symptoms may result in less interference with employment and ability to work (Beck et al., 2010).

Breast cancer is characterized by significant disease-related and treatment-related symptoms, but with a generally favorable prognosis. The American Cancer Society (2015) predicted that 229,060 women would be diagnosed with breast cancer in 2015, making breast cancer the most frequently diagnosed cancer for women. The expected 5-year survival rate for women with localized breast cancer is 89% (ACS, 2015). While women diagnosed with breast cancer may have increased survival when compared to other cancers, they often face a prolonged period of survivorship, which may include

uncertainty and residual symptom burden from treatment effect. Aggressive, multimodal and multi-agent treatment may be associated with significant toxicities and side effects that, when combined with tumor and disease-related symptoms, significantly diminish quality of life (Kayl & Meyers, 2006).

Considerable evidence suggests variability in the trajectories, or change in symptom prevalence, severity, and distress, over the courses of chemotherapy treatment for breast cancer (Dodd, Cho, Cooper, & Miaskowski, 2010). Describing heterogeneity, correlates, and outcomes of different symptom trajectories will lead to more effective therapeutic models for symptom management. There is a large body of literature devoted to the description of single symptoms and, more recently, symptom clustering. To date, most studies have focused on relationships between variables, such as the occurrence or association of specific symptoms in combination or relationships between demographic and clinical variables and symptom presentation (Dodd et al., 2010). Prevalence is often studied as opposed to severity or distress. Additionally, determination of which symptoms should be included in an analysis is often based on which symptoms are the more prevalent symptoms, not which symptoms are the more severe or distressing symptoms. Methods for determining which symptoms to study are often a priori, using the literature and guided by theory. While this method is practical, important symptoms that may be severe or distressing could remain inadvertently understudied. More recent analyses have focused on identifying homogeneous classes of persons who share a common symptom trajectory profile (Dodd et al., 2010; Miaskowski et al., 2006; Pud et al., 2008). Understanding trajectories of symptoms that occur in individuals may elucidate potential targets, or at-risk individuals, and common etiologies for symptoms

profiles, which may inform the development of better targeted interventions aimed at the reduction of symptoms during treatment.

Recently, this topic has received increased attention, although well-designed longitudinal studies of breast cancer symptoms are rare (Dodd et al., 2010; Kayl & Meyers, 2006; Lee et al., 2004). There is a growing body of literature devoted to describing symptom trajectories in women with breast cancer, but because the symptom experience is complicated and highly individualized, studies that develop trajectories based on daily symptom severity reporting and attempt to distinguish classes on the basis of personal and clinical variables are needed (Cleeland, Fisch & Dunn, 2011). The purpose of this study was to examine patient-reported symptoms experienced daily by women with breast cancer over multiple cycles of chemotherapy, identifying classes of women experiencing similar symptom trajectories.

Specific Aims

Aim 1

To determine the trajectories and profile classes associated with the severity of 10 symptoms (fatigue, pain, disturbed sleep, depressed mood, anxiety, nausea and vomiting, diarrhea, distress associated with changing appearance, sore mouth, and trouble thinking) reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer.

RQ 1.1: What are the trajectories of the severity of individual symptoms reported by women undergoing chemotherapy for breast cancer during cycle 2 and during cycle 3?

RQ 1.2: What are the trajectory profile classes, if any, associated with the severity of individual symptoms reported by women undergoing chemotherapy for breast cancer during cycle 2 and during cycle 3?

RQ 1.3: Do the profile classes associated with the severity of individual symptoms differ between cycle 2 and cycle 3 of chemotherapy?

Aim 2

To identify multisymptom trajectory profile classes of patients undergoing cycles 2 and 3 of chemotherapy for breast cancer.

RQ 2.1: What multisymptom profile classes can be identified in a cohort of women undergoing chemotherapy treatment for breast cancer during cycle 2 and during cycle 3?

RQ 2.2: Do the multisymptom profile classes differ between cycle 2 and cycle 3 of chemotherapy?

Aim 3

To determine if membership in differing multisymptom trajectory profiles is determined by various demographic, clinical, and symptom variables?

RQ 3.1: To what extent are differing symptom trajectory profiles associated with variations in age, chemotherapy regimen, stage of disease, marital status, employment, education, and the presentation of other symptoms at moderate to severe severity?

Aim 4

To determine if differing multisymptom trajectory profiles are associated with variations in change in functional status, days of missed work, and hours spent lying down reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer.

RQ 4.1: To what extent are differing symptom trajectory profiles associated with variations in change in functional status, days of missed work, and hours spent lying down as reported by women undergoing chemotherapy for breast cancer?

Background

This section provides an overview of symptoms associated with breast cancer, including a description of prevalent symptoms, antecedents to symptoms, co-occurring symptoms, consequences of symptoms, and subgroups of individuals with similar symptom experiences. Reports that focused on symptoms across varying cancer diagnoses and specific to breast cancer were included to support the identified aims and research questions. Pertinent studies from 1986 to 2016 were identified through a systematic search in the Cumulative Index to Nursing and Allied Health and PubMed.

Symptoms

Symptoms are self-reported, subjective phenomena that indicate a change in normal functioning, sensation, or appearance due to disease (Rhodes & Watson, 1987). Symptom reports describe the intensity, timing, level of distress, quality, and clustering of symptoms as well as the relationship between symptoms and demographic, clinical, and outcome variables (Dodd, Miaskowski, & Paul, 2001; Kim, McGuire, Tulman, & Barsevick, 2005; Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Rhodes & Watson, 1987). The trajectory of cancer symptoms, or change in the presence and severity of the symptom over time, is dynamic throughout the course of treatment and survival (Payne, 2002). Cancer symptoms may have multiple etiologies, and may occur in response to disease-related tumor burden or treatment-related side effects, such as the acute and sometimes chronic effects of surgery, chemotherapy, or radiation (Payne, Piper, Rabinowitz, & Zimmerman, 2006).

Wood, Nail, Gilster, Winters, and Elsea (2006) suggest that cancer symptoms are more frequently associated with treatment than with tumor burden and can exist even in

the absence of detectable tumor burden, such as in women with breast cancer undergoing adjuvant therapy after tumor resection. Treatment-related symptoms usually begin at the onset of treatment, persist throughout treatment, and slowly decline thereafter, although treatment-related symptoms may persist at some level through survivorship (Wood et al., 2006).

Generally, challenges in the study of symptoms include difficulty determining whether symptoms are the result of tumor burden effects or treatment-related effects, obtaining serial data in longitudinal designs, and controlling for confounding variables, such as comorbidities, pharmacological agents, and the use of other symptom management strategies (Wood et al., 2006). Confounding variables, particularly pharmacological agents, prove difficult to control for when patients engage in both self-prescribed and medically prescribed therapies for symptom management. For example, patients experiencing sleep disturbance may utilize therapies such as meditation, napping, exercise, and medications, including those that are both over-the-counter and prescription strength, to increase sleep time and quantity. It may be difficult to capture and control for all of these therapies in a study of sleep disturbance.

Symptoms in patients with breast cancer are often related to the effects of treatment as opposed to the effects of tumor burden, as the breast tumor itself does not typically cause symptoms. Because of this, symptoms present during treatment of breast cancer may be attributed to the effects of treatment alone. This allows for a unique setting in which treatment-related symptoms may be studied with minimal interference from disease-related symptoms (Kim, Barsevick, Tulman, & McDermott, 2008). As a result, most studies involving the symptoms of those with breast cancer are focused on

periods of treatment, such as cycles of chemotherapy or radiation, or postsurgical intervals.

Over time, the science of cancer-related symptoms has become increasingly complex. Reports range from simple cross-sectional studies of symptom prevalence to correlations between symptoms and antecedents and consequences to studies of co-occurring symptoms to longitudinal studies of the trajectories of individual and multiple symptoms. More recently, reports describe classes of individuals who experience similar trajectories and correlates of those trajectories using newer statistical modeling methods.

Prevalent Symptoms in Breast Cancer

There is an abundance of literature supporting a high prevalence of disturbing symptoms during chemotherapy in women with breast cancer. The prevalence, possible etiologies, and trajectories of highly prevalent symptoms, including fatigue, sleep disturbance, pain, nausea and vomiting, trouble thinking, and mood disturbance, are discussed below.

Fatigue

Fatigue is a complex, multidimensional symptom that patients may subjectively describe as weakness, weariness, sleepiness, tiredness, lack of energy, exhaustion, lethargy, or malaise (Bower et al., 2000; Winningham et al., 1994). Fatigue is the most commonly reported and most distressing symptom associated with chemotherapy in the broader cancer literature (Payne, 2002; Payne et al., 2006). The prevalence of fatigue in women with breast cancer varies across reports from 13% to 100% (Bender, Ergun, Rosenzweigh, Cohen, & Sereika, 2005; Bower et al., 2011; Browall, Persson, Ahlberg, Karlsson, & Danielson, 2009; Downie, Fan, Houede-tchen, & Tannock, 2006; Gaston-

Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Given, Given, Azzouz, & Stommel, 2001; Jacobsen et al., 1999; Kim et al., 2008; Liu et al., 2009; Nieboer et al., 2005; So et al., 2009; Tchen et al., 2003). The specific mechanisms underlying cancer-related fatigue are unknown, although proposed theories included pro-inflammatory cytokines, HPA axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation (National Comprehensive Cancer Network, 2010). Cancer-related fatigue may result from depression, sleep disturbance, side effects of chemotherapy, endocrine imbalances, anemia, decreased ability to process nutrients, and increased energy requirements (Kim et al., 2005; National Comprehensive Cancer Network, 2010; Ware, Kosinski, & Keller, 1996). Women with breast cancer report higher levels of fatigue when compared with women with no cancer history both before and after initiation of chemotherapy (Bower et al., 2001; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Jacobsen et al., 1999; Nieboer et al., 2005; Payne et al., 2006). Cancer patients often experience the highest levels of fatigue 48 hours after chemotherapy treatment, and while fatigue increases with the initiation of treatment, it does not appear to increase over time following the first cycle (Barsevick et al., 2004; Byar, Berger, Bakken, & Cetak, 2006; Jacobsen et al., 1999; Neiboer et al., 2005; Payne, 2002; Payne et al., 2006; Wilmoth, Coleman, Smith, & Davis, 2005). In addition, fatigue increases after chemotherapy initiation and may persist for years following completion of breast cancer treatment (Berger & Higginbotham, 2000; Jacobsen et al., 1999; Payne et al., 2006; Winningham et al., 1994; Wilmoth et al., 2004; Janz et al., 2007).

Sleep Disturbance

Significant disturbances in sleep are reported by cancer patients, including difficulty falling asleep and staying asleep (National Comprehensive Cancer Network, 2011). Over half of women (58-99%) report difficulty obtaining quality sleep during and following treatment for breast cancer (Beck et al., 2010; Bender et al., 2005; Berger & Higginbotham, 2000; Bower et al., 2011; Fortner et al., 2002; Given et al., 2001; Kim et al., 2008; Lee et al., 2005; Janz et al., 2007). Sleep disturbance in women with breast cancer may be associated with the use of antiemetic protocols, including steroids, and the presence of menopausal symptoms, including hot flashes (Prigozin, Uziely, & Musgrave, 2010). Beck et al. (2010) reported that 65% of women begin chemotherapy for breast cancer with a history of poor sleep in the month proceeding therapy initiation. In their sample, women had the poorest sleep quality on the first night following chemotherapy (Beck et al., 2010). During chemotherapy treatment for breast cancer, the frequency and duration of nighttime awakening and reports of difficulty falling asleep and falling back asleep after awakening increase above normal limits (Berger & Higginbotham, 2000; Fortner et al., 2002).

Pain

Pain occurs in approximately 33% of patients undergoing treatment and 75% of patients with advanced disease for cancer generally (National Comprehensive Cancer Network, 2011). Up to 70% of women receiving treatment for breast cancer experience pain (Bender et al., 2005; Gaston-Johansson et al., 1999; Given et al., 2001; So et al., 2009). Pain may be associated with treatment, with tumor, or unrelated to either and may be classified as acute, chronic, or breakthrough pain (National Comprehensive Cancer

Network, 2011). More specifically, women with breast cancer may experience post-surgical pain, neuropathic pain related to chemotherapy treatment, pain as a result of radiation-induced dermatitis, or pain related to sensorial alterations in the chest wall, arm, and axilla following surgery (Gaston-Johansson et al., 1999).

Nausea and Vomiting

Despite advances in antiemetic pharmacologic agents, over half of all cancer patients suffer from nausea and vomiting during chemotherapy treatment (Lee et al., 2005; Molassiotis, Yam, Yung, Chan, & Mok, 2002). Up to 80% of women with breast cancer experience gastrointestinal symptoms (Browall et al., 2009; Kim et al., 2008; Lee et al., 2005; Tchen et al., 2003). The pathways involved in the development of nausea and vomiting are complex and some mechanisms are not well understood, but may include neurotransmitters and neural pathways, the vomiting center in the brain stem, the chemoreceptor trigger zone, and chemicals (Molassiotis et al., 2002). Of importance, women may experience a variety of types of nausea and vomiting, including anticipatory nausea, influenced by nonpharmacological factors such as demographic characteristics and anxiety, acute nausea and vomiting, or nausea that presents during the immediate days following chemotherapy administration, and/or delayed nausea and vomiting, which typically presents several days after chemotherapy administration (Lee et al., 2005; Molassiotis et al., 2002).

Trouble Thinking

The symptoms of trouble thinking, which may include difficulty with concentration and memory, are prevalent among women receiving treatment for breast cancer and reported to occur in between 15 and 50% of women (Downie et al., 2006).

Cognitive changes may initiate with chemotherapy administration and continue through this use of hormonal therapies, including aromatase inhibitors (Downie et al., 2006; Merriman et al., 2015). Cognitive dysfunction may be mediated by estrogen deprivation, a hormone that promotes synaptic and neural plasticity in the brain (Merriman et al., 2015). Chemotherapeutic agents and aromatase inhibitors may result in reduction of estrogen, and consequently, changes in cognitive function (Merriman et al., 2015).

Mood Disturbance

From the broader cancer literature, all patients experience some level of mood disturbance associated with a cancer diagnosis and treatment, and up to 40% of patients experience significant distress (National Comprehensive Cancer Network, 2010). The symptoms of mood disturbance and their reported prevalence in women with breast cancer include depression (24-54%) (Bower et al., 2011; Gaston-Johansson et al., 1999; Kim et al., 2008; Liu et al., 2009; So et al., 2009) and anxiety (6-74%) (Bender et al., 2005; Browall et al., 2009; So et al., 2009). Mood disturbance may be related to anxiety, diagnostic testing, worries about disease progression, concern about an inability to perform usual functions, and concerns about the future (Gaston-Johansson et al., 1999). Chemotherapy may reduce a patient's ability to function both physically and cognitively and increase morbidity, leading to increased mood disturbance (Gaston-Johansson et al., 1999). Additionally, symptoms of mood disturbance, including depressed mood and anxiety, are reported to increase from baseline, but remain stable over time (Nieboer et al., 2005).

Antecedents

Understanding potential antecedents to symptom expression may assist clinicians in targeting individuals at risk for the development of symptoms. A brief summary of each demographic antecedent (age, marital status, employment, education status, and income) and each clinical factor antecedent (stage of disease and chemotherapy regimen) is provided in Table 1.1.

While age does not appear as an antecedent to either fatigue or pain (Browall et al., 2008; deJong, Candel, Schouten, Abu-Saad, & Courtens, 2004; deJong, Kester, Schouten, Abu-Saad, & Courtens, 2006; Goldstein et al., 2012; Huang, Chen, Liang, & Miaskowski, 2014; Jacobsen et al., 1999; Von Ah, Kang, & Carpenter, 2008), increasing age may predict the presence of disturbed sleep, although reports are conflicting (Beck et al., 2010; Browall et al., 2008; Colagiuri et al., 2011; Onselen et al., 2012). Beck et al. (2010) found that younger women experienced higher quality of sleep based on several sleep measures, including time in bed, total sleep time, and higher sleep percent. Additionally, Colagiuri et al. (2011) found that older age predicted sleep difficulty as measured by self-report. In contrast, Browall et al. (2008) described a lack of correlation between age and disturbed sleep. This difference in findings may be explained by differing samples, where Beck et al. (2010) and Colagiuri et al. (2011) studied women with ages ranging from 28-75 years and 26-70 years, respectively, and Browall et al. (2008) focused on older women only, with ages ranging from 55-77 years. If disturbed sleep may be predicted by the presence of menopausal symptoms, including hot flashes, studies including samples of both premenopausal and postmenopausal women would be more likely to find significant associations between younger age and better sleep.

Table 1.1 Antecedents of Symptoms in Women With Breast Cancer

Antecedent	Symptom	Evidence
Age	Fatigue	0 (deJong et al., 2004) [b]
		0 (deJong et al., 2006) [b]
		0 (Von Ah, Kang, & Carpenter, 2008) [b]
		0 (Jacobsen et al., 1999) [b]
		0 (Browall et al., 2008) [b]
		0 (Goldstein et al., 2012) [b]
		0 (Huang et al., 2014) [b]
	Disturbed Sleep	+ (Beck et al., 2010) [b]
		0 (Browall et al., 2008) [b]
		+ (Colagiuri et al., 2011)
		0 (Onselen et al., 2012)
	Depressed Mood	0 (Browall et al., 2008) [b]
		- (Gold et al., 2016) [b]
	Anxiety	0 (Browall et al., 2008) [b]
		- (Gold et al., 2016) [b]
	Pain	0 (Browall et al., 2008) [b]
	Nausea and Vomiting	0 (Browall et al., 2008) [b]
		- (Molassiotis et al., 2002) [b]
Marital Status	Fatigue	Divorced women more fatigued than women living with a partner (deJong et al., 2004) [b]
		Married women more fatigued (Huang et al., 2013) [b]
		Married women receiving Doxorubicin experience later fatigue when compared to non-partnered women (deJong et al., 2006) [b]
		0 (Jacobsen et al., 1999) [b]
	Disturbed Sleep	0 (Colagiuri et al., 2011)
		0 (Onselen et al., 2012) [b]
Employment	Fatigue	0 (deJong et al., 2004) [b]
		0 (deJong et al., 2006) [b]
		0 (Huang et al., 2014) [b]
	Disturbed Sleep	Unemployment associated with disturbed sleep (Onselen et al., 2012) [b]
	Depressed Mood	0 (Gold et al., 2016) [b]
	Anxiety	0 (Gold et al., 2016) [b]

Table 1.1 continued

Antecedent	Symptom	Evidence
Education Status	Fatigue	0 (deJong et al., 2004) [b]
		+ (Huang et al., 2013) [b]
		0 (deJong et al., 2006) [b]
		0 (Von Ah et al., 2008) [b]
		0 (Jacobsen et al., 1999) [b]
		0 (Goldstein et al., 2012) [b]
	Sleep Disturbance	0 (Beck et al., 2010) [b]
		0 (Colagiuri et al., 2011)
		+ (Onselen et al., 2012)
	Depressed Mood	0 (Gold et al., 2016) [b]
	Anxiety	0 (Gold et al., 2016) [b]
Income	Fatigue	0 (Von Ah et al., 2008) [b]
		0 (Jacobsen et al., 1999) [b]
	Disturbed Sleep	0 (Colagiuri et al., 2011)
	Depressed Mood	0 (Gold et al., 2016) [b]
	Anxiety	0 (Gold et al., 2016) [b]
Stage of Disease	Fatigue	0 (deJong et al., 2004) [b]
		0 (Von Ah et al., 2008) [b]
		0 (Jacobsen et al., 1999) [b]
	Sleep Disturbance	0 (Beck et al., 2010) [b]
		0 (Colagiuri et al., 2011)
		0 (Onselen et al., 2012) [b]
	Nausea and Vomiting	Later stage predicts increased nausea and vomiting (Molassiotis et al., 2002) [b]
Chemotherapy Regimen	Fatigue	0 (Berger, 1998) [b]
		0 (Berger & Farr, 1999) [b]
		CMF stable fatigue during treatment with late effect fatigue, Doxorubicin increase in fatigue at initial measurement (deJong et al., 2004) [b]
		CMF lower fatigue peak than Doxorubicin, Cyclophosphamide late fatigue peak (de Jong et al., 2006) [b]

[a] +, antecedent positively correlated with symptom, -, antecedent negatively correlated with symptom, 0, no relationship between antecedent and symptom identified

[b] denotes a longitudinal or repeated-measures design

Additionally, reports of the relationship between age and mood disturbance and age and nausea and vomiting are similarly conflicting. For example, while Gold et al. (2016) found that younger women experienced increased depressed mood and anxiety when compared to older women, Browall et al. (2008) found no association between age and mood disturbance. Again, Browall et al. (2008), with a sample of older women only, did not identify differences between younger and older women in these symptoms. While Browall et al. (2008) found no relationship between age and nausea and vomiting, Molassiotis et al. (2002) found that younger age was predictive of increased acute nausea and vomiting.

Marital status as a predictor variable of symptoms in breast cancer is reported with mixed findings. While deJong et al. (2004) found that divorced women were more fatigued when compared to women living with a partner, Huang et al. (2013) found that married women were more fatigued when compared to nonmarried women. Additionally, Jacobsen et al. (1999) found no relationship between marital status and fatigue and Colagiuri et al. (2011) and Onselen et al. (2012) found no relationship between marital status and disturbed sleep.

Lack of employment is associated with increases in disturbed sleep (Onselen et al., 2012). Employment status is not reported to influence fatigue or mood disturbance in women with breast cancer (deJong et al., 2004; deJong et al., 2006; Gold et al., 2016; Huang et al., 2014; Onselen et al., 2012).

Education status as an antecedent of symptoms in breast cancer is also reported with conflicting findings. While Huang et al. (2013) found that women with higher education reported higher fatigue, others have reported a lack of relationship between

education status and fatigue (deJong et al., 2004; deJong et al., 2006; Goldstein et al., 2012; Jacobsen et al., 1999; Von Ah et al., 2008). Huang et al. (2013) studied a sample of women with a large variability of educational levels, and suggest that a lack of association between educational status and fatigue in other studies may be attributable to homogeneity in educational status among the samples of other studies, where most women had at least some college education. Onselen et al. (2012) found that increased education was associated with increased sleep disturbance and suggest that this relationship may be mediated by higher levels of distress related to increased knowledge about disease and treatment. Alternatively, others have found no relationship between education status and sleep disturbance (Beck et al., 2010; Colagiuri et al., 2011). Additionally, Gold et al. (2016) found no relationship between educational status and the symptoms of mood disturbance.

A relationship between income and either fatigue or mood disturbance has not been found in women with breast cancer (Gold et al., 2016; Jacobsen et al., 1999; Von Ah et al., 2008). Similarly, income has not been associated with disturbed sleep in women with breast cancer (Colagiuri et al., 2011).

Stage of disease has not been related to the presence of either fatigue or sleep disturbance (Beck et al., 2010; Colagiuri et al., 2011; deJong et al., 2004; Jacobsen et al., 1999; Onselen et al., 2010; Von Ah et al., 2008). Molassiotis et al. (2002) found that later stage of disease predicted increased nausea and vomiting and suggest that the additive effects of nausea and vomiting may be attributable to progressive illness.

Finally, chemotherapy regimen has been studied as a potential antecedent of fatigue in breast cancer, with conflicting findings. In cross-sectional studies, Berger

(1998) and Berger and Farr (1999) found that levels of fatigue 48 hours after each of the first 3 chemotherapy treatments were not significantly different when comparing cohorts of women who received CMF, Doxorubicin with Cyclophosphamide, and CAF. In a longitudinal study of the trajectory of fatigue, deJong et al. (2004) found that women receiving CMF reported stable fatigue during chemotherapy with late effect fatigue and women receiving Doxorubicin reported increases in fatigue just after chemotherapy receipt. In another longitudinal study of the trajectory of fatigue, deJong et al. (2006) reported significant differences in the course of fatigue between those receiving CMF and those receiving Doxorubicin, with fatigue peaking at a later time for those receiving Cyclophosphamide. Differing findings concerned with the relationship between chemotherapy regimen and fatigue may be related to methodological differences among the studies, including the design and measurement time-points.

Co-Occurring Symptoms

Symptoms may co-occur in women during treatment for breast cancer. The collective consequence of simultaneous multiple symptoms may result in increased impairment when compared to the consequence of a single symptom (Barsevick, 2007; Dodd et al., 2001; Kim et al., 2008; Lee et al., 2004). The study of multiple symptoms simultaneously allows for the identification of shared symptom trajectories, symptom burden, and symptom mechanisms (Cleeland et al., 2003). A brief summary of co-occurring symptoms, focused on fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea and vomiting, and trouble thinking, is provided in Table 1.2. The reported symptom co-occurrences were found through correlational studies and studies of symptom clusters.

Table 1.2 Co-Occurring Symptoms in Women With Breast Cancer

Symptom	Co-Occurring Symptom	Evidence
Fatigue	Disturbed Sleep	+ (Berger & Higginbotham, 2000) [b]
		+ (Ancoli-Israel et al., 2006)
		+ (Jacobsen et al., 1999) [b]
		+ (Broeckel et al., 1998)
		+ (Berger & Farr, 1999) [b]
		+ (Liu et al., 2012) [b]
		+ (Bower et al., 2011)
		+ (Berger, 1998) [b]
		+ (Goldstein et al., 2012) [b]
		+ (Berger et al., 2007)
		+ (Berger et al., 2010)
		+ (Bender et al., 2005) [b]
		+ (Onselen et al., 2012) [b]
		+ (Kim et al., 2008) [b]
		+ (Liu et al., 2009) [b]
		0 (Prigozin et al., 2010)
	Depressed Mood	+ (Huang et al., 2013) [b]
		+ (Von Ah et al., 2008) [b]
		+ (Jacobsen et al., 1999) [b]
		+ (Ancoli-Israel et al., 2006)
		+ (Byar et al., 2006) [b]
		+ (Niebor et al., 2005) [b]
		+ (Bower et al., 2011)
		+ (Gaston-Johansson, et al., 1999)
		+ (Goldstein et al., 2012) [b]
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		+ (Liu et al., 2009) [b]
		+ (Prigozin et al., 2010)
	Anxiety	+ (Byar et al., 2006) [b]
		+ (Dragomir & Fodoreanu, 2013)
		+ (Bender et al., 2005)
		+ (Prigozin et al., 2010)
	Pain	+ (Jacobsen et al., 1999) [b]
		+ (Niebor et al., 2005) [b]
		+ (Gaston-Johansson, et al., 1999)
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
	Nausea and Vomiting	+ (Jacobsen et al., 1999) [b]
		+ (Molassiotis et al., 2002) [b]
		0 (Prigozin et al., 2010)

Table 1.2 continued

Symptom	Co-Occurring Symptom	Evidence
Fatigue, cont.	Trouble Thinking	+ (Jacobsen et al., 1999) [b]
		+ (Merriman et al., 2015) [b]
		+ (Bender et al., 2005)
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
Disturbed Sleep	Fatigue	+ (Berger & Higginbotham, 2000) [b]
		+ (Ancoli-Israel et al., 2006)
		+ (Jacobsen et al., 1999) [b]
		+ (Broeckel et al., 1998)
		+ (Berger & Farr, 1999) [b]
		+ (Liu et al., 2012) [b]
		+ (Bower et al., 2011)
		+ (Berger, 1998) [b]
		+ (Goldstein et al., 2012) [b]
		+ (Berger et al., 2007)
		+ (Berger et al., 2010)
		+ (Bender et al., 2005) [b]
		+ (Onselen et al., 2012) [b]
		+ (Kim et al., 2008) [b]
		+ (Liu et al., 2009) [b]
		0 (Prigozin et al., 2010)
	Depressed Mood	+ (Ancoli-Israel et al., 2006)
		+ (Colagiuri et al., 2011)
		+ (Berger et al., 2010)
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		+ (Liu et al., 2009) [b]
		0 (Prigozin et al., 2010)
	Anxiety	+ (Colagiuri et al., 2011)
		+ (Bender et al., 2005) [b]
		0 (Prigozin et al., 2010)
	Pain	+ (Fortner et al., 2002)
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
	Nausea and Vomiting	0 (Prigozin et al., 2010)
	Trouble Thinking	+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)

Table 1.2 continued

Symptom	Co-Occurring Symptom	Evidence
Depressed Mood	Fatigue	+ (Von Ah et al., 2008) [b]
		+ (Jacobsen et al., 1999) [b]
		+ (Ancoli-Israel et al., 2006)
		+ (Byar et al., 2006) [b]
		+ (Niebor et al., 2005) [b]
		+ (Bower et al., 2011)
		+ (Gaston-Johansson, et al., 1999)
		+ (Goldstein et al., 2012) [b]
		+ (Prigozin et al., 2010)
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		+ (Liu et al., 2009) [b]
	Disturbed Sleep	+ (Ancoli-Israel et al., 2006)
		+ (Colagiuri et al., 2011)
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		+ (Liu et al., 2009) [b]
		0 (Prigozin et al., 2010)
	Anxiety	+ (Gold et al., 2016) [b]
		+ (Prigozin et al., 2010)
		+ (Bender et al., 2005) [b]
	Pain	+ (Gaston-Johansson, et al., 1999)
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
	Nausea and Vomiting	0 (Prigozin et al., 2010)
	Trouble Thinking	+ (Merriman et al., 2015) [b]
		+ (Bender et al., 2005)
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
Anxiety	Fatigue	+ (Byar et al., 2006)
		+ (Dragomir & Fodoreanu, 2013)
		+ (Bender et al., 2005) [b]
		0 (Prigozin et al., 2010)
	Disturbed Sleep	+ (Colagiuri et al., 2011)
		+ (Bender et al., 2005) [b]
		0 (Prigozin et al., 2010)
	Depressed Mood	+ (Gold et al., 2016) [b]
		+ (Prigozin et al., 2010)
		+ (Bender et al., 2005) [b]
	Pain	+ (Bender et al., 2005) [b]
		0 (Prigozin et al., 2010)

Table 1.2 continued

Symptom	Co-Occurring Symptom	Evidence
Anxiety, cont.	Nausea and Vomiting	+ (Molassiotis et al., 2002) [b] 0 (Prigozin et al., 2010)
	Trouble Thinking	+ (Merriman et al., 2015) [b] + (Bender et al., 2005) [b] 0 (Prigozin et al., 2010)
Pain	Fatigue	+ (Jacobsen et al., 1999) [b] + (Niebor et al., 2005) + (Gaston-Johansson, et al., 1999) + (Bender et al., 2005) [b] + (Kim et al., 2008) [b] 0 (Prigozin et al., 2010)
	Depressed Mood	+ (Gaston-Johansson, et al., 1999) + (Bender et al., 2005) [b] + (Kim et al., 2008) [b] 0 (Prigozin et al., 2010)
	Disturbed Sleep	+ (Fortner et al., 2002) + (Bender et al., 2005) [b] + (Kim et al., 2008) [b] 0 (Prigozin et al., 2010)
	Anxiety	+ (Bender et al., 2005) 0 (Prigozin et al., 2010)
	Nausea and Vomiting	0 (Prigozin et al., 2010)
	Trouble Thinking	+ (Bender et al., 2005) [b] + (Kim et al., 2008) 0 (Prigozin et al., 2010)
Nausea and Vomiting	Fatigue	+ (Jacobsen et al., 1999) [b] + (Molassiotis et al., 2002) [b] 0 (Prigozin et al., 2010)
	Disturbed Sleep	0 (Prigozin et al., 2010)
	Depressed Mood	0 (Prigozin et al., 2010)
	Anxiety	+ (Molassiotis et al., 2002) [b] 0 (Prigozin et al., 2010)
	Pain	0 (Prigozin et al., 2010)
	Trouble Thinking	0 (Prigozin et al., 2010)

Table 1.2 continued

Symptom	Co-Occurring Symptom	Evidence
Trouble Thinking	Fatigue	+ (Jacobsen et al., 1999) [b]
		+ (Merriman et al., 2015) [b]
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
	Disturbed Sleep	+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008)
		0 (Prigozin et al., 2010)
	Depressed Mood	+ (Merriman et al., 2015) [b]
		+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
	Anxiety	+ (Merriman et al., 2015) [b]
		+ (Bender et al., 2005) [b]
		0 (Prigozin et al., 2010)
	Pain	+ (Bender et al., 2005) [b]
		+ (Kim et al., 2008) [b]
		0 (Prigozin et al., 2010)
		0 (Merriman et al., 2015) [b]
	Nausea and Vomiting	0 (Prigozin et al., 2010)

[a] +, co-occurring symptoms positively correlated, 0, no relationship between two symptoms identified
[b] denotes a longitudinal or repeated-measures design

Fatigue is commonly reported to co-occur with other symptoms in women with breast cancer, including disturbed sleep (Ancoli-Israel et al., 2006; Bender et al., 2005; Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Berger, Farr, Kuhn, Fischer, & Agrawal, 2007; Berger, Wielgus, Hertzog, Fischer, & Farr, 2010; Bower et al., 2011; Broeckel et al., 1998; Goldstein et al., 2012; Jacobsen et al., 1999; Kim et al., 2008; Liu et al., 2009; Liu et al., 2012; Onselen et al., 2012). Only one report was found where fatigue did not co-occur with disturbed sleep when the correlation of symptoms were studied in women with breast cancer (Prigozin et al., 2010). Symptoms of mood disturbance often co-occur with fatigue in women with breast cancer, including depressed mood (Ancoli-Israel et al., 2006; Bender et al., 2005; Bower et al., 2011; Byar et al., 2006; Gaston-Johansson et al., 1999; Goldstein et al., 2012; Huang et al., 2013; Jacobsen et al., 1999; Kim et al., 2008; Liu et al., 2009; Niebor et al., 2005; Prigozin et al., 2010; Von Ah et al., 2008) and anxiety (Bender et al., 2005; Byar et al., 2006; Dragomir & Fodoreanu, 2013; Prigozin et al., 2010). Additionally, pain is reported to co-occur with fatigue in all but one study of women with breast cancer where both symptoms were included in analyses of correlations or clusters (Bender et al., 2005; Gaston-Johansson et al., 1999; Jacobsen et al., 1999; Kim et al., 2008; Niebor et al., 2005). Only Prigozin et al. (2010) reported on a lack of a strong correlation between pain and fatigue in their analysis. The relationship between nausea and vomiting with fatigue is reported with conflicting findings. While Jacobsen et al. (1999) and Molassiotis et al. (2002) found these two symptoms strongly correlated in breast cancer, Prigozin et al. (2010) did not. Trouble thinking has also been reported to co-occur with fatigue in several studies of the symptoms experienced by women with breast cancer (Bender et al., 2005; Jacobsen et al.,

1999; Kim et al., 2008; Merriman et al., 2015), with only Prigozin et al. (2010) reporting a lack of strong correlation between these two symptoms.

In addition to the relation to fatigue described earlier, disturbed sleep has been reported to co-occur with several other symptoms in women with breast cancer. Depressed mood (Ancoli-Israel et al., 2006; Bender et al., 2005; Berger et al., 2010; Colagiuri et al., 2011; Kim et al., 2008; Liu et al., 2009) and anxiety (Bender et al., 2005 ; Colagiuri et al., 2011) are reported to correlate with disturbed sleep in women with breast cancer. Only Prigozin et al. (2010) did not find a strong relationship between symptoms of mood disturbance and disturbed sleep. Additionally, pain (Bender et al., 2005; Fortner et al., 2002; Kim et al., 2008) and trouble thinking (Bender et al., 2005; Kim et al., 2008) are reported to co-occur with disturbed sleep, in all reviewed studies, with the exception of Prigozin et al. (2010). Prigozin et al. (2010) also reported on a lack of strong correlation between nausea and vomiting and disturbed sleep.

The symptoms of mood disturbance (depressed mood and anxiety) are reported to co-occur (Bender et al., 2005; Gold et al., 2016; Prigozin et al., 2010). The co-occurrence of depressed mood and anxiety with fatigue and disturbed sleep are previously described. Depressed mood is also reported to co-occur with pain (Bender et al., 2005; Gaston-Johansson et al., 1999; Kim et al., 2008) and trouble thinking (Bender et al., 2005; Kim et al., 2008; Merriman et al., 2015). In addition, anxiety is reported to co-occur with pain (Bender et al., 2005), nausea and vomiting (Molassiotis et al., 2002), and trouble thinking (Bender et al., 2005; Merriman et al., 2015). Prigozin et al. (2010) found an insignificant correlation between depressed mood and pain, depressed mood and nausea and vomiting, depressed mood and trouble thinking, anxiety and pain, anxiety and

nausea and vomiting, and anxiety and trouble thinking.

As previously described, pain is reported to co-occur with fatigue, disturbed sleep, depressed mood, and anxiety. Pain is also reported to co-occur with trouble thinking (Bender et al., 2005; Kim et al., 2008), although Prigozin et al. (2010) did not find a strong correlation between these two symptoms. Additionally Prigozin et al. (2010) did not find a strong correlation between pain and nausea and vomiting. Finally, nausea and vomiting is reported to co-occur with fatigue and anxiety as previously described, but not with disturbed sleep, depressed mood, pain, or trouble thinking (Prigozin et al., 2010).

Consequences

Symptoms may influence outcomes, including changes in quality of life and functional status, changes in activity level, loss of employment, and interruption of treatment (Bradley et al., 2007; Cleeland et al., 2003; Kayl & Meyers, 2006). A brief summary of three potential consequences, changes in functional status and activity level and hours spent lying down, is provided in Table 1.3.

Decline in functional status is associated with several symptoms in women with breast cancer, including fatigue (Ancoli-Israel et al., 2006; Berger & Higginbotham, 2000; Downie et al., 2006; Huang et al., 2013), disturbed sleep (Ancoli-Israel et al., 2006; Beck et al., 2010; Colagiuri et al., 2011; Fortner et al., 2002; Onselen et al., 2012), depressed mood (Ancoli-Israel et al., 2006; Gold et al., 2016; Ng et al., 2015), anxiety (Gold et al., 2016; Ng et al., 2015), and nausea and vomiting (Lee et al., 2005). Additionally, fatigue, disturbed sleep, and nausea and vomiting are reported to correlate with decline in activity level during treatment in women with breast cancer (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Colagiuri et al., 2011; deJong

Table 1.3 Consequences of Symptoms in Women With Breast Cancer

Consequence	Symptom	Evidence
Functional Status	Fatigue	- (Berger & Higginbotham, 2000) [b]
		- (Huang et al., 2013) [b]
		- (Ancoli-Israel et al., 2006)
		- (Downie et al., 2006)
	Disturbed Sleep	- (Beck et al., 2010) [b]
		- (Ancoli-Israel et al., 2006)
		- (Colagiuri et al., 2011)
		- (Fortner et al., 2002)
		- (Onselen et al., 2012) [b]
	Depressed Mood	- (Ancoli-Israel et al., 2006)
		- (Ng et al., 2015) [b]
		- (Gold et al., 2016) [b]
	Anxiety	- (Ng et al., 2015) [b]
		- (Gold et al., 2016) [b]
	Nausea and Vomiting	- (Lee et al., 2005) [b]
Activity Level	Fatigue	- (Berger & Higginbotham, 2000) [b]
		- (deJong et al., 2004) [b]
		- (Jacobsen et al., 1999) [b]
		- (Berger & Farr, 1999) [b]
		- (Berger, 1998) [b]
	Disturbed Sleep	- (Colagiuri et al., 2011)
	Nausea and Vomiting	- (Lee et al., 2005) [b]
Hours Lying Down	Nausea and Vomiting	+ (Lee et al., 2005) [b]

[a] +, consequence positively correlated with symptom, -, consequence negatively correlated with symptom, 0, no relationship between consequence and symptom identified

[b] denotes a longitudinal or repeated-measures design

et al., 2004; Jacobsen et al., 1999; Lee et al., 2005). Increased nausea and vomiting is associated with increased hours spent lying down (Lee et al., 2005).

Subgroup Studies in Breast Cancer

Despite the abundance of reports of co-occurring symptoms within breast cancer, there are several inconsistencies in the methods used to determine whether symptoms co-occur. One inconsistency is the method used to determine which symptoms to include in the analysis. Across the breast cancer literature, four symptoms: pain, psychological distress, fatigue, and sleep disturbance, are consistently reported as significant and distressing and are often reported as co-occurring. In contrast, there are limited reports on the co-occurrence other highly prevalent and distressing symptoms, including cognitive impairment, menopausal symptoms, and gastrointestinal symptoms. These other symptoms are commonly left out of correlational and symptom cluster studies. Reports cite the use of expert panels, the use of minimal available data in secondary analyses, or simply neglect to describe the a priori method used to determine which symptoms to study (Bender et al., 2005; Dodd et al., 2010; Gaston-Johansson et al., 1999; Glaus et al., 2006; Liu et al., 2009; So et al., 2009). When studying symptom clusters, an analysis that allows the symptoms that are actually reported by the participants in the sample to guide the determination of which symptoms to include in studies of co-occurrence is optimal.

Another inconsistency in the symptom literature is a lack of common statistical approaches used to identify co-occurring symptoms (Dodd et al., 2010). Multiple approaches are reported, including correlational studies, regression, factor analysis, and structural equation modeling. The goal of these approaches is to identify significant

predictors of outcomes, such as symptoms and describe how dependent and independent variables are related, including co-occurring symptoms (Jung & Wickerama, 2007). Important advancements in statistical modeling, such as cluster analysis, finite mixture analysis, latent class analysis, and growth mixture modeling, have allowed for the identification of homogeneous classes that share a common profile or pattern on several factors of interest, such as symptom presentation (Colder, Richardson, Campbell, Ruel, & Flay, 2002; Muthen & Muthen, 2000). These approaches focus on the relationships among individuals and the goal is to classify individuals into distinct groups, where individuals within a group are more similar than individuals between groups (Jung & Wickerama, 2007). The identification of classes of individuals, sometimes called subgroups, may help to identify at-risk individuals who may benefit from specific targeted symptom management during treatment (Dodd et al., 2001).

Table 1.4 presents a brief overview of several recent reports where classes of women with breast cancer displaying similar symptom experiences were identified using various approaches, including pattern-based, cluster analysis, latent class analysis, and mixture modeling. For each reviewed study, the statistical methods, a description of the identified classes, and any correlates associated with class membership are summarized. A brief discussion of Cluster Analysis and Latent Class Analysis is presented, followed by a discussion of the usefulness of Latent Growth Mixture Modeling techniques in subgroup studies.

Cluster Analysis

Among studies in breast cancer, a longitudinal study of the symptoms of pain, fatigue, sleep disturbance, and depression in breast cancer identified four classes

Table 1.4 Subgroup Studies in Breast Cancer

Analysis	Reference	Symptom	Sample Size	Measurement Times	Classes	Correlates
Pattern-Based	Deshields, Tibbs, Fan, & Taylor (2006)	Depression	*n*=84	Patterns Determination applied to CES-D threshold placement at end-of-treatment baseline, and 3 and 6 months	5: Never Depressed (60.7%), Become Depressed (3.6%), Recover (9.5%), Stay Depressed (11.9%), Vacillate (14.3%)	-Become Depressed class had more children at home -Vacillate class had fewer children at home -Never Depressed class had least anxiety and QOL problems
Hierarchical Clusters Analysis	Dodd et al. (2010)	Fatigue Sleep Disturbance Pain Depression	*n*=112	Hierarchical Clusters Analysis applied to symptom scores at baseline, end of CTX, and one year post-treatment	4: All Low (52.2%), Mild (5.3%), Moderate (34.0%), All High (8.5%) (at baseline); 4: All Low (39.3%), Mild (22.3%), Moderate (27.7%), All High (10.6%) (at end of CTX treatment); 3: Mild (76.6%), Moderate (16.0%), All High (3.2%) (at one-year)	-All High class reported poorer functional status and QOL
	Gwede, Small, Munster, Andrykowski, & Jacobsen (2008)	Multi-Symptom (MSAS)	*n*=133	Hierarchical Clusters Analysis applied to MSAS scores at baseline, end of CTX	2: High Symptoms (33.8%), Low Symptoms (66.2%)	-High Symptoms class more likely to have stage I disease -High Symptoms class more likely to report greater symptom prevalence and poorer QOL at end of treatment
Latent Class Analysis	Langford et al. (2016)	Pain Fatigue Sleep Disturbance Depression	*n*=391	Latent Class Analysis applied to symptom scores the week following CTX	3: All Low (35.8%), All Moderate (48.3%), All High (15.9%)	-All High class had a lower functional status, higher comorbidity profile, higher symptom burden, poorer quality of life

Table 1.4 continued

Analysis	Reference	Symptom	Sample Size	Measurement Times	Classes	Correlates
Mixture Models	Henselmans, Helgeson, Seltman, de Vries (2010)	Psychological Distress	*n*=171	Finite Mixture Model applied to psychological distress during the first year after diagnosis using 5 time-points (intercept at diagnosis)	4: No Distress (36%), Recovery (33%), Late (15%), Chronic (15%)	-Recovery class and Chronic class had lower sense of mastery, were less optimistic
	Helgeson, Snyder, & Seltman (2004)	Physical and Psychological Adjustment	*n*=287	Finite Mixture Modeling applied to SF-36 (MCS) measured at 4, 7, 13, 19, 31, 43, 55 months post-diagnosis	4 for MCS: Traj1 (12.2%), Traj2 (26.5%), Traj3 (18.1%), Traj4 (43.2%) 4 for PCS: Traj1 (19.5%), Traj2 (2.1%), Traj3 (23.3%), Traj4 (55.1%)	-Personal and social resources at the beginning of study distinguished different classes of MCS and PCS
	Bidstrup et al. (2015)	Distress Anxiety Depression	*n*=323	Finite Mixture Modeling applied to symptom scores at diagnosis,4, 8 months	3: Depression, 5: Distress, 2: Anxiety	-Most Distressed class had younger women, women without a partner, less education, chemotherapy
	Dunn et al. (2015)	Depression	*n*=398	Growth Mixture Modeling applied to CES-D prior to and monthly for 6 months after surgery	4: Resilient (38.9%), Subsyndromal (45.2%), Delayed (11.3%), Peak (4.5%)	-Subsyndromal class younger than women in Resilient class -Subsyndromal, Delayed, and Peak classes had higher mean trait and state anxiety scores prior to surgery compared to Resilient
	Lam et al. (2010)	Psychological Distress	*n*=285	Growth Mixture Modeling applied to Chinese Health Questionnaire scores at baseline postsurgery and 1,4,8-months after	4: Resilient (66.3%), Chronic (15.4%), Recovered (11.5%) Delayed-recovery (6.6%)	-Resilient class had less distress -Resilient class had less problems with satisfaction with treatment decisions -Age, education, occupation, stage of disease associated with class membership

Table 1.4 continued

Analysis	Reference	Symptom	Sample Size	Measurement Times	Classes	Correlates
	Lam, Shing, Bonanno, Mancini, & Fielding (2012)	Psychological Distress	*n*=186 women from (Lam et al., 2010)	Multivariate analyses applied to anxiety, depression, cancer distress, and social morbidity at 6-year	4: Resilient (66.3%), Chronic (15.4%), Recovered (11.5%) Delayed-recovery (6.6%)	-Chronic and Delayed-Recovery classes had higher 6-year anxiety -Chronic class had higher depression
	Wang, Chang, Chen, & Hsu (2014)	Post-traumatic Growth	*n*=124	Growth Mixture Modeling applied to PTG scores at day 1, and 3,6,12 months after surgery	4: Stable high (27.4%), High Decreasing (39.4%), Low Increasing (16.9%), Low Decreasing (16.9%)	-Low Deceasing class more NA, more anxiety, worse MCS -High Decreasing class negative associates between PTG and NA, depression and anxiety
	Onselen et al. (2012)	Sleep Disturbance	*n*=398	Growth Mixture Modeling applied to sleep disturbance scores monthly for 6 months following surgery	3: Low (39.7%), High (55.0%), Decreasing (5.3%)	-High class had younger age, lower KPS, higher SCQ, hot flashes -Decreasing class had CTX - Mastectomy or breast reconstruction -Decreasing & High classes had higher fatigue -High class had higher trait anxiety, state anxiety, CES-D
	Gold et al. (2016)	Anxiety Depression	*n*=335	Growth Mixture Modeling applied to Spielberger State-Trait Anxiety Inventories and CES-D scores at prior to and 6 months after surgery	4: Higher Anxiety and Subsyndromal (44.5%), Lower and Anxiety and Resilient (32.5%), Higher Anxiety and Resilient (11.6%), Lower Anxiety and Subsyndromal (9.3%)	-Higher Anxiety and Subsyndromal class younger -Higher Anxiety and Resilient and Higher Anxiety and Subsyndromal classes more non-white -Both Subsyndromal classes lower KPS scores -Higher Anxiety and Subsyndromal class lower physical lower QOL

with similar symptom trajectories (Dodd et al., 2010). Over three measurement times, baseline, post-treatment, and 1-year follow-up, a class with all low symptoms, a class with mild symptoms, a class with moderate symptoms, and a class with all high symptoms were fitted using cluster analysis. All four classes were found at baseline and post-treatment, and only the low symptoms class was not found at 1-year follow-up. The all high symptoms class reported poorer functional status and QOL when compared to the other classes. Gwede et al. (2008) also used Cluster Analysis to fit two classes, high and low symptoms over two measurement times, baseline and end of chemotherapy. The high symptoms class was more likely to have less advanced staging and report greater symptom prevalence and poorer QOL following treatment. A disadvantage of cluster analysis in subgroup studies is the assumption that classification is perfectly reliable, while in reality, classes based on longitudinal trajectories of symptoms are likely to have more ambiguous boundaries. Therefore, conclusions about antecedents and consequences to these classifications may be erroneous (Colder et al., 2002). Importantly, cluster analysis only allows for studying one dimension of change in a variable, where, for example, symptoms severity and distress associated with a symptom could not be simultaneously studied (Colder et al., 2002). Additionally, this method does not allow for the easy identification of individual change in symptom experience over time, or the ability to follow an individual's growth model and map it to a class trend.

Latent Class Analysis

Langford et al. (2016) used latent class analysis (LCA) to identify classes of women with breast cancer who experienced a common symptom presentation of four symptoms: pain, fatigue, sleep disturbance, and depression, during the week following

chemotherapy administration. Three classes were identified: low, moderate, and all high. Potential antecedents and consequences to class membership were studied, and participants in the all high class had a lower functional status, higher comorbidity profile, higher symptom burden, and poorer quality of life. Importantly, LCA was used to determine classes of women who experienced a common symptom presentation in a cross-sectional design, at a single measurement time following chemotherapy administration. LCA does not allow for modeling trajectories over time. When studying classes of individuals with similar symptom experiences, a statistical method that allows for the statistical inference of trajectories of individuals and modeling of classes based on change over time is optimal.

Latent Growth Mixture Modeling

Conventional latent growth modeling allows for modeling of individual differences in growth on an outcome, providing latent growth factor means and variances. Latent growth mixture modeling (LGMM) further allows for the identification of discrete classes of individuals on the basis of common trajectories of growth, wherein each latent class has its own model of growth. The categorical latent variables represent the category or class that describes groups of individuals who are homogeneous within that class and are heterogeneous across classes (Muthen & Muthen, 2000). Classes are defined on the basis of different trajectories of change. The goal of LGMM is to add classes stepwise until the model shows the smallest number of latent classes that can describe the associations among a set of observed measures (Muthen & Muthen, 2000). Further, the probability of membership in a class and variances within the classes are estimated for each individual, accounting for unreliability of classification (Colder et al., 2002).

Finally, LGMM may relate the probability of class membership to antecedents and may relate the probability of a given consequence based on class membership (Muthen & Muthen, 2000).

There are a few studies that have used LGMM, and similar methods of Finite Mixture Modeling, to identify distinct classes of women with breast cancer experiencing similar symptom trajectories during various time points ranging from diagnosis through end of treatment and into survivorship. Among studies of the symptoms of mood disturbance, depressed mood and anxiety, there are several that have applied these methods to measures of these symptoms over time with varying findings (Bidstrup et al., 2015; Dunn et al., 2015; Gold et al., 2016; Helgeson et al., 2004; Henselmans et al., 2010; Lam et al., 2010; Wang et al., 2014). Henselmans et al. (2010), Lam et al. (2010), and Gold et al. (2016) described four classes of psychological distress that were similar in trajectories, but different class count percentages. Helgeson et al. (2004) described four classes for physical adjustment and four classes for psychological adjustment over several years of follow-up. Dunn et al. (2015) described four classes of depression and Bidstrup et al. (2015) described three classes of depression, five classes of distress, and 2 classes of anxiety. Finally, Wang et al. (2014) described four classes of posttraumatic growth during the 1st year after surgery for breast cancer. Varying findings may be attributed to differences in sample demographics, differing measurement time points, and differences in the instruments used to measure varying symptoms. Additionally, Onselen et al. (2012) used LGMM to describe three classes explaining the trajectories of disturbed sleep.

These reports are especially pertinent to clinical care as identification of classes

using LGMM allows model specification that includes potential antecedents, covariates, and consequences of class membership, including demographic and clinical variables. For example, Lam et al. (2010) described four classes of the trajectory of psychological distress: resilient, chronic, recovered, and delayed-recover classes. Distinguishers of class membership were determined, finding that those in the resilient class had less distress from symptoms and less problems with satisfaction with treatment decisions. In this sample, age, stage of disease, education, and occupation were also associated with class membership, suggesting a potential risk profile that clinicians could apply in practice (Lam et al., 2010). While the methods described in these papers assist in the development of future studies and the results are promising, much work is needed to replicate findings in the symptoms of mood disturbance and disturbed sleep and study additional prevalent symptoms experienced by women with breast cancer, such as fatigue, pain, and nausea and vomiting.

Summary

In summary, prevalent and distressing symptoms reported by women receiving treatment for breast cancer include fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea and vomiting, and trouble thinking. Demographic and clinical variables may act as antecedents to symptom presentation. Symptoms co-occur in women undergoing treatment for breast cancer and are associated with consequences, such as decreases in functional status, quality of life, and activity. Newer approaches to studying classes of women with similar symptom experiences, including LGMM, enhance the scientific understanding of the symptom trajectories unique to individuals and the potential antecedents, covariates, and consequences of these trajectories.

Theoretical Framework

Several theoretical frameworks exist that underpin cancer-related symptom research. Four of the more relevant frameworks to symptom cluster research include the Theory of Unpleasant Symptoms, the Symptom Management Model, the Symptom Interaction Framework, and Sickness Behavior (Barsevick, 2007; Dodd et al., 2001).

The Theory of Unpleasant Symptoms describes the complex and multidimensional nature of the symptom experience with three major components: the actual symptoms, influencing factors that assist in the development of the symptoms, such as tumor burden and treatment, and the consequences of the symptoms, such as declining functional status or inability to continue employment (Lenz et al., 1997). In addition, each symptom is conceptualized to be a multidimensional experience, involving the dimensions of intensity, timing, and quality. Among the influencing factors are physiologic factors, such as normally functioning bodily systems, pathology, trauma, and level of energy. Finally, consequences or outcomes may include functional performance outcomes or cognitive activity outcomes (Lenz et al., 1997).

While the Theory of Unpleasant Symptoms presents a more linear process of antecedents, symptoms, and consequences, the Symptom Management Model describes an interrelationship between the symptom experience, symptom management strategies, and patient outcomes (Dodd et al., 2001). The symptom experience is the individual's perception of the dimensions of a symptom. Symptom management strategies refer to changing methods for coping with and decreasing the symptom and the symptom outcome. Symptom outcomes refer to symptom status, functional status, emotional state, self-care, quality of life, cost, mortality, and morbidity (Barsevick, 2007; Dodd et al.,

2001).

The Symptom Interaction Framework describes synergistic relationship or interaction among symptoms and argues for the possibility of a common underlying etiology (Parker, Kimble, Dunbar, & Clark, 2005). Sickness Behavior refers to a constellation of behavioral and physiologic responses, possibly a symptom cluster, first observed in animals after administration of pro-inflammatory cytokines (Cleeland et al., 2003). Studies in humans reveal a similar response to inflammatory cytokines released in response to infection that act in the brain to induce common symptoms of sickness, such as loss of appetite, sleepiness, withdrawal, fever, aching, and fatigue (Kelley et al., 2003). Both the Symptom Interaction Framework and Sickness Behavior point to a common causal mechanism for the presence of multiple symptoms.

All of these theories acknowledge and signify the multiplicative nature of the concurrence of multiple symptoms (Lenz & Pugh, 2008). Additionally, these models describe the existence of factors that may influence the development of a symptom cluster, suggesting the potential for a common etiology, and how a symptom cluster may influence outcomes. None of these models describe how to identify symptoms that co-occur in classes of individuals with varying frequency and severity during chemotherapy treatment. This study utilized constructs shared across the four theories: the multiplicative nature of symptoms and the existence of antecedents and consequences to symptoms. In addition to these ideas, this study assumed that symptoms co-occur in individuals in such a way that those individuals can be subclassified based on their unique symptom trajectories. The methodological approach captured the unique symptom experience of the individual while describing the synergistic relationship

among symptoms within class membership. This study further examined whether class-membership was predicted by antecedents such as age, chemotherapy regimen, or stage of disease, that uniquely precede the development of a symptom trajectory, and whether class-membership preceded the development of outcomes, such as variation in functional status, days of missed work, or hours spent laying down (see Figure 1.1).

Significance of the Study

While prolongation of life and achieving a disease-free state is the primary goal of cancer therapy, clinicians must be aware of the symptoms associated with tumor burden and cancer treatment, the mechanisms that support symptoms, and approaches for managing symptoms (Wood et al., 2006). Not only are symptoms contributors to decreased quality of life and ability to function, but they may also interrupt treatment and influence treatment effectiveness (Beck et al., 2010; Bradley et al., 2007). Prompt evaluation of symptoms reduces use of emergency room and hospitalization, cost of treatment, and patient distress (Byar et al., 2006; Cleeland et al., 2000).

Through examining the growth of symptoms during the course of breast cancer chemotherapy using latent growth mixture modeling (LGMM), this study provides a significant contribution to the current body of symptom literature. A unique contribution of this study is the richness of the symptom data available for analysis. Ten symptoms with daily reporting were studied in an exploratory method. All symptoms were used to define the model, as opposed to predetermining a few symptoms based on the literature. This allowed for an exploratory analysis. The trajectory of multiple symptoms was simultaneously modeled to identify latent classes of individuals who exhibited similar symptom trajectories. In addition, antecedents of the latent classes were incorporated

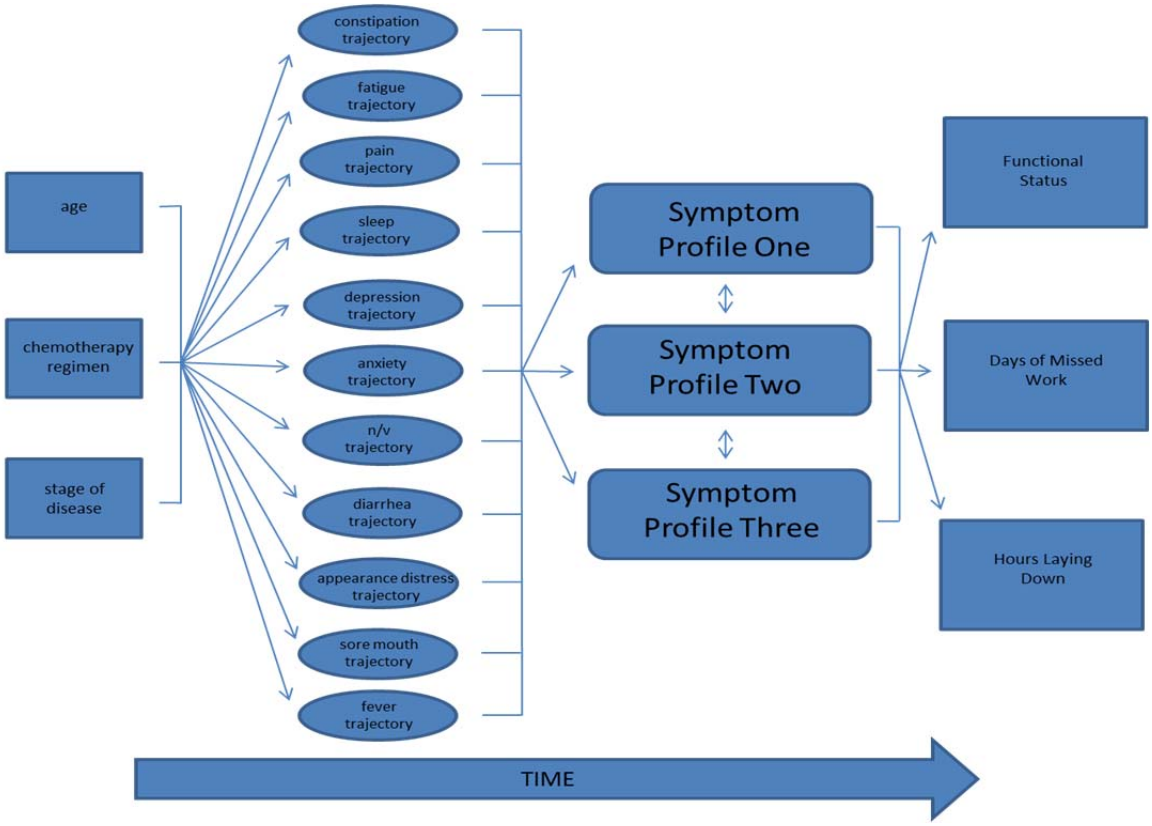

Figure 1.1 Theoretical framework.

with class membership, allowing for the examination of predictors of the different class trajectories, suggesting potential etiological factors that may be involved in the various symptom trajectories. Finally, the latent classes themselves were used as potential correlates of outcomes to allow for predetermination of individuals at risk for poor health outcomes.

Identification of groups of patients who experience a similar multisymptom profile trajectory, along with potential antecedents and consequences to that particular multisymptom profile trajectory, will allow clinicians the ability to identify at-risk individuals prior to and throughout the treatment process. Identifying at-risk individuals through the use of antecedents or correlates or through modeling symptom profiles during

early chemotherapy cycles and knowing which of these profiles exhibit poor outcomes may allow clinicians to intervene or modify treatment to prevent poor outcomes.

Research Design and Methods

This study was a secondary analysis of data collected as part of two longitudinal, randomized controlled trials that tested the use of an automated telephone-linked-care system for monitoring symptoms and intervening in the presence of symptoms during chemotherapy: "Telephone-linked Care for Cancer Symptoms Management (TLC-Chemo Alert)," which was funded by the NIH/DHHS (R01 CA89474 Mooney, PI) and "Symptom Care @ Home (SCH)," which was funded by the NIH/DHHS (R01 CA120558 Mooney, PI). Additionally, data were included from a nonrandomized, longitudinal study utilizing the same automated telephone-linked-care system for data collection of the presence of symptoms during chemotherapy: "Symptom Care by Phone (SCP2)" (Mooney, PI).

Description of Parent Studies

Study 1: Telephone-linked Care for Cancer Symptoms Management (TLC-Chemo Alert)

The purpose of the TLC-Chemo Alert trial, henceforth referred to as Study 1, was to test the efficacy of the telephone-linked-care automated system in the symptom management of adults receiving chemotherapy as compared to a control group of daily telephone data collection without alerts. The methods, including a description of the TLC automated system, are further described by Mooney, Beck, Friedman, Farzanfar, and Wong (2014). Participants were randomly assigned to an intervention group or a control group. All participants, regardless of group assignment, were instructed to participate in a daily phone call with the TLC automated system, where they were asked

to report on the severity of and distress associated with ten symptoms: pain, fatigue, nausea/vomiting, fever, trouble sleeping, anxiety, depressed mood, sore mouth, diarrhea, and constipation. Participants were asked whether symptoms were present during the past 24 hours and, if present, they rated severity and distress on a Likert scale (0-10) for all symptoms with the exception of fever. If fever was reported, participants entered the highest temperature numerically and distress associated with fever was measured. For the experimental group, two thresholds were set to alert the participant's healthcare provider and team, either an alert when a symptom was rated as greater than or equal to 5 or 7 (depending on the symptom) and trend alerts based on a pattern of moderate to severe levels reported over three out of the past 7 days. The control group used the same TLC automated system to report on the presence of symptoms and rated those symptoms in the same manner as the experimental group. No provider alerts were generated for the control group, although participants in both groups were advised to notify their provider for any concerns about their symptoms. There was no effect for the main hypothesis that the experimental group would have less symptom severity, symptom distress, and symptom interference with normal activities when compared to the control group. Therefore, data from all participants in Study 1 with a breast cancer diagnosis, regardless of study group, were utilized in this secondary analysis.

The sample for Study 1 was stratified within each of 11 provider teams. All patients who met the eligibility criteria were invited to participate.

Criteria for inclusion (participants from Study 1):

- Histological diagnosis of cancer
- At the end of their first cycle of a chemotherapy that was planned for at

least 6 months

- Reported at least one symptom of moderate or greater intensity during their first chemotherapy cycle
- 18 years of age or older
- Able to speak and read English or Spanish
- Physically and mentally able to participate
- Care under the direction of one of the 11 designated provider teams
- Access to a telephone on a daily basis

Criteria for exclusion (participants from Study 1):

- Receiving concurrent radiation therapy or biotherapy agents

For Study 1, participants were recruited from four ambulatory oncology clinics in two states in the U.S., including a community cancer center in the southeast, two community practices in the west, and a clinical cancer center in the west. Eleven provider teams (oncologists and nurses) consented to participate in the study. Potential study subjects were identified from the patient roster for each of the 11 provider teams, and eligibility criteria was reviewed. Each eligible, potential participant was sent a letter of introduction, describing the study in detail. Potential participants were given a phone number to call if they had questions and a prepaid postcard to send in if they did not wish to participate in a screening interview. A screening telephone interview was conducted with potential participants to explain the study, answer questions, obtain verbal informed consent, background socio-demographic information, eligibility criteria, and set up study visit appointments. Eligibility based on experience of poorly controlled symptoms during their first cycle of chemotherapy was also reviewed during this phone call, where the

patient was asked to rate the highest level of severity and distress experienced on each symptom and their overall degree of interference with normal activities during the first cycle of chemotherapy. For those eligible patients who gave verbal informed consent during the phone call, an appointment was made with a research assistant to obtain written informed consent, enroll the subject in the study, and demonstrate the telephone data collection system.

A total of 250 participants were accrued in Study 1. Of the total *n* (250), 223 participants completed the study through cycle 3, of which, 94 were diagnosed with breast cancer.

Study 2: Symptom Care @ Home (SCH)

The purpose of Study 2 was to test the efficacy of the an integrated, computer-based symptom monitoring system combined with self-care strategies and Nurse Practitioner delivered, guideline-based symptom care in decreasing symptom severity and distress and interference with functional performance. Participants were randomized to an experimental intervention group or a control group. All participants participated in a daily call with the automated SCH system, the same system used in Study 1, expanded to include four new components. First, participants were asked to report on the presence of 11 symptoms: fatigue, trouble sleeping, nausea and vomiting, pain, feeling blue or down, feeling nervous or anxious, distressed over appearance, diarrhea, constipation, sore mouth, fever, and trouble thinking or concentrating. For all symptoms, when present, participants were asked to rate the severity of and distress associated with the symptoms on a Likert scale (0-10), with the exception of fever. If fever was present, participants reported the highest temperature numerically and the distress associated with it.

Additionally, the Study 2 experimental participants were given self-care symptom management suggestions by the SCH system, automated provider alerts for uncontrolled symptoms, and unrelieved symptoms at moderate or greater levels generated an alert to the study Nurse Practitioner who initiated follow-up care. For the 11 symptoms, 29 different responses generated an alert, for either a severity rating of 5 or greater or a pattern of responses, such as a symptom reported at moderate or greater levels during 3 of the past 7 days. Participants in the usual care group were not given self-care strategies nor had unrelieved symptoms alerted to their provider or managed by the study Nurse Practitioner, but were reminded to call their healthcare provider for symptom concerns. Preliminary data analysis suggests that there were differences in reported symptoms between the groups, with a potential main effect of the intervention on symptom severity, distress, or interference with functional performance. For that purpose, only data collected from participants randomized to the control group were utilized in this secondary analysis.

The sample for Study 2 was stratified from six provider practices. All patients who met the eligibility criteria were invited to participate.

Criteria for inclusion (participants from Study 2):

- Histological diagnosis of cancer
- A life expectancy of at least 3 months
- Cognitively able to participate
- Beginning a new course of chemotherapy planned for a minimum of 3 cycles
- 18 years of age or older

- Able to speak and read English
- Care under the direction of 1 of the 6 provider practices
- Access to a telephone on a daily basis

Criteria for exclusion (participants from Study 2):

- Receiving concurrent radiation therapy or biotherapy agents

For Study 2, potential participants were recruited from four oncology practices at a cancer center in the western United States and two oncology practices at a public hospital in the southern United States. Six provider practices consented to participate in the study. Potential study subjects were identified from patient rosters for each provider practice. The eligibility criteria were verified by data from the medical record and review by the medical team. Potential participants were approached at their treatment planning visit or by phone prior to the first chemotherapy visit. During initial contact, the research assistant explained the study, answered questions, obtained verbal informed consent, obtained socio-demographic background information, verified eligibility, and set up a study entry visit. For those eligible patients who gave verbal informed consent, a study entry appointment was arranged where staff obtained written informed consent, obtained initial study measures, opened random assignment, explained the telephone data collection system, and answered questions.

A total of 358 participants were accrued in Study 2, 178 were randomized to the control group and 180 to the experimental group. Of the total *n* (358), 156 participants were diagnosed with breast cancer, with 89 of those in the control group.

Study 3: Symptom Care by Phone (SCP2)

The purpose of Study 3 was to develop a database of genotype/phenotypes of cancer treatment related symptoms and toxicities for at least 400 individuals receiving cancer chemotherapy. The objective of this study was to collect descriptive information about the phenotype and to have banked DNA for the genotype. Participants were recruited to participate in a daily call with the automated SCH system, where they were asked to report on severity of and distress associated with the same eleven symptoms as those reported in SCH. Sampling procedures were continued from Study 2 and conducted in the same manner. At the time of this secondary analysis, 38 participants were accrued in Study 3. Of the total *n* (38), 29 were diagnosed with breast cancer.

Measures

All 3 parent studies utilized similar instrumentation, but included varying symptoms. Demographic and disease-related data were collected at baseline from the participant and from the medical record in all three studies. Demographic data included age, gender, race/ethnicity, employment status, education, and socioeconomic status. Disease factors included primary cancer diagnosis, extent of disease, and details of the chemotherapy protocol.

For Study 1, both experimental and control groups used the TLC data collection system, which assessed prevalence on 10 selected symptoms and the overall degree of interference with normal activities during the past 24 hours. If a symptom was present, the patient was asked a series of specific questions about the symptom and how they were currently managing it. The TLC Conversation was as follows:

- Greeting; asked patient for personal password

- Patient entered password and TLC retrieved file and extended personal salutation
- TLC asked whether patient had experienced each of the 10 specific symptoms during past 24 hours
- TLC asked presence, severity and distress data for each of the 10 symptoms, with the exception of fever, which, if present, TLC asked for the highest temperature and distress associated with it.
- For each symptom present, TLC asked questions specific to that symptom
- If more than 1 symptom was present, the system cycled back to the next symptom
- TLC asked the overall degree of symptom interference with normal activities
- TLC asked if any patient or provider-initiated contact (notification of study team if yes)
- Personal message from provider team (rotated among 7 messages)
- Closing, TLC reminded participant about calling healthcare team with any concerns

For the Study 2 control group and Study 3 participants, the daily SCH data collection system was used to assess, over the previous 24 hours, prevalence of 11 symptoms and the overall degree of interference with normal activities. If a symptom was present, the patient was asked a series of specific questions about the symptom and how they were currently managing it. Study 3 was conducted in the same manner. The SCH conversation was as follows:

- Greeting; asked patient for personal password
- Patient entered password and SCH retrieved file and extended personal salutation
- SCH asked whether patient had experienced each of the 11 specific symptoms during past 24 hours or whether they were too ill to talk on the phone in the SCH study
- SCH asked presence, severity and distress data for each of the 11 symptoms, with the exception of fever, which, if present, SCH asked for the highest temperature and distress associated with it.
- For each symptom present, SCH asked questions specific to that symptom
- If more than one symptom was present, the system cycled back to the next symptom
- SCH asked the overall degree of symptom interference with normal activities and amount of time spent lying down
- Personal message from provider team (rotated among seven messages)
- Closing, SCH reminded participant about calling healthcare team with any concerns

In all studies, participants were instructed to call the automated system number by noon each day, and if the patient forgot, the automated system called the participant to obtain the daily ratings, decreasing the potential for missing data. For Study 1, the call compliance for participants with breast cancer (*n*=94) was 70.1%. For Study 2, the call compliance for participants with breast cancer in the control group (*n*=89) was 91.4%. For Study 3, the call compliance for participants with breast cancer (*n*=25) was 65.3%.

Single-item indicators were used to assess each symptom to eliminate the potential for diluted impact of particular symptom seen in summative symptom measures (Mooney et al., 2014). Participants were asked, "During the past 24 hours did you experience (symptoms)?" A no response was scored as zero and a yes response led to questions using a 1 to 10 Likert scale for the severity associated with that particular symptoms.

In Study 1, functional status was measured using the 12-Item Short-Form Health Survey, SF-12 (Version 2). In Study 2 and Study 3, functional status was measured using the 36-Item Short-Form Health Survey, SF-36 monthly during study participation. The SF-36 is a health survey composed of 36 questions that document, through a 5-scale profile, both physical and mental functioning and well-being. The SF-12 is a shorter subset of the SF-36, composed of 12 items. The SF-12 was developed after it was determined that the SF-36 physical and mental component summary scales capture about 85% of the reliable variance in the full SF-36. The SF-12 assumes that these two outcome measures are satisfactory for most purposes. Additionally, this reproduction of these two components in the SF-12 is accurate enough to warrant the use of published norms for SF-36 summary measures in interpreting SF-12 summary measures (Ware et al., 1996). Both scales are widely used and have reported reliability and validity across many patient populations (Mchorney, Ware, Lu, & Sherbourne, 1993; McHorney, Ware, Lu, & Sherbourne, 1994; Ware et al., 1996).

A daily measure of days of missed work was asked for those participants in Study 2 and Study 3 who reported being employed. A daily measure of hours spent lying down over the past 24 hours was collected for participants in Study 2 and Study 3.

In all studies, baseline data were collected prior chemotherapy cycle 2 (in Study 1) and chemotherapy cycle 1 (in Study 2 and Study 3). Daily symptom data were collected using the automated system during cycles 2 and 3 for Study 1 and during cycles 1, 2, and 3 for Study 2 and Study 3. In all studies, monthly functional status was collected.

Sample

All participants in Study 1 and Study 3 with a breast cancer diagnosis who met the eligibility criteria and all participants in Study 2 with a breast cancer diagnosis who met the eligibility criteria and were randomized to the control group were included in this secondary analysis. Participants were excluded from the sample if they did not complete the parents study through cycles 2 and 3 of chemotherapy. For the current study, 279 women with breast cancer were combined from the three parent studies. Eighty women were not included who were randomized to the intervention group for Study 2. One-hundred sixty-six women who completed study measures through cycles 2 and 3 of chemotherapy were identified. For cycle 2, 165 of those women reported on symptom severity at least 3 days during chemotherapy and for cycle 3, 155 of those women reported on symptom severity at least 3 days during chemotherapy (see Figure 1.2). Because growth mixture modeling requires multiple measurement time points, only women with at least 3 days of symptoms severity (0-10) over the first 14 days of the cycle were included in the models. For cycle 2, only 1 woman was excluded for this reason and for cycle 3 only 10 women were excluded as a result of less than three daily calls. These same women were excluded from tests of distinguishers of class membership including clinical, demographic, and symptom variables because they were

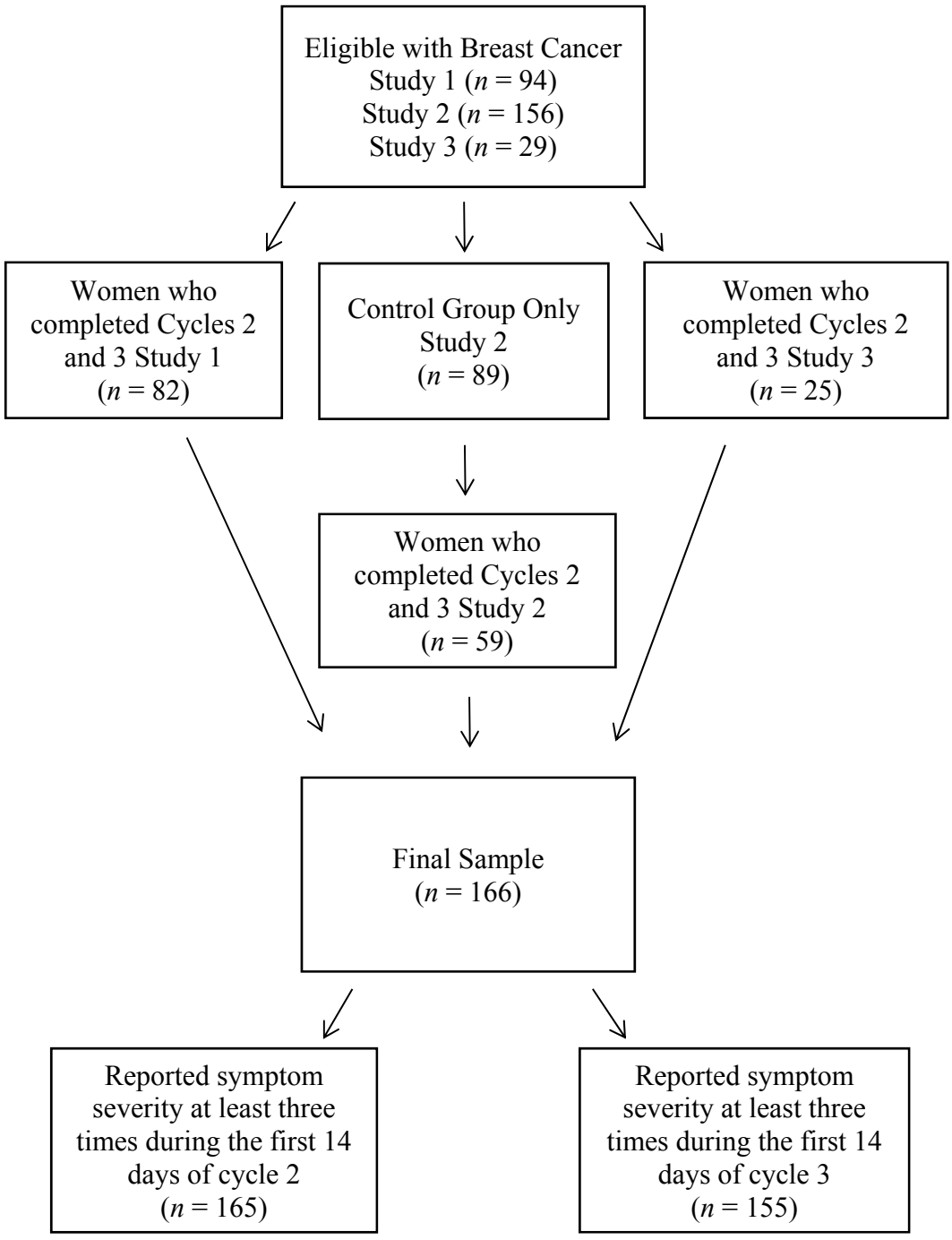

Figure 1.2 Sampling procedures.

not assigned a predicted class membership in the original models.

The total sample size for this secondary analysis was 165 women in cycle 2 and 155 women in cycle 3. Although this sample size is relatively small, it was adequate to apply the proposed statistical analysis. A limitation of the proposed analysis methods (growth mixture modeling) is the requirement for multiple measurement time points; at least three time points is preferred (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009). With this comes the requirement for a larger sample size to increase power and allow for the assumed attrition rates. There is no general rule for determining sample size applicable to all situations in growth modeling; however, the Monte Carlo method has been recommended (Muthen & Muthen, 2002). Assuming the missing data from the sample are random, the Monte Carlo method would estimate a sample size requirement between 150 and 250 participants (Muthen & Muthen, 2002). Regardless, given the nature and limitations of a secondary analysis, the data for 166 participants were available and included in this study. Because growth mixture modeling requires multiple measurement time points, only women with at least 3 days of symptoms severity (0-10) over the first 14 days of the cycle were included in the models. For cycle 2, only 1 woman was excluded for this reason and for cycle 3 only 10 women were excluded as a result of less than 3 daily calls. These same women were excluded from tests of distinguishers of class membership including clinical, demographic, and symptom variables because they were not assigned a predicted class membership in the original models.

Data Procedures

Data included in this study were daily symptom severity reports on eight symptoms common to all three parent studies (fatigue, pain, disturbed sleep, depressed mood, anxiety, nausea, diarrhea, and sore mouth) and two symptoms unique to Study 2 and Study 3 (distress associated with changing appearance and trouble thinking) for the first 14 days of cycles 2 and 3 of chemotherapy for all participants. Additionally, functional status measures, as measured by the SF-12 in Study 1 and the SF-36 in Study 2 and Study 3, were included. Days of missed work and hours spent lying down were used for participants in Study 2 and Study 3.

Data from all studies were cleaned and combined into one SPSS file for analysis purposes. The data for this secondary analysis had an initial data cleaning in the course of the analysis and dissemination of the primary studies. Additionally, outliers and extreme cases were identified prior to initiating data analysis.

This secondary analysis was reviewed by the Institutional Review Board (IRB) at the University of Utah. Subjects were identified only by their original study identification number. All computer files were password protected.

Analysis

The Software Statistical Package for the Social Sciences (SPSS), version 23.0 was used for data management and data analysis and MPlus, version 6.0 was used for data analysis. The data were cleaned and transformed to a person-period data set, where each individual has multiple records, one for each period in which he or she was observed (Singer & Willet, 2003). The person-period data set contained a subject identifier, a time indicator (time of measurement), outcome variables (symptom scores for each symptom

on a Likert scale 0-10 and functional status scores measured by SF-12/36), and correlate variables (demographic and disease-related variables). Alpha was set at 0.05 to reduce type I error.

Means, standard deviations, and evaluation of distributions were described for sample data, including age, ethnicity, marital status, employment, education status, income, stage of disease, and chemotherapy regimen.

Specific Aim 1

Specific aim 1 was to determine the trajectories and profile classes associated with the severity of 10 symptoms (fatigue, pain, disturbed sleep, depressed mood, anxiety, nausea, diarrhea, sore mouth, distress associated with changing appearance, and trouble thinking) reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer.

Research Question 1.1: What are the trajectories of the severity of individual symptoms reported by women undergoing chemotherapy for breast cancer during cycle 2 and cycle 3?

To accommodate for varying cycle lengths, only data collected during the first 14 days of each cycle for all measures were included in the analysis. The prevalence of each symptom (fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea/vomiting, sore mouth, and diarrhea) within the entire sample and of two individual symptoms (distress associated with changing appearance and trouble thinking) within a subsample of participants from Study 2 and Study 3 over the first 14 days of cycles 2 and 3 of chemotherapy was determined. Additionally, the prevalence of these sample symptoms at moderate to severe levels (rated 4-10) was determined. The number of days where

each symptom was reported at a level 0, reported at a level 1-10, and reported at a level 4-10 for each individual symptom over the first 14 days of cycles 2 and 3 of chemotherapy were also determined.

An exploratory analysis was conducted to describe how individuals in the data set changed over time on each symptom using graphical visualization and conventional growth mixture modeling for each cycle of chemotherapy (cycle 2 and cycle 3 separately). This analysis provided an intercept, slope, and quadratic term that described the baseline measure and rate of change for each symptom, as well as profile classes that describe groups of individuals who have a similar intercept, slope, and quadratic term for each individual symptom. First, an aggregate model with an intercept, slope, and quadratic function for each symptom was described. Second, a latent class model with classes that have unique intercepts, slopes, and quadratic terms for each symptom were described.

Simple regression models are designed for cross-sectional data, and provide an intercept and slope that represents the relationship between a correlate and an outcome variable. The model is fitted to the sample data and population parameters are estimated, i.e., the intercept, slope, and variances. A "goodness-of-fit" statistic is provided that quantifies the correspondence between the fitted model and the sample data. In a well-fitted model, the estimated population parameters can be used to draw conclusions about the direction and magnitude of the effect of the correlate variable. Alternatively, analysis of longitudinal data requires the use of growth modeling, or statistical models that embody two types of research questions: questions about within-person change and questions about between-person change. For example, the model must first address the

question of how each individual's pain changes over the course of chemotherapy, the within-person change. Then the model must address the question of how individuals' pain trajectories vary by some observed or unobserved correlate variable, the between-person change. The assessment of both within-person and between-person change requires the model to have components at two levels: the level-1 submodel that describes the within-person change and the level-2 submodel that describes the between-person change. Combined, these two submodels form the multilevel statistical model. Conventional growth modeling allows for the examination of within-person and between-person change simultaneously, allowing for the mathematical representation of population behaviors (Singer & Willet, 2003).

Empirical growth plots were formed by plotting each person's symptom severity score versus time for each of the 10 symptoms. Data points indicated the severity of the individual symptom reported by the participant for each day during the first 14 days of the cycle of chemotherapy (cycle 2 and cycle 3 separately). Cycle length (the number of data points) was set at 14 days. Inspection of graphs allowed for a visual evaluation of the within-person trajectories of the severity of each symptom.

Taking the example of pain, plots were formed for each individual in the sample that demonstrated the individual's pain score over the time of measurement, one data point for each measurement time (see Figure 1.3). Nonparametric smoothed trajectories were superimposed on the individual empirical growth plots to begin to understand the variability, direction, and functional form of the symptom trajectory.

In keeping the example of pain, for each individual empirical growth plot of pain, a line was superimposed over the plot that "connected" the pain score at each

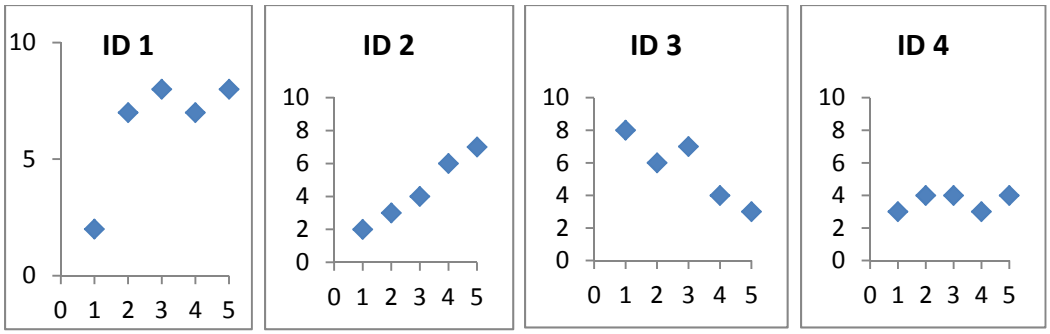

Figure 1.3 Example of plots of pain severity score for 4 participants over 5 days of one cycle (days 1-5). Days 1-5 are included in these plots to simplify the example. The actual visualization included data points for each day 1-14 during the cycle of chemotherapy (one graph for each participant for cycle 2 and for cycle 3), instead of only days 1-5 shown here. Pain severity is located to the *y*-axis and day is located to the *x*-axis.

measurement time (see Figure 1.4). Interindividual differences in change on individual symptoms over time were explored by plotting the entire set of smoothed individual trajectories on a single graph. The observed data (or plots) were omitted to decrease clutter and allow for easier visualization of the variability in trajectories. An average change trajectory for the entire group was added to the graph to help compare individual change with group change. The average change trajectory was calculated by determining time-specific means for the symptom of interest, plotting these means, and then applying the same nonparametric smoothed trajectory to the plot.

Continuing with the example of the plots of 4 participant's pain severity over days 1-5 of a chemotherapy cycle, the 4 participant's trajectories were combined on a single graph with an average change trajectory superimposed (see Figure 1.5).

The mathematical form of growth for each symptom was determined using conventional polynomial growth models. The level-1 submodel hypothesized about the shape of each person's true trajectory of change over time. Individual growth parameters, intercept, slope, and quadratic terms, were calculated for each person in the sample. The individual growth intercept represented the "starting point" for the individual on the measure of interest, in this case, initial pain score. The individual growth slope represented the rate of change for the individual on the measure of interest, in this case, the rate of change in the individual's pain score. In the level-1 submodel, individuals had their own intercept, slope, and possibly quadratic term, and thus their own trajectory. Individual growth trajectories for each symptom were displayed graphically by plotting the regression line for each individual in the sample on a single graph, allowing for visual examination of variability in the true individual trajectories.

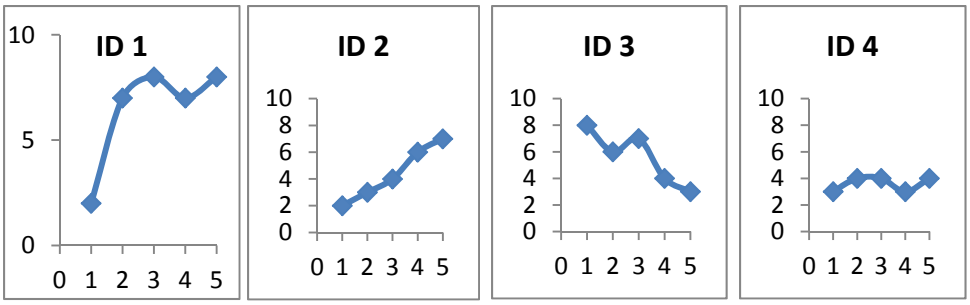

Figure 1.4 Example of plots of pain severity score for 4 participants over 5 days of one cycle (days 1-5) with a smoothed trajectory line superimposed. The actual visualization included plots for each day 1-14 during the cycle of chemotherapy (one graph for each participant for cycle 2 and for cycle 3), instead of just days 1-5 shown here. Pain severity is located to the *y*-axis and day is located to the *x*-axis.

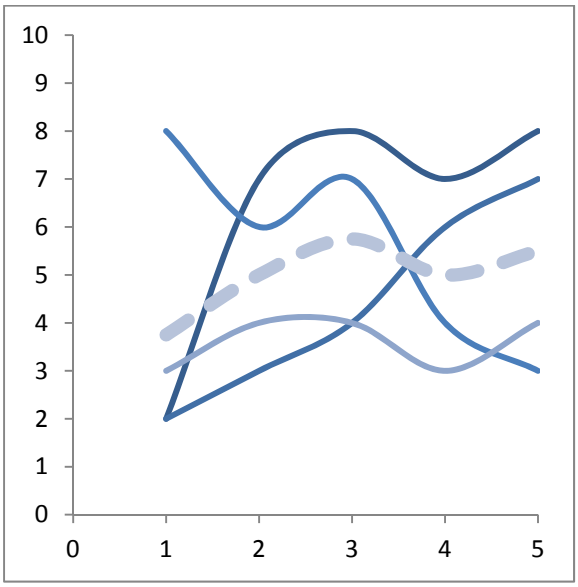

Figure 1.5 Example of set of smoothed trajectories of pain severity for 4 participants over 5 days of one cycle (days 1-5) on a single graph. The actual visualization included plots for each day 1-14 during the cycle of chemotherapy (one graph for each participant for cycle 2 and for cycle 3), instead of just days 1-5 shown here. Pain severity is located to the *y*-axis and day is located to the *x*-axis.

Next, the level-2 submodel for interindividual change on each symptom was studied. The level-2 submodel mathematically displayed the variability in individuals. The level-2 submodel provided an intercept and slope that represented the variability in the individual intercepts, or the average true initial status, and the average true rate of change in the variable of interest. This model was used to describe the average trajectory of each symptom over the 2 cycles of chemotherapy. Model determination was by maximum likelihood methods, or the determination of population parameters (intercept and slope and possibly a quadratic or cubic function) that maximize the probability of observing a particular set of data. In other words, the intercept, slope, and/or quadratic term were calculated for each symptom that maximized the probability of observing the data retrieved from the sample. The model started with an intercept-only model and then a slope was added to the model. If the slope was significantly different from zero, it was included in the model. Next, a quadratic function was added to the model using maximum likelihood estimates. If the quadratic function differs significantly from zero, it was included. A cubic function was tested in the same fashion. The model that best fit each symptom was selected on the basis of model chi square test, CFI, and RMSEA (Muthen, 2004).

For example, our individual pain plots showed a best fit line that demonstrated the individual pain intercept and the rate of change in the individual's pain score (the level-1 submodel) (see Figure 1.6). Next the population intercept and slope on pain were determined (the level-2 submodel) (see Figure 1.7).

This model was used to describe the average trajectory of the eight individual symptoms common to all three parent studies (fatigue, disturbed sleep, depressed mood,

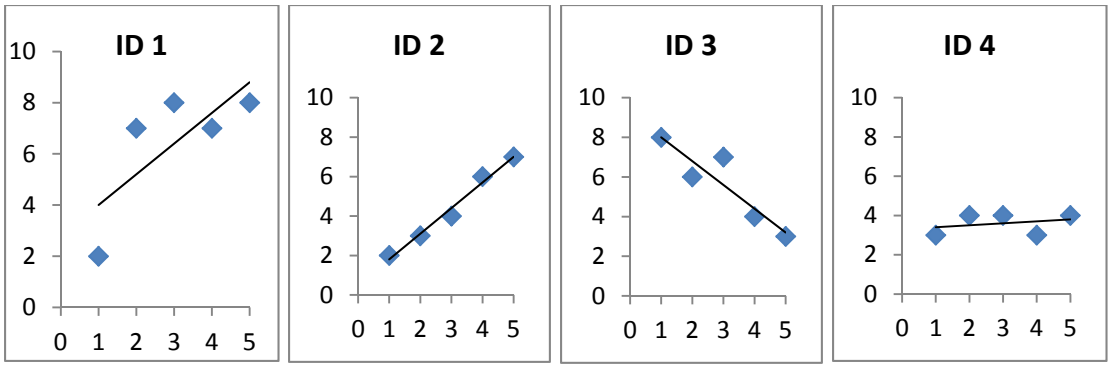

Figure 1.6 Example of plots of pain severity score for 4 participants over 5 days of one cycle (days 1-5) with best fit line superimposed. An individual pain intercept and rate of change (slope) could be calculated with this line. Pain severity is located to the *y*-axis and day is located to the *x*-axis.

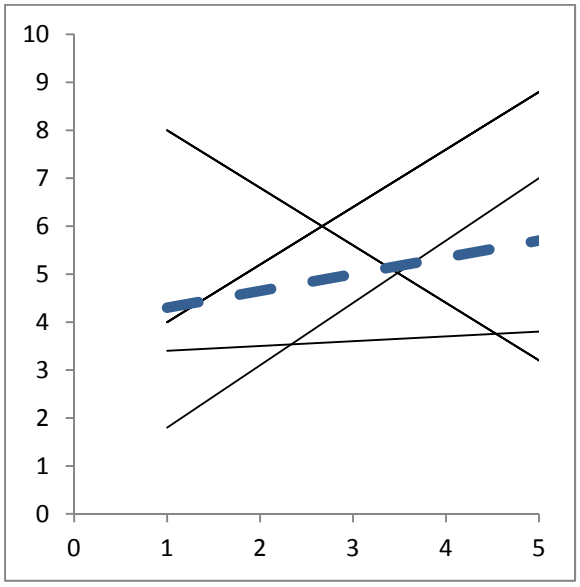

Figure 1.7 Example of the collection of best fit trajectories across all 4 participants and an average change trajectory line (dashed) over 5 days of one cycle (days 1-5) of chemotherapy. Population intercept and slope could be determined on this average change trajectory line. Pain severity is located to the y-axis and day is located to the x-axis.

anxiety, pain, nausea/vomiting, sore mouth, and diarrhea) and a subsample of only data gathered from participants in Study 2 and Study 3 for two symptoms unique to those parent studies (distress associated with changing appearance and trouble thinking).

Research Question 1.2: What are the trajectory profile classes, if any, associated with the severity of individual symptoms reported by women undergoing chemotherapy for breast cancer during cycle 2 and cycle 3?

After identifying the best growth model for each symptom with quantified intercepts, slopes, and possibly quadratic and/or cubic functions, the number of latent classes for each symptom was determined on the basis of means of the growth factors, using Latent Growth Mixture Modeling (LGMM). An unobserved categorical variable, the latent class variable, was added to the model to represent the latent classes (Colder et al., 2002). Each latent class corresponded to a subpopulation that had its own set of parameter values (intercept and slope). Variances and covariances of these growth factors within each class were also estimated to allow for within-class heterogeneity (Colder et al., 2002; Collins & Lanza, 2010; Muthen & Muthen, 2000). While the growth curve analysis used to address Research Question 1.1 produced growth factors and variance components for the entire sample on the symptom of interest, LGMM estimated a new latent categorical variables that identified distinct classes on the basis of differences in any combination of their intercepts, slopes, and within-class variances in intercepts and slopes (Dunn et al., 2008). A unique feature was that this method used a formal statistical procedure to test whether the hypothesized trajectories actually emerged from the data rather than assumed the existence of a particular number of trajectories or classes (Andruff et al., 2009).

The simplest assumption, a single-class model was hypothesized first. Then classes were added to the model to determine the solution (the number of classes) that best fit the data. Intercepts, slopes, and possibly quadratic or cubic functions were determined for each class. Models were evaluated on the Bayesian information criterion (BIC), used to evaluate improvement in model fit when additional classes were added. Smaller BIC values suggested a better model fit (Colder et al., 2002; Muthen & Muthen, 2000). If the addition of a class resulted in a reduction in the BIC value relative to the BIC from the previous model (without the added class), then the new model was considered an improvement and the class was retained. The addition of classes continued until the BIC did not decrease with the addition of a class.

Model selection was determined by multiple additional criteria, including the "K" versus "K-1" class models to determine whether a model with K classes fit the data better than a model with "K-1" classes with the parametric bootstrapped likelihood ratio (BLRT) and Vuong-Lo-Mendell-Rubin Likelihood Ratio Tests (VLMR) (Dunn et al., 2011; Jung & Wickerama, 2008; Nylund, Asparouhov, et al., 2007; Nylund, Bellmore, et al., 2007). Additionally, entropy, a summary measure of classification based on the probability of membership in each class for each individual that ranges from 0 to 1.0, was used to evaluate the models (Colder et al., 2002). The closer entropy values were to 1.0, the better the classification. Finally, the best-fitting model was examined for the number of subjects in each class (greater than 5% of the sample) and graphed visually to determine if the predicted trajectories made clinical and theoretical sense (Onselen et al., 2012).

To assist with model convergence problems, MPlus software incorporated the use

of random starting values to avoid local solutions in GMM (Jung & Wickerama, 2008). Missing data were accommodated by MPlus version 6.0 through use of Full Information Maximum Likelihood and the use of the Expectation-Maximization algorithm (Dunn et al., 2011; Onselen et al., 2012).

In keeping with the example of pain over the first 5 days of a cycle of chemotherapy, classes were fitted to the model that demonstrated a unique slope and intercept for pain (see Figure 1.8). Intercept referred to a baseline measure of pain and slope referred to the rate of change of pain over time during the first 14 days of each cycle. The class referred to a group of individuals within the sample who had a similar growth in their pain trajectory, or in other words, a similar slope and intercept for pain.

This individual symptom growth mixture modeling provided classes that displayed homogenous trajectories across each symptom that were heterogeneous from other classes. For example, a potential result might include a class that reported a moderate intercept and increasing severity of pain during the first 14 days of cycle 2; a class that reported a low intercept and a stable severity of pain during the first 14 days of cycle 2; and a class that reported a low intercept and an increasing severity of pain during the first 14 days of cycle 2. For each of these 3 classes, a unique intercept and slope for pain were calculated that demonstrated the baseline measure and rate of change for pain as reported by the participants in the class.

This model was used to describe the latent trajectory classes associated with the 8 individual symptoms common to all three parent studies (fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea/vomiting, sore mouth, and diarrhea) and a subsample of only data gathered from participants in Study 2 and Study 3 for 2 symptoms

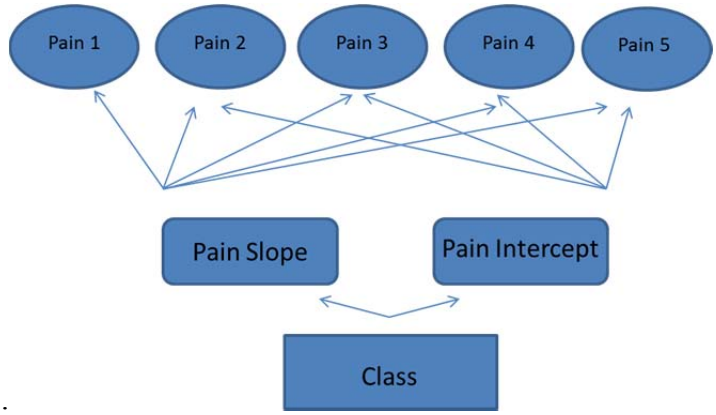

Figure 1.8 Form of growth for pain (example of linear form of growth for single symptom with 5 time points of interest). The class referred to a grouping of individuals with similar slopes and intercepts. Referring back to Figure 1.5, IDs 1 and 2 logically fell into a same class, as their trajectories were almost parallel, suggesting a similar slope. IDs 3 and 4 represented 2 other classes, as one had a more flat trajectory (stable pain over time) and the other had a trajectory that decreased over time.

unique to those parent studies (distress associated with changing appearance and trouble thinking).

Research Question 1.3: Do the profile classes associated with the severity of individual symptoms differ between cycle 2 and cycle 3 of chemotherapy?

Posterior probabilities and class assignments for each individual were saved into an output text file and extracted into the data set to be used for further analysis (Jung & Wickerama, 2008). Crosstabs were used to compare predicted class memberships extracted from the individual symptom growth mixture models between the two cycles of chemotherapy to test for movement in individuals to different classes between cycles.

Specific Aim 2

Specific aim 2 was to identify multisymptom trajectory profile classes of patients undergoing cycles 2 and 3 of chemotherapy for breast cancer.

Research Question 2.1: What multisymptom profile classes can be identified in a cohort of women undergoing chemotherapy treatment for breast cancer during cycle 2 and cycle 3?

After establishing the number of trajectory classes for each of the symptoms, latent classes were modeled on the basis of growth trajectories from multiple symptoms that display growth trajectories of interest, or those trajectories with significant variability over time (see Figure 1.9). These models represent the multisymptom models. Interesting growth trajectories included those symptoms with an average trajectory of slope that is significantly different from zero and/or those symptoms that had at least two latent classes that represent the average. For each cycle, a cross-tabulation was created using the highest class probability for each symptom of interest from the original

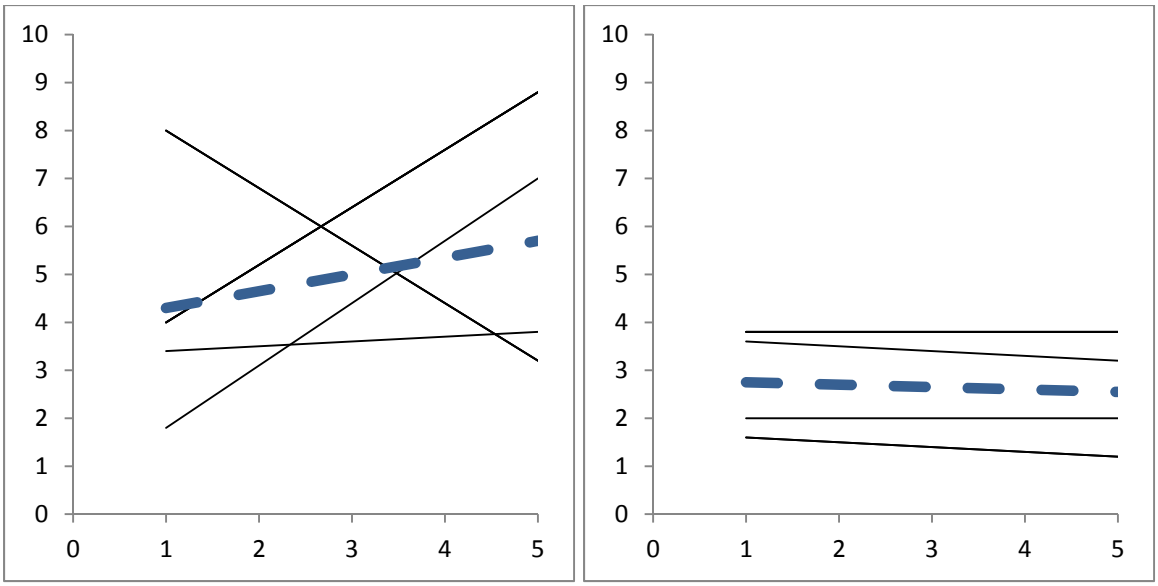

Figure 1.9 Example of plots of pain severity and diarrhea severity scores for two groups of 4 participants over 5 days of one cycle (days 1-5). The collection of best fit trajectories across all 4 participants and an average change trajectory line (dashed) for pain is on the left. The collection of best fit trajectories across all 4 participants and an average change trajectory line (dashed) for diarrhea is on the right. Population intercept and slope could be determined on this average change trajectory line. The trajectory for pain has an increasing slope, suggesting variability in pain across the population over time. The trajectory for diarrhea has a flatter slope, suggesting less variability in diarrhea across the population over time. In this case, diarrhea would not be included in the latent growth mixture analysis, while pain would be included. Pain and diarrhea severity are located to the y-axis and day is located to the x-axis.

individual symptom models. The cross-tabulation was used to estimate latent classes in the multisymptom model. An initial 1-class model was tested, and subsequent classes were added in descending order on the basis of cell-sizes in the cross-tabulation to determine the best model fit. Evaluation of the model was based on criteria as described above. While conventional growth modeling estimated a mean growth curve under the assumption that all individuals in the sample come from a single population, LGMM estimated a mean growth curve for each class (Colder et al., 2002). This multisymptom model provided classes that displayed homogenous trajectories across multiple symptoms that were heterogeneous from other classes. For example, a potential result might include a class that reports a high severity of pain, fatigue, and depressed mood; a class that reports low severity of pain, fatigue, and depressed mood; and a class that reports moderate severity of pain, fatigue, and depressed mood (see Figure 1.10). For each of these 3 classes, a unique intercept and slope for each symptom is calculated that demonstrates the baseline measure and rate of change for each symptom as reported by the participants in that class.

Specific Aim 3

Specific aim 3 was to determine if membership in differing individual symptom trajectory classes is determined by various demographic, clinical, and symptom variables.

Research Question 3.1: To what extent are differing symptom trajectory classes associated with variations in age, chemotherapy regimen, stage of disease, marital status, employment, education, and the presentation of other symptoms at moderate to severe levels?

After identifying the latent class solutions that best fit the data, differences among

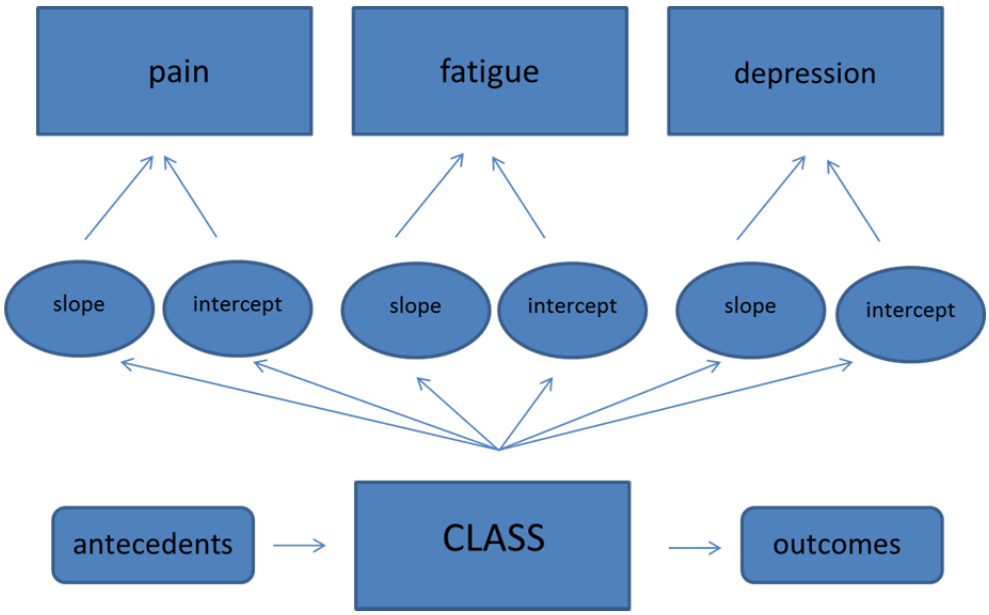

Figure 1.10 Latent growth mixture model for multiple symptoms.

the predicted classes for the individual symptoms were examined for potential antecedents (age, marital status, employment, education status, income, stage of disease, and chemotherapy regimen) using independent-samples *t* tests and ANOVA for tests of mean differences and chi-square for tests of association among categories. Additionally, it was determined whether the number of days with a summative score of fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting at moderate to severe levels during cycle 2 was an antecedent to individual symptom class membership during cycle 3 using independent-samples *t* tests and ANOVA. Differences among the predicted classes for the individual symptoms was also examined for potential co-occurring symptoms at moderate to severe levels using independent-samples *t* tests and ANOVA. While it is preferred to examine potential antecedents and co-occurring symptoms of the growth in different latent classes by incorporating these variables into increasingly complex structural models, this requires larger samples, especially when class counts may be small in the selected model (Dunn et al., 2011). Because our sample size was relatively small, posterior probabilities and class assignments for each individual were saved into an output text file and extracted into the data set to be used for further analysis in tests of mean differences across the classes on antecedents and co-occurring symptoms outside the model. Class membership then became a correlate for these variables (Jung & Wickerama, 2008). Because chi-square tests assume that each cell has an expected frequency of five or more, small cell sizes were accounted for with Fisher's exact chi-square. This technique allowed for tests of association among categories when cell sizes had an expected frequency of five or less (Green & Salkind, 2008).

Demographic and clinical variables were included as potential antecedents of

class membership using independent-samples *t* tests, ANOVA and chi-Square. Chemotherapy regimen was constrained to two theoretically relevant variables of interest, whether or not the individual received Doxorubicin and whether or not the individual received Taxane separately. Adjustments were not made for missing data on the demographic and clinical variables. Therefore, the sample for each of these individual analyses was dependent on the largest set of complete data across groups (Langford et al., 2016).

The overall symptom severity during cycle 2 was included as a potential antecedent of individual symptom class membership during cycle 3 using independent-samples *t* tests and ANOVA. Overall symptom severity for cycle 2 was calculated by combining the number of days where participants scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea. The total number of moderate to severe days for these symptoms combined was then compared to the extracted class membership for the individual symptoms in cycle 3 using independent-samples *t* tests and ANOVA. Follow-up post hoc contrasts were conducted to evaluate pairwise differences among the means for significant differences in class membership during cycle 3 based on overall symptom severity during cycle 2. In cases where equal variances were not assumed, the Dunnett's *C* test was used, which does not assume equal variances among the factor levels.

Tests of mean differences across classes on the number of moderate to severe days reported for several symptoms were conducted using independent-samples *t* tests and ANOVA. Summative scores for each symptom included the number of days subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain,

and nausea and vomiting individually within each cycle. These summative scores were then compared to class membership for the individual symptoms in cycle 2 and 3. In cases where classes did not display homogeneity of variance, the Welch statistic, a robust test that allows violation of this assumption, was used. Where appropriate, follow-up post hoc contrasts were conducted to evaluate pairwise differences among the means for significant differences in class membership on the dependent variable of interest. In cases where equal variances were not assumed, the Dunnett's *C* test was used, which does not assume equal variances among the factor levels.

Specific Aim 4

Specific aim 4 was to determine if differing multisymptom trajectory profiles are associated with variations in change in functional status, days of missed work, and hours spent lying down reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer.

Research Question 4.1: To what extent are differing symptom trajectory profiles associated with variations in change in functional status, days of missed work, and hours spent lying down as reported by women undergoing chemotherapy for breast cancer?

After identifying the latent class solutions that best fit the data, differences among the predicted classes for the individual symptoms were examined for important outcomes using independent-samples *t* tests and ANOVA for tests of mean differences. As described above, predicted class memberships were extracted from the model and used for further analysis in tests of mean differences across the classes on covariates outside the model. Because Study 1 measured functional status with the SF-12 and Study 2 and Study 3 measured functional status with the SF-36, standardized z-scores were used in

the regression analysis. First, baseline functional status (pre-cycle 2) scores for the sample from each parent study were compared to the norm for the SF-36 to ensure the two samples were relatively similar in distribution to the population norm. If the sample mean and standard deviation were not significantly different from the norm for the SF-36, then the sample scores for each study were used and z-scores were calculated. Next, the baseline functional status score and the post-cycle 3 functional status score were used to compute a change score for each participant. The change score was then converted to a z-score, and the z-scores were used to test for mean differences among the trajectory classes to determine whether individual symptom classes are associated with variations in change in functional status over cycles 2 and 3 of chemotherapy.

Daily measures of hours spent lying down were averaged for each individual. Days of missed work were summed for all employed participants for each cycle 2 and 3. Tests of mean differences across the predicted classes were conducted on the average hours spent lying down and summed days of missed work using independent-samples *t* tests and ANOVA. The methods used for analysis are presented in Table 1.5.

Table 1.5 Summary of the Analysis

Specific Aim	**Research Question**	**Statistical Analysis**
Aim 1 Determine the trajectories and profile classes associated with the severity of ten symptoms (fatigue, pain, disturbed sleep, depressed mood, anxiety, nausea, diarrhea, distress associated with changing appearance, sore mouth, and trouble thinking) reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer.	**1.1** What are the trajectories of the severity of individual symptoms reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer? **1.2** What are the profile classes, if any, associated with the severity of individual symptoms reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer? **1.3** Do the profile classes associated with the severity of individual symptoms differ between cycle 2 and cycle 3 of chemotherapy?	**1.1 Single Symptom Latent Growth Mixture Analysis** **1.2 Latent Growth Mixture Model for Individual Symptoms** **1.3 Crosstabs**

Table 1.5 continued

Specific Aim	Research Question	Statistical Analysis
Aim 2 Identify multisymptom trajectory profile classes of patients undergoing cycles 2 and 3 of chemotherapy for breast cancer.	**2.1** What symptom profile classes can be identified in a cohort of women undergoing chemotherapy treatment for breast cancer during cycle 2 and during cycle 3? **2.2** Do the multisymptom profile classes differ between cycle 2 and cycle 3 of chemotherapy?	**2.1 Multisymptom Latent Growth Mixture Model** **2.2 Crosstabs**
Aim 3 Determine if membership in differing multisymptom trajectory profiles is determined by various demographic, clinical, and symptom variables?	**3.1** To what extent are differing symptom trajectory profiles associated with variations in age, chemotherapy regimen, stage of disease, marital status, employment, education, and the presentation of other symptoms at moderate to severe severity?	**Independent-samples *t* tests, ANOVA and chi-square**
Aim 4 Determine if differing multisymptom trajectory profiles are associated with variations in change in functional status, days of missed work, and hours spent lying down reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer.	**4.1** To what extent are differing symptom trajectory profiles associated with variations in change in functional status, days of missed work, and hours spent lying down as reported by women undergoing chemotherapy for breast cancer?	**Independent-samples *t* tests, ANOVA and chi-square**

Overview of Dissertation

The dissertation is organized into 5 chapters. This chapter introduces the problem statement with specific aims, provides background and review of the relevant literature, and details the methods used in this study. Chapters 2, 3, and 4 are written in manuscript format. Chapter 2 discusses the results of the Latent Growth Mixture Models for the individual symptoms and the multisymptom models. Chapter 3 presents the results of the studies of associations between various demographic, clinical, and symptom variables with symptom class membership extracted from the selected models for fatigue and disturbed sleep. Chapter 4 presents the results of the studies of associations between various demographic, clinical, and symptom variables with symptom class membership extracted from the selected models for the symptoms of mood disturbance. Chapter 5 provides a synthesis of the findings across all four specific aims of this study, the limitations inherent to this secondary analysis, and potential directions for future research and clinical practice.

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CHAPTER 2

IDENTIFICATION OF DISTINCT CLASSES OF WOMEN WITH BREAST CANCER BASED ON SYMPTOM TRAJECTORIES

Prepared to reformat for submission to *Quality of Life Research*

Abstract

The purpose of this study was to examine 10 patient-reported symptoms experienced daily by women with breast cancer over multiple cycles of chemotherapy, exploring potential classes of women experiencing similar symptom trajectories.

A secondary analysis was conducted utilizing data collected from women (*n*=166) undergoing chemotherapy for breast cancer during cycles 2 and 3 and who self-reported on the severity of 10 symptoms through daily phone calls to an automated system. Latent Growth Mixture Modeling was used to identify classes of women experiencing similar symptom trajectories.

Participants ranged in age between 24 and 80 years (mean age 52.91 years), were mostly Caucasion (91.46%) and the largest proportion of the sample was diagnosed with stage II breast cancer (40.36%). Fatigue, disturbed sleep, depressed mood, and anxiety were commonly reported at moderate to severe levels (4 or greater on a 10 point scale) during the two cycles of chemotherapy. The multisymptom model did not reveal distinct subgroup classes; however, 4 individual symptoms did have distinct subgroups including a 3-class solution that was determined to be the best fit for fatigue and 2-class solutions that were selected for disturbed sleep, depressed mood, and anxiety. For the other 6 symptoms, no distinct subgroups were identified.

Three classes of fatigue were identified, including those with mild improving fatigue (59% of women in cycle 2 and 64% in cycle 3), low moderate improving to mild fatigue (30% of women in cycle 2 and 25% in cycle 2), and high moderate improving fatigue (11% of women in both cycles). Two classes of disturbed sleep were identified, including mild improving disturbed sleep (89% of women in cycle 2 and 81% in cycle 3) and moderate worsening disturbed sleep during cycle 2 (11% of women) and mild

worsening disturbed sleep during cycle 3 (19% of women). For depressed mood, 2 classes were identified, with the majority (91% of respondents in cycle 2 and 94% in cycle 3) reporting a minimal level of depressed mood and a small class with a moderate level of depressed mood (9% of respondents in cycle 2 and 6% in cycle 3). Two latent trajectories of anxiety were also revealed, including a minimal anxiety class (95% of respondents in cycle 2 and 92% in cycle 3) and a moderate anxiety class (5% of respondents in cycle 2 and 8% in cycle 3).

For fatigue, disturbed sleep, depressed mood, and anxiety, a class of women reported symptoms at moderate levels during both cycles, suggesting that clinicians should carefully review symptom patterns early in the course of treatment to identify women experiencing moderate to severe symptoms. These women are likely to continue with higher symptom presentation throughout the cycle of chemotherapy and may benefit from intensifying symptom intervention. Consideration should be given to the limitations of LGMM in identifying distinct subgroups with a modest sample size and daily symptom reporting with patterns that included days with zero severity.

Introduction

Breast cancer is the most frequently diagnosed cancer for women, but has a relatively high 5-year survival rate of 89% for women with localized cancer (American Cancer Society, 2015). While women diagnosed with breast cancer may have increased survival when compared to other cancers, they often face significant symptoms during and following treatment (Bradley, Neumark, Luo, & Schenk, 2007). Aggressive, multimodal and multi-agent treatment may be associated with significant toxicities and side effects that, when combined with tumor and disease-related symptoms, significantly

diminish quality of life, ability to function, interfere with activity and employment, interrupt treatment and, consequently, influence treatment effectiveness (Bradley et al., 2007; Cleeland et al., 2003; Kayl & Meyers, 2006).

Symptoms are self-reported, subjective phenomena that indicate a change in normal functioning, sensation, or appearance due to disease (Rhodes & Watson, 1987). Considerable evidence suggests variability in the trajectories, or change in symptom prevalence and severity over the course of chemotherapy treatment for breast cancer (Dodd, Cho, Cooper, & Miaskowski, 2010). Describing heterogeneity, correlates, and outcomes of different symptom trajectories allows clinicians to target women who may be at higher risk for increased symptom burden and poor outcomes related to the symptom experience. There is a large body of literature devoted to the description of single symptoms and symptom clustering. There is evidence to support the existence of common groups and trajectories of symptoms that occur during treatment for cancer (Miaskowski et al., 2006). To date, most studies have been focused on symptom prevalence and the occurrence or association of specific symptoms in combination (Dodd et al., 2010). While useful for understanding the presence of symptoms overall within samples and at meaningful single time points, these studies do not account for individual change in symptom presentation over time (Henly, Wyman, & Findorff, 2011). Determination of which symptoms are included in an analysis is often based on which symptoms are the more prevalent symptoms, not which symptoms are more severe. While this method is practical, important symptoms that may be severe or distressing could remain inadvertently understudied.

Advances in technology-use for collecting self-reported symptom data and

longitudinal statistical modeling techniques have allowed for newer methodological approaches to studying classes of symptom trajectories, identifying homogeneous classes of persons who share common symptom trajectories (Dodd et al., 2010; Henly et al., 2011; Lam et al., 2010; Onselen et al., 2012; Pud et al., 2008; Wang, Chang, Chen, Chen, & Hsu, 2014). Conventional latent growth modeling allows for modeling of individual differences in growth on an outcome, providing latent growth factor means and variances. Latent growth mixture modeling (LGMM) further allows for the identification of discrete classes of individuals on the basis of common trajectories of growth, wherein each latent class has its own model of growth. The categorical latent variables represent the class that describes groups of individuals who are homogeneous within that class and are heterogeneous across classes (Muthen & Muthen, 2000). The goal of LGMM is to add classes stepwise until the model shows the smallest number of latent classes that can describe the associations among a set of observed measures (Muthen & Muthen, 2000). One benefit of LGMM over other methods of class identification is that the probability of membership in a class and variances within the classes are estimated for each individual, accounting for unreliability of classification (Colder, Richardson, Campbell, Ruel, & Flay, 2002). Finally, LGMM provides the probability of class membership, which can then be used to study correlate variables and may relate the probability of a given outcome based on class membership (Muthen & Muthen, 2000).

LGMM has been applied to symptom data for women with breast cancer during various stages of the disease and treatment, identifying classes of women with similar trajectories for depression, psychosocial distress, and trouble sleeping individually and a multisymptom trajectory model of pain, fatigue, sleep disturbance, and depression (Dunn

et al., 2011; Lam et al., 2010; Langford et al., 2016; Onselen et al., 2012). Based on symptom prevalence, evaluated monthly before, during, and following chemotherapy, these studies have identified 3-5 classes of distinct trajectories of the symptoms of interest (Dunn et al., 2011; Lam et al., 2010; Langford et al., 2016; Onselen et al., 2012). While this topic has received increased attention, well-designed longitudinal studies of breast cancer symptoms are needed to replicate findings and continue studying individual and multisymptom trajectory classes (Dodd et al., 2010; Dunn et al., 2011; Henselmans et al., 2010; Lam et al., 2010; Lee et al., 2004; Onselen et al., 2012). Additionally, no study has modeled the self-reported severity of symptoms using daily measures during distinct cycles of chemotherapy. The purpose of this study was to examine self-reported symptom severity experienced daily by women with breast cancer over multiple cycles of chemotherapy, exploring potential classes of women experiencing similar symptom trajectories, and to examine whether the classes differ between 2 cycles. Understanding trajectories of symptoms that occur in individuals may elucidate potential targets, or at-risk individuals, and common etiologies for symptoms profiles, which may inform the development of targeted interventions aimed at the reduction of symptoms during treatment.

Methods

Participants and Setting

This study was a secondary analysis of longitudinal data pooled from three trials of a symptom monitoring and behavioral intervention in women undergoing chemotherapy for breast cancer. Study 1 and Study 2 tested the use of an automated telephone-linked-care system for monitoring symptoms and intervening in the presence

of symptoms during chemotherapy. Study 3 was an observational study utilizing the same automated telephone-linked-care system for data collection. Each of the studies used the same data collection methods, the telephone-linked-care automated system, further described by Mooney, Beck, Friedman, Farzanfar, and Wong (2014).

For Study 1, participants were recruited from four ambulatory clinics in two states in the United States, including a community cancer center in the southeast, two community practices in the west, and a clinical cancer center in the west. For Studies 2 and 3, participants were recruited from two academic, multidisciplinary practice settings in the Midwest and the western United States. While in both Study 1 and Study 2, participants were randomly assigned to a usual care group or a symptom management intervention group, preliminary data analysis suggests differences in reported symptoms between the control and intervention groups in study 2 only. Therefore, data from all eligible participants in Study 1 with a breast cancer diagnosis, regardless of study group, and only data collected from eligible participants randomized to the control in Study 2 were utilized in this secondary analysis. Study 3 involved no intervention and data from all eligible participants was utilized in this secondary analysis. Because data from cycle 1 was not available for Study 1, we chose to include data from cycles 2 and 3 for this secondary analysis. Only women who reported on at least 3 days during the cycle of chemotherapy were included in the study sample to allow for application of the analysis methods.

A cohort of 259 women with breast cancer were pooled from the 3 parent studies, 94 from Study 1, 156 from Study 2 and 29 from Study 3. Thirteen women who did not complete study measures through cycles 2 and 3 and 80 women who were randomized to

the intervention group for Study 2 were excluded. This yielded a total data set of 166 women, of which 165 completed measures on at least 3 days during cycle 2 and 155 completed measures on at least 3 days during cycle 3.

Measures

All 3 parent studies utilized similar instrumentation. We collected demographic and disease-related data at study entry from the participant and from the medical record. Demographic data included age, gender, race and ethnicity, marital status, education, employment, and income. Disease factors included primary cancer diagnosis, extent of disease at diagnosis, and details of chemotherapy protocol. Rather than summative symptom measures, we used single-item indicators to assess each symptom to better appreciate changes in specific symptoms. Single-item indicators have acceptable reliability and validity in symptom studies (Cleeland & Mendoza, 2011; Mooney et al., 2014). The investigator-developed instrument employed conditional branching such that participants were first asked, "During the past 24 hours did you experience (symptoms)?" A no response was scored as zero and a yes response yielded a question asking the participant to score the symptom severity using a 1 (low) to 10 (high) Likert scale. Symptoms assessed included fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea/vomiting, sore mouth, and diarrhea across all three parent studies. Two additional symptoms, distress associated with changing appearance and trouble thinking, were assessed in Studies 2 and 3. A subsample, consisting of participants enrolled in those 2 parent studies only, was used in analyses that included those 2 symptoms.

Study Procedures

This secondary analysis was reviewed by the Institutional Review Board (IRB) at the University of Utah. Subjects were identified only by their original study identification number. All participants signed a written, informed consent upon initiation of participation in the original studies.

Statistical Analysis

MPlus, version 6.0, was used for mixture model analyses and the Software Statistical Package for the Social Sciences (SPSS), version 23.0, was used for data management and analysis of the demographics. Alpha was set at 0.05 and no adjustments were made for multiplicity in this hypothesis-generating study.

Descriptive statistics and frequency distributions were generated on the sample characteristics. To accommodate for varying cycle lengths, only data from the first 14 days of each cycle were included in the analysis. The prevalence of individual symptoms during the first 14 days of each cycle was determined. An exploratory analysis was conducted to describe how individuals in the data set changed over time on each symptom; using graphical visualization and conventional growth modeling (cycle 2 and cycle 3 separately). This analysis provided an intercept and slope that describe the baseline measure and rate of change for each symptom during each cycle. Cycles were studied individually to capture potential differences in the symptom trajectories of consecutive cycles.

After establishing the growth form for each of the 10 symptoms, latent classes were modeled on the basis of growth trajectories from multiple symptoms. Latent growth mixture models provided classes that display homogenous trajectories of

individuals' symptom experience that are heterogeneous from other classes. Using the more prevalent symptoms in our sample, an exploratory method was employed, building the effort towards a multisymptom latent growth curve, adding first fatigue and disturbed sleep, followed by symptoms of mood disturbance, pain, and nausea. An initial 1-class model was tested, and subsequent classes were added in ascending order to determine the best model fit. Each latent class corresponded to a subpopulation that has its own set of parameter values (intercept and slope) (Singer & Willett, 2003). Step-wise models were evaluated on the Bayesian information criterion (BIC), used to evaluate improvement in model fit with the addition of classes. Smaller BIC values suggested a better model fit (Colder et al., 2002; Muthen & Muthen, 2000). If the addition of a class resulted in a reduction in the BIC value relative to the BIC from the previous model (without the added class), then the new model was considered an improvement and the class was retained. The addition of classes continued until the BIC did not decrease with the addition of a class. Additionally, entropy was used to evaluate the probabilities of membership in each class for each individual. Entropy is a summary measure of classification based on these probabilities that ranges from 0 to 1.0 (Colder et al., 2002). The closer entropy values are to 1.0, the better the classification. Finally, the best-fitting model was examined for the number of subjects in each class (greater than 5% of the sample) and graphed visually to determine if the predicted trajectories were clinically and theoretically relevant (Onselen et al., 2012).

After identifying the potential multisymptom latent classes, the number of latent classes for each individual symptom was determined on the basis of means of the growth factors, using LGMM as described above.

Results

A total of 166 women with breast cancer participated in the study. Patient demographic and clinical characteristics are summarized in Table 2.1. Participants ranged in age between 24 and 80 years (mean age 52.91 years, *SD* = 10.8). The majority of participants were White (91.46%), married (75%), and not currently working (62.8%). The largest proportion of the sample was diagnosed with Stage II disease (40.36%) and had at least some education beyond high school (75.3%). All study participants were receiving the second and third cycles of a multicycle chemotherapeutic regimen. Data regarding dose density and use of anti-emetic agents were not available.

Prevalence and Trajectories of Individual Symptoms

Call compliance was 78.4% of days during the first 14 days of cycle 2 and 78.0% of days during the first 14 days of cycle 3. The prevalence of individual symptoms during each cycle and the prevalence of moderate to severe levels of symptoms during the first 14 days of each cycle are reported in Table 2.2. The percent of days reported of total cycle days with severity of zero, severity of 1-10, and severity of 4-10 (moderate to severe levels) are also presented in Table 2.2. Symptoms were common during both cycles and reported at moderate to severe levels. Fatigue was the most prevalent symptom, reported by 92.7% and 94.9% of women in each cycle 2 and 3, respectively. Disturbed sleep, pain, nausea and vomiting, depressed mood, and anxiety were also highly prevalent. Growth factors for the 1-class model for each symptom are presented in Table 2.3.

Table 2.1 Sample Demographic and Clinical Characteristics (*n* =166)

Characteristic	**Mean**	***SD***
Age (in years)	52.90	10.8
Characteristic	***n***	**%**
Ethnicity		
Non-Hispanic	162	97.6%
Hispanic	2	1.2%
Unknown	2	1.2%
Marital Status		
Partnered	123	74.1%
Nonpartnered	41	24.7%
Unknown	2	1.2%
Employment		
Full-time	48	29.2%
Part-time	13	7.8%
Not Employed	103	62.0%
Unknown	2	1.0%
Education Status		
High school	3	22.3%
Some College	52	31.3%
Associate Degree	15	9.0%
Bachelor Degree	36	21.7%
Postgraduate	22	13.2%
Unknown	4	2.5%
Income		
Less than $9,999	8	4.8%
$10,000-29,999	16	9.6%
$30,000-49,000	37	22.3%
$50,000-69,000	20	12.1%
$70,000 or More	57	34.3%
Unknown	10	6.1%
Declined to State	18	10.8%
Stage of Disease		
Stage I	20	12.1%
Stage II	67	40.3%
Stage III	38	22.9%
Stage IV	36	21.7%
Unknown	5	3.0%
Chemotherapy Regimen		
Cyclophosphamide with Doxorubicin	68	41.0%
Docetaxel	23	13.9%
Cyclophosphamide with Methotrexate and 5-FU	16	9.6%
Docetaxel with Carboplatin	13	7.8%
Cyclophosphamide with Docetaxel	12	7.2%
Cyclophosphamide with Doxorubicin and Docetaxel	9	5.4%
Cyclophosphamide with Doxorubicin and 5-FU	6	3.6%
Cyclophosphamide with 5-FU	4	2.4%
Other	15	9.1%

Table 2.2 Symptom Prevalence and Mean Number of Days at Moderate to Severe Levels

Symptom	Cycle	No. (%) of Women Reported Symptom Severity Greater than 0 at Least Once	Mean no. Days (*SD*), Range of Symptom Reported with Severity Greater than 0	No. (%) of Women Reported Symptom Severity Greater than 3 at Least Once	Mean no. Days (*SD*), Range of Symptom Reported with Severity Greater than 3	No. Days (%) Symptom Reported Level 0	No. Days (%) Symptom Reported Level 1-10	No. Days (%) Symptom Reported Level 4-10
Physical Symptoms								
Fatigue [a]	2	153 (92.7%)	7.53 (3.69), 1-14	115 (69.7%)	5.09 (3.47), 1-14	659 (36.4%)	1,152 (63.6%)	585 (32.3%)
	3	148 (94.9%)	7.09 (3.93), 1-14	105 (67.3%)	4.95 (3.70), 1-14	654 (38.4%)	1,050 (61.6%)	520 (30.5%)
Disturbed Sleep [a]	2	126 (76.4%)	3.63 (2.56), 1-13	103 (62.4%)	2.87 (2.07), 1-13	1,354 (74.8%)	457 (25.2%)	296 (16.3%)
	3	110 (70.5%)	3.40 (2.64), 1-13	85 (54.5%)	2.46 (1.76), 1-11	1,330 (78.1%)	374 (21.9%)	209 (12.3%)
Pain [a]	2	124 (75.2%)	4.55 (3.20), 1-14	75 (45.5%)	3.51 (2.95), 1-13	1,247 (68.9%)	564 (31.1%)	263 (14.5%)
	3	104 (66.7%)	5.16 (3.74), 1-14	66 (42.3%)	4.15 (3.33), 1-14	1,167 (68.5%)	537 (31.5%)	274 (16.1%)
Nausea and Vomiting [a]	2	116 (70.3%)	3.90 (2.92), 1-13	78 (47.3%)	2.66 (2.28), 1-11	1,359 (75.0%)	542 (29.9%)	208 (11.5%)
	3	111 (71.2%)	4.05 (3.31), 1-14	63 (40.4%)	3.14 (2.63), 1-12	1,254 (73.6%)	450 (26.4%)	198 (11.6%)
Diarrhea [a]	2	69 (41.8%)	2.13 (1.53), 1-8	30 (18.2%)	1.83 (0.87), 1-4	1,664 (91.9%)	147 (8.1%)	55 (3.0%)
	3	49 (31.4%)	2.63 (1.82), 1-10	23 (14.7%)	2.17 (1.53), 1-6	1,575 (92.4%)	129 (7.6%)	49 (2.9%)
Sore Mouth [a]	2	68 (41.2%)	3.62 (2.34), 1-11	38 (23.0%)	3.11 (2.29), 1-10	1,565 (86.4%)	246 (13.6%)	118 (6.5%)
	3	68 (43.6%)	3.32 (2.61), 1-13	38 (24.4%)	2.66 (2.72), 1-13	1,478 (86.7%)	216 (12.7%)	91 (5.3%)
Trouble Thinking [b]	2	46 (27.9%)	2.67 (1.97), 1-11	28 (17.0%)	2.50 (2.19), 1-10	884 (93.2%)	64 (6.8%)	37 (3.9%)
	3	31 (19.9%)	3.26 (2.11), 1-9	21 (13.5%)	1.95 (1.07), 1-5	776 (94.1%)	46 (5.6%)	20 (2.4%)
Appearance [b]	2	38 (23.0%)	3.32 (2.57), 1-12	25 (15.2%)	3.16 (2.37), 1-9	882 (93.0%)	66 (7.0%)	42 (4.4%)
	3	15 (9.6%)	3.27 (3.97), 1-13	10 (6.4%)	3.50 (4.50), 1-12	801 (97.1%)	24 (2.9%)	17 (2.1%)
Mood Disturbance Symptoms								
Depressed Mood [a]	2	99 (60.0%)	3.60 (3.21), 1-13	70 (42.4%)	3.23 (2.84), 1-12	1,455 (80.3%)	356 (19.7%)	226 (12.5%)
	3	83 (53.2%)	3.47 (3.11), 1-14	55 (35.3%)	2.87 (2.86), 1-13	1,416 (83.1%)	288 (16.9%)	158 (9.3%)
Anxiety [a]	2	77 (46.7%)	3.34 (3.17), 1-13	47 (28.5%)	2.91 (2.83), 1-11	1,544 (85.3%)	267 (14.7%)	147 (8.2%)
	3	62 (39.7%)	3.56 (3.62), 1-13	40 (25.6%)	2.65 (2.56), 1-9	1,483 (87.0%)	221 (13.0%)	106 (6.2%)

[a] *n*=165, cycle 2; *n*=156, cycle 3; 1811(78.4%) days reported cycle 2, 1704(78.0%) days reported cycle 3; 499(21.6%) days missing cycle 2, 480(22.0%) days missing cycle 3
[b] *n*=84, cycle 2; *n*=75, cycle 3; 948 (80.6%) days reported cycle 2, 825 (79.6%) days reported cycle 3; 228 (19.4%) days missing cycle 2, 211 (20.4%) days missing cycle 3

Table 2.3 Results of Latent Growth Mixture Analysis (*n*=165, *n*=156)

Symptom	Cycle	Intercept	Slope	Quadratic Term
Fatigue	Cycle 2	2.69*	0.05	-0.01*
	Cycle 3	2.27*	0.19*	-0.02*
Disturbed Sleep	Cycle 2	1.95*	-0.22*	0.01*
	Cycle 3	1.01*	-0.03	0.00
Depressed Mood	Cycle 2	0.93*	0.02	-0.00
	Cycle 3	0.52*	0.13*	-0.01*
Anxiety	Cycle 2	0.75*	-0.04	0.00
	Cycle 3	0.60*	-0.01	-0.00
Pain	Cycle 2	1.14*	0.08	-0.01*
	Cycle 3	1.10*	0.11*	-1.01*
Nausea and Vomiting	Cycle 2	1.63*	-0.15*	0.00
	Cycle 3	0.89*	0.11*	-0.01*
Diarrhea	Cycle 2	0.14*	0.05*	-0.00*
	Cycle 3	0.25*	0.02	-0.00*
Trouble Thinking	Cycle 2	0.56*	-0.09*	0.00
	Cycle 3	0.26*	-0.01	0.00
Sore Mouth	Cycle 2	0.02	0.16*	-0.01*
	Cycle 3	0.09*	0.10*	-0.01
Change in Appearance	Cycle 2	0.87*	-0.15*	0.01*
	Cycle 3	0.13	-0.01	0.00

*$p<.05$

Multisymptom Latent Growth Mixture Model

Multisymptom models did not converge and classes could not be discerned. Without convergence, no fit statistics were available to compare various models.

Individual Symptom Latent Growth Mixture Models

Multiclass latent growth mixture models were evaluated for the individual symptoms and fit indices are presented in Table 2.4. Multiclass models were retained for fatigue, disturbed sleep, depressed mood, and anxiety. For trouble thinking, the 2-class model converged, but was not retained because class counts were less than 5% for one class. For diarrhea, nausea and vomiting, and pain, 2-class models converged, but the results were not trustworthy due to a nonpositive definite first-order derivative product matrix. For sore mouth and distress with changing appearance, the best log likelihood value was not replicated for the 2-class model. Models were not retained for trouble thinking, diarrhea, nausea, pain, sore mouth, and distress with changing appearances.

For fatigue, a 3-class solution was selected with mild improving, low moderate improving to mild, and high moderate improving classes during both cycles. Intercept, slopes, and quadratic terms for the individual symptom classes are presented in Table 2.5 and trajectory graphs are presented in Figure 2.1. The majority of women were in the mild improving fatigue class (59% for cycle 2 and 64% for cycle 3). These individuals had a low fatigue severity level at day 1 of each cycle (2.25 ± 0.29, 1.76 ± 0.24). Individuals in the low moderate improving to mild fatigue class had a moderate fatigue severity level at day 1 of each cycle (3.21 ± 0.52, 2.52 ± 0.39) and individuals in the high moderate improving fatigue class had a severe level of fatigue at day 1 (5.66 ± 0.73, 5.43 ± 0.51), maintaining that level through day 5 and then had a slight decline in fatigue to

Table 2.4 Model Fit for Latent Growth Mixture Models

Model	Log Likelihood	BIC[c]	Entropy	Posterior Probability	Class Proportions
1 class	-4,309.41	8,651.70	N/A	N/A	N/A
2 class	-3,954.18	7,948.98	.944	.988, .989	69%, 31%
3 class	-3,847.23	7,742.81	.944	.977, .950, .982	59%, 30%, 11%
4 class	-3,800.81	7,657.70	.943	.950, .960, .984, .935	57%, 12%, 22%, 10%
1 class	-4,062.06	8,156.06	N/A	N/A	N/A
2 class	-3,652.62	7,344.68	.963	.998, .968	72%, 28%
3 class	-3,570.33	7,187.62	.941	.986, .950, .960	64%, 25%, 11%
4 class	-3,538.36	7,131.18	.881	.935, .869, 1.000, .956	53%, 22%, 22%, 3%
1 class	-4,067.91	8,168.70			
2 class	-3,906.86	7,854.34	.984	.997, .995	89%, 11%
3 class	-3,855.66	7,759.66	.958	.945, .989,.968	84%, 10%, 5%
1 class	-3,582.73	7,197.38			
2 class	-3,441.79	6,923.02	.925	.981, .980	81%, 19%
3 class	-3,385.73	6,818.42	.962	.987, .995,.969	82%, 14%, 5%
1 class	-3,861.42	7,755.71	N/A	N/A	N/A
2 class	-3,470.9	6,982.42	.990	.997, .995	91%, 9%
3 class	-3,359.91	6,768.17	.987	.998, .992,.961	84%, 9%, 7%
1 class	-3,362.53	6,756.98	N/A	N/A	N/A
2 class	-2,827.07	5,792.57	1.000	1.000, 1.000	94%, 6%
3 class	-2,782.16	5,611.26	.998	1.000, .989, 1.000	94%, 5%, 2%
1 class	-3,509.86	7,052.60	N/A	N/A	N/A
2 class	-3,029.89	6,100.39	1.000	1.000, 1.000	95%, 5%
3 class	-2,918.53	5,887.40	.995	.992, 1.000	85%, 12%, 3%
1 class	-3,076.95	6,185.83	N/A	N/A	N/A
2 class	-2,621.09	5,281.63	.997	.999, 1.000	92%, 8%
3 class	-2,552.07	5,151.09	.995	.999, .991, 1.000	90%, 6%, 4%

Table 2.4 continued

Model	Log Likelihood	BIC[c]	Entropy	Posterior Probability	Class Proportions
1 class	-2,454.71	4,942.29	N/A	N/A	N/A
2 class	-2,219.35	4,479.31	.997	.999, 1.000	98%, 2%
1 class	-2,003.35	4,038.62	N/A	N/A	N/A
2 class	-1,766.92	3,573.29	.994	1.000, .999	98%, 2%
1 class	-2,573.34	5,179.56	N/A	N/A	N/A
2 class [a]	-2,463.73	4,968.08	.985	.981, .999	89%, 11%
1 class	-2,106.29	4,244.52	N/A	N/A	N/A
2 class [a]	-1,925.72	3,890.88	.995	.999, .996	94%, 6%
1 class	-3,555.29	7,143.46	N/A	N/A	N/A
2 class [a]	-3,241.06	6,522.74	.990	1.000, .981	85%, 15%
1 class	-3,407.89	6,847.71	N/A	N/A	N/A
2 class [a]	-3,055.22	6,149.88	.980	.987, .997	84%, 16%
1 class	-4,281.51	8,595.90	N/A	N/A	N/A
2 class [a]	-4,047.23	8,135.08	.965	.988, .994	85%, 15%
1 class	-3,590.76	7,213.45	N/A	N/A	N/A
2 class [a]	-3,223.28	6,486.00	.975	.997, .982	81%, 19%
1 class	-3,267.50	6,567.88	N/A	N/A	N/A
2 class [b]					
1 class	-2,906.92	5,845.77	N/A	N/A	N/A
2 class [b]					
1 class	-1,663.20	5,425.06	N/A	N/A	N/A
2 class [b]					
1 class	-1,977.58	4,040.89	N/A	N/A	N/A
2 class [b]					

[a] Results not trustworthy for parameters due to nonpositive definite first-order derivative product matrices.
[b] The best log likelihood value was not replicated.
[c] Bayesian Information Criterion

Table 2.5 Growth Factor Means and Predicted Frequencies for Each Class

Class	Intercept	Slope	Quadratic Term	Class Count
Fatigue				
	Cycle 2			
Mild Improving	2.25*	-0.26*	0.01*	97.94
Low Moderate Improving to Mild	3.21*	0.32	-0.03*	51.46
High Moderate Improving	5.66*	0.34	0.01	18.26
	Cycle 3			
Mild Improving	1.76*	-0.12	0.00	106.24
Low Moderate Improving to Mild	2.52*	0.65*	-0.06*	41.50
High Moderate Improving	5.43*	0.60*	-0.06*	18.26
Disturbed Sleep				
	Cycle 2			
Mild Improving	1.74*	-0.20*	0.01	145.85
Moderate Worsening	3.76*	-0.28	0.03	18.15
	Cycle 3			
Mild Improving	0.87*	-0.07	0.00	133.65
Mild Worsening	1.66*	0.14	0.00	31.35
Depressed Mood				
	Cycle 2			
Consistently Mild	0.78*	-0.04	0.00	148.50
Consistently Moderate	4.04*	0.22	-0.01	14.85
	Cycle 3			
Consistently Mild	0.27	0.13	-0.01	155.10
Moderate Improving	4.82*	0.23	-0.02*	9.90
Anxiety				
	Cycle 2			
Consistently Mild	0.69*	-0.10*	0.01*	156.75
Consistently Moderate	4.90*	0.03	0.00	8.25
	Cycle 3			
Consistently Mild	0.34*	-0.03	0.00	156.75
Low Moderate Improving to Mild	3.53*	0.17	-0.02	8.25

*$p<.05$

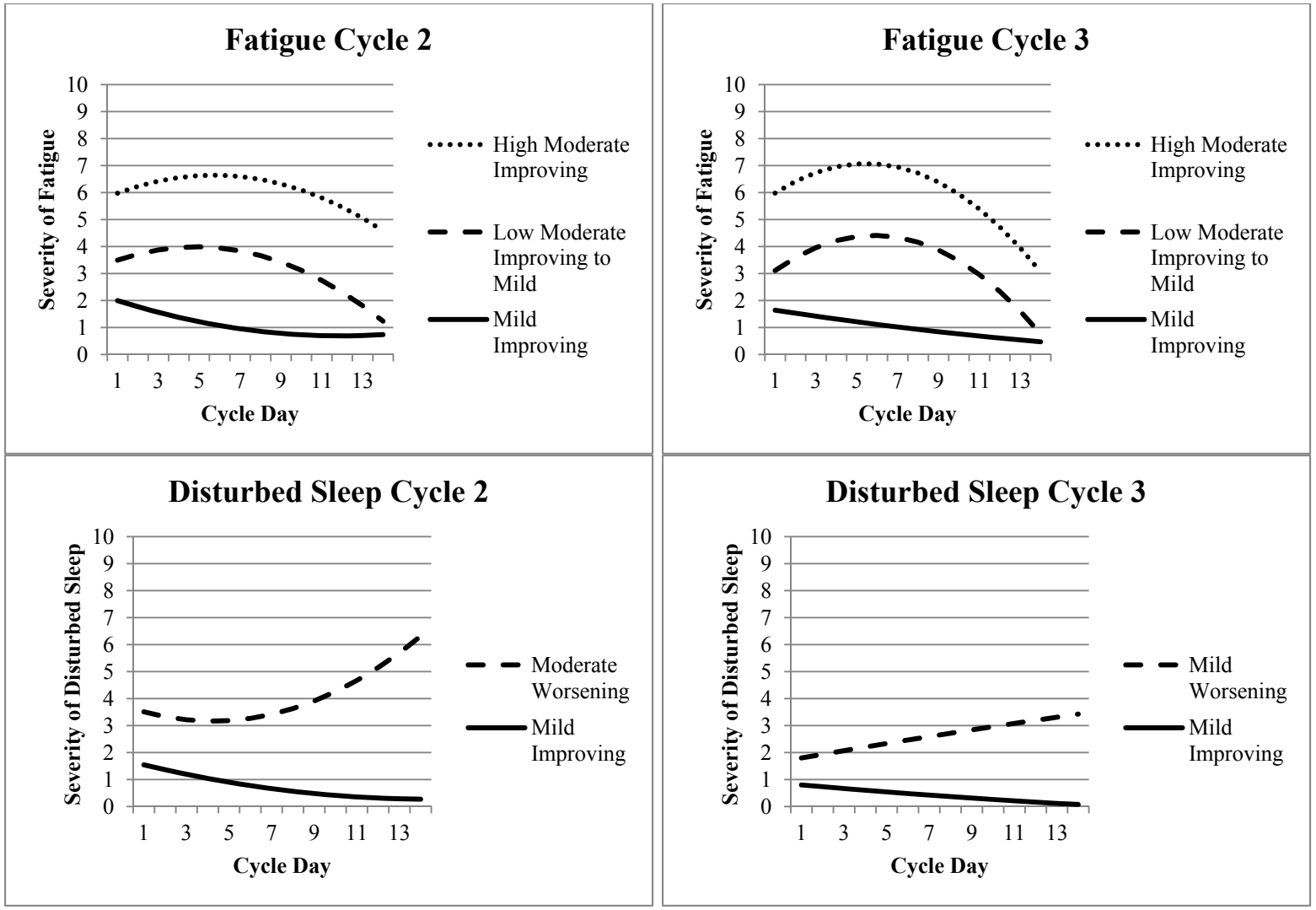

Figure 2.1 Individual symptom trajectory models.

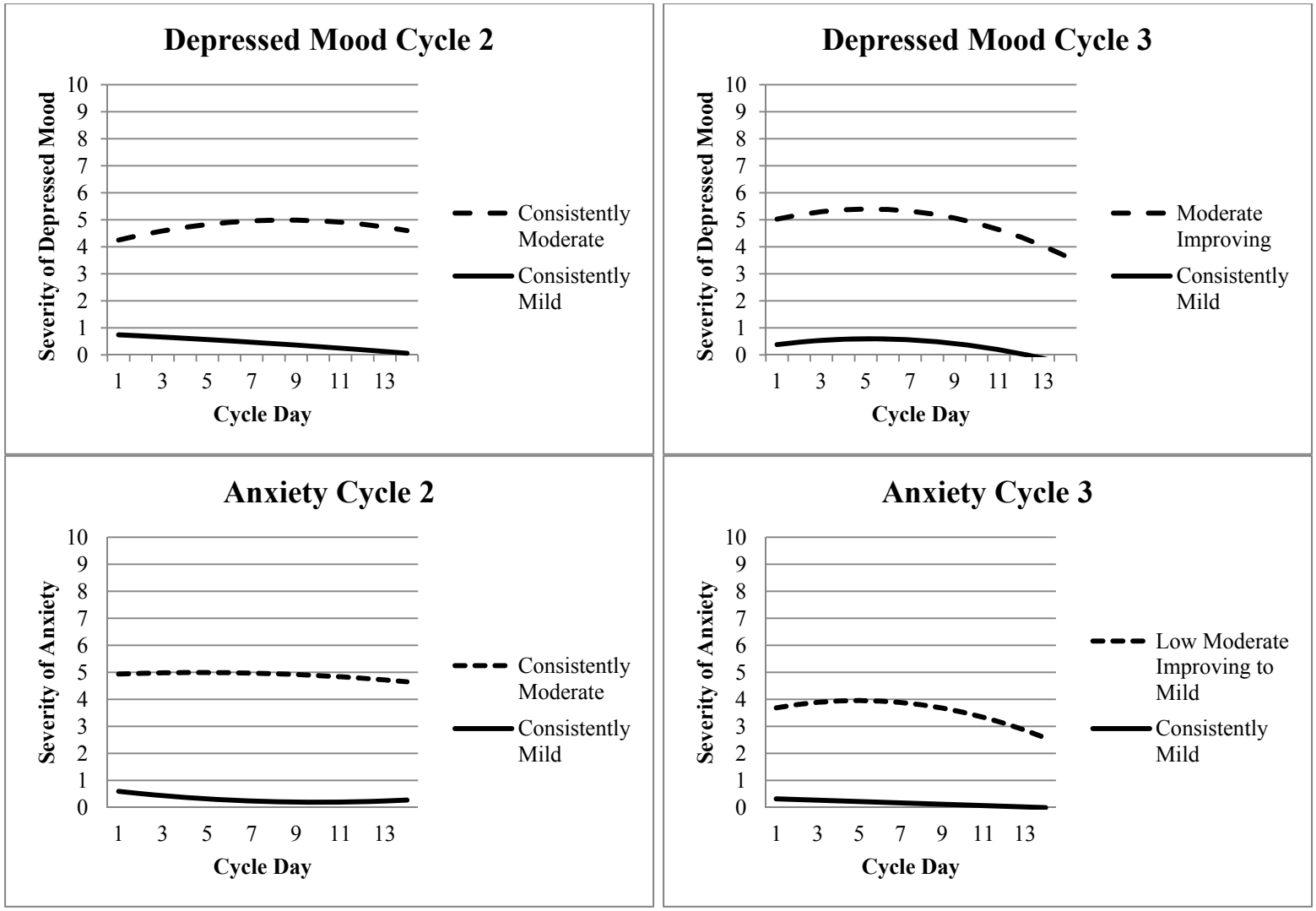

Figure 2.1 continued

day 14 of each cycle. In both cycles, 11% of participants were in the high moderate improving fatigue class.

For disturbed sleep, depressed mood, and anxiety, 2-class solutions were retained. For disturbed sleep, two classes were identified: a mild improving disturbed sleep class and a moderate worsening disturbed sleep class during cycle 2 and a mild improving and a mild worsening disturbed sleep class during cycle 3. The majority of subjects were in the mild improving disturbed sleep classes (89% for cycle 2 and 81% for cycle 3) and had a low severity of disturbed sleep at day 1 (1.74 ± 0.20, 0.87 ± 0.13) for each cycle and remained stable over the 14 days. A smaller percentage of participants were in the worsening disturbed sleep classes (11% in cycle 2 and 19% in cycle 3) and had a higher severity of disturbed sleep at cycle day 1 in both cycles (3.76 ± 1.05, 1.66 ±0.49) that increased over the 14 days. This class started with a slightly higher severity of disturbed sleep during cycle 2 when compared to cycle 3.

The majority of subjects were in the consistently mild depressed mood class (91% in cycle 2 and 94% in cycle 3) with a low severity of depressed mood on day 1 (0.78 ± 0.16, 0.27 ± 0.09) which they maintained over the first 14 days of both cycles. Nine percent of women during cycle 2 were in the consistently moderate depressed mood class and reported moderate severity on day 1 (4.04 ± 0.76), which they maintained over the first 14 days of both cycles. During cycle 3, 6% of women were in the moderate improving depressed mood class and reported moderate severity on day 1 (4.82 ± 0.63), which improved slightly over the first 14 days of chemotherapy.

The majority of subjects were in the consistently mild anxiety classes (95% in cycle 2 and 92% in cycle 3) and reported low levels of anxiety on cycle day 1 (0.69 ±

0.13, 0.34 ± 0.07) that remained stable over the first 14 days of both cycles. During cycle 2, 5% of women were in the consistently moderate anxiety class and reported moderate levels of anxiety on cycle day 1 (4.92 ± 1.70) that remained stable across the cycle. During cycle 3, 8% of women were in the low moderate improving to mild anxiety class and reported moderate anxiety on cycle day 1 (3.53 ± 0.61) that improved to mild levels over the first 14 days of chemotherapy. Women in the moderate anxiety class did report higher severity of anxiety in cycle 2 when compared to cycle 3.

Discussion

Results of this study contribute to a growing body of literature concerned with the trajectories of individual and multiple symptoms that are experienced by women receiving chemotherapy for breast cancer. Three classes displaying homogenous trajectories of fatigue severity were identified: mild improving fatigue, low moderate improving to mild fatigue, and high moderate improving fatigue. Two classes displaying homogenous trajectories of disturbed sleep were identified: mild improving disturbed sleep during both cycles and moderate worsening disturbed sleep during cycle 2 and mild worsening disturbed sleep during cycle 3. Two classes of both depressed mood and anxiety were identified, including consistently mild depressed mood during both cycles and consistently moderate depressed mood during cycle 2 and moderate improving depressed mood during cycle 3. Additionally, consistently mild anxiety classes were identified during both cycles and a consistently moderate anxiety class during cycle 2 and a low moderate improving to mild anxiety class during cycle 3 were described. Classes were not identified for the other 6 symptoms and a multisymptom model was not retained. A unique contribution of this study is the richness of the symptom data

available for analysis. Ten symptoms with daily reporting on symptom severity rather than symptom prevalence alone over 2 cycles of chemotherapy were studied in an exploratory method.

The lack of class identification for some individual symptoms and multiple symptoms in combination warrants some discussion. Some of the symptoms, including sore mouth, trouble thinking, distress associated with changing appearance and diarrhea, were comparatively rare, reported overwhelming at a level zero. Rare events may not have trajectories that can be modeled individually or in combination with other symptoms or may require a larger sample size and consideration of distributional assumptions in attempting to recover classes of women with homogenous trajectories. The use of differing methodological approaches may allow for better explanations of these rare symptoms. For example, cross-sectional designs using specific measurement time points and with specific chemotherapy regimens when these symptoms are expected to be present may better explain rare symptoms.

With regards to pain and nausea and vomiting, a multiclass model using only the more prevalent symptoms, our study was likely underpowered given the modest sample size and large variability in the number of days with reported symptoms. For nausea and vomiting and pain, it is possible that a 2-class model could represent the trajectories of these symptoms, but given the number of parameters needed for model estimation, the results were untrustworthy. With a larger sample, these models might have been retained. Additionally, a multiclass model with multiple symptoms may have been recovered with a larger sample. Several recent reports suggest that symptoms may exist in combination during chemotherapy and individuals may be at risk for these concurrent

symptoms (Bender, Ergun, Rosenzweigh, Cohen, & Sereika, 2005; Berger & Farr, 1999; Berger & Higginbotham, 2000; Bower et al., 2011; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Byar, Berger, Bakken, & Cetak, 2006; Dodd et al., 2010; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Jacobson et al., 1999; Langford et al., 2016; Liu et al., 2009; Liu et al., 2012; Molassiotis, Yam, Yung, Chan, & Mok, 2002; Osoba et al., 1997; Poon et al., 2013; So et al., 2009). In our sample, the more prevalent symptoms, including fatigue, disturbed sleep, depressed mood, and anxiety, presented as hugely variable in the number of days these symptoms were reported and at varying levels. While a mixture distribution may well-represent the diversity in these symptoms, we did not have the sample size needed to recover classes in a multisymptom model. There is no general rule for determining sample size applicable to all situations in growth modeling; however, the Monte Carlo method is recommended (Muthen & Muthen, 2002). Assuming the missing data from the sample are random, the Monte Carlo method estimated a sample size requirement between 150 and 250 participants. The sample in the study was borderline adequate to apply LGMM, and it is likely that given the number of days with zero on many symptoms and the large variability in the number of days with the more prevalent symptoms at varying levels, a larger sample was needed.

Only one report of successful class identification with multiple symptoms in breast cancer was found in the literature, but with important differences methodologically from this study. Langford et al. (2016) identified a multisymptom model using Latent Class Analysis (LCA) of the symptom cluster of pain, fatigue, sleep disturbance, and depression unique to three classes of women with breast cancer. In contrast to the current

study, a larger sample of women (*n*=391) were evaluated the week after chemotherapy administration in a cross-sectional design and data were studied using LCA. LCA does not allow individuals to vary within classes as LGMM does, and may have allowed for model convergence but with constraints. Constraining the model may be useful in studies with smaller sample sizes and with a large number of data with a zero value, but comes with limitations inherent to not allowing individual growth to vary within the classes.

While any or all of these reasons may have contributed to the failure of the multi-symptom LGMM to identify classes, further study is needed to clarify whether LGMM can be used to identify classes of women with similar severity trajectories on multiple symptoms. It is possible that an increased variability in rare symptoms could be found with a larger sample. Additionally, larger samples and model constraints may allow for identification of classes using multiple highly prevalent symptoms. Future studies using complex longitudinal data sets to study cancer-related symptoms need to consider the variability within the data to be analyzed using these methods and account for the limitations inherent to LGMM.

In an exploratory modeling of the individual symptoms, a three-class model was retained for fatigue and two-class models were retained for disturbed sleep, depressed mood, and anxiety individually. Fatigue was reported at a severity greater than zero by 92.7% of women during cycle 2 and 94.9% of women during cycle 3, consistent with the prevalence of fatigue during chemotherapy found in other studies (Bender et al., 2005; Bower et al., 2011; Browall, Persson, Ahlberg, Karlsson, & Danielson, 2009; Downie, Fan, Houede-tchen, Yi, & Tannock, 2006; Gaston-Johannson et al., 1999; Given, Given, Azzouz, & Stommeml, 2001; Jacobsen et al., 1999; Kim, Barsevick, Tulman, &

McDermott, 2008; Liu et al., 2009; Nieboer et al., 2005; So et al., 2009; Tchen et al., 2003). In contrast to previous studies, this analysis used fatigue severity rather than prevalence to model change. The overall 1-class model predicted a fatigue level of 2.69 on the first day of cycle 2 and 2.27 on the first day of cycle 3. During both cycles, the fatigue severity remained stable across the first 14 days. This finding is consistent with findings reported by Huang, Chen, Liang, and Miaskowski (2014), who found that average fatigue severity ranged from 1.92-3.09 over the 12 months following breast cancer surgery. This 1-class model allows for little discussion of those women (69.7% of respondents in cycle 2 and 67.3% in cycle 3) who reported moderate to severe levels of fatigue (ranging from 4-10) during the two cycles of chemotherapy.

Three patterns of fatigue were described in the LGMM model, including mild improving fatigue (59% of respondents in cycle 2 and 64% in cycle 3), low moderate improving to mild fatigue (31% of respondents in cycle 2 and 25% in cycle 3), and high moderate improving fatigue (11% of respondents in both cycles) classes. Across all three classes, the level of fatigue improved during the first 14 days of chemotherapy during both cycles, but was still present at day 14, consistent with previous findings that fatigue persists throughout treatment, but does not worsen over time (Byar et al., 2006; deJong, Candel, Schouten, Abu-Saad, & Courtens, 2004; Jacobsen et al., 1999; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Sitzia & Huggins, 1998). Additionally, the intercepts and slopes and visualization of over the 2 cycles of chemotherapy suggest that fatigue in cycle 2 did not differ in pattern during cycle 3, similar to previously reported findings of fatigue patterns over multiple courses of chemotherapy (Berger, 1998; Jacobsen et al., 1999).

Disturbed sleep was reported by 76.4% of women during cycle 2 and 70.5% of women during cycle 3. While other studies have report that over half of women report difficulty obtaining quality sleep during and following treatment for breast cancer, those numbers were higher in our sample (Beck et al., 2010; Bender et al., 2005; Berger & Higginbotham, 2000; Bower et al., 2011; Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002; Given et al., 2001; Janz et al., 2007; Kim et al., 2008; Lee, Dibble, Pickett, & Luce, 2005). In the overall 1-class model, women reported disturbed sleep severity of 1.59 on the first day of cycle 2 and 1.01 on the first day of cycle 3, not representing well the women who experience a significant number of days with moderate to severe disturbed sleep. Two patterns of disturbed sleep were described by the LGMM model, including a mild improving disturbed sleep class (89% of respondents in cycle 2 and 81% in cycle 3) and a moderate worsening disturbed sleep class during cycle 2 (11% of respondents) and a mild worsening disturbed sleep class during cycle 3 (19% of respondents). The severity of disturbed sleep improved slightly over time in the mild improving disturbed sleep class during both cycles, while the severity of disturbed sleep began at a moderate level and increased for the moderate worsening disturbed sleep class during cycle 2 and began at mild level and increased for the mild worsening disturbed sleep class during cycle 3. This suggests that some women will experience progression in the severity of disturbed sleep over the course of the cycle.

Sixty percent of women reported depressed mood during cycle 2 and 53.2% of women reported depressed mood during cycle 3. During cycle 2, 46.7% of women reported anxiety and 39.7% of women reported anxiety during cycle 3. The prevalence of these symptoms was similar to previously reported findings (Bower et al., 2011;

Gaston-Johansson et al., 1999; Kim et al., 2008; Liu et al., 2009; So et al., 2009). During cycle 2, 42.2% of women reported moderate to severe levels of depressed mood and 35.3% of women reported moderate to severe levels of depressed mood during cycle 3. During cycle 2, 28.5% of women reported moderate to severe levels of anxiety and 25.6% of women reported moderate to severe levels of anxiety during cycle 3. While a large number of women who reported moderate to severe levels of depressed mood during both cycles, the 1-class model for depressed mood indicated an average baseline severity of 0.93 during cycle 2 and 0.53 during cycle 3 that remained stable over time. The LGMM recovered two classes of depressed mood, a consistently mild depressed mood class during both cycles (91% of respondents in cycle 2 and 94% in cycle 3) and a consistently moderate depressed mood class during cycle 2 (9% of respondents) and a moderate improving depressed mood class during cycle 3 (6% of respondents). While the consistently mild depressed mood class experienced a severity of less than 1 over both cycles, the moderate improving depressed mood class during cycle 2 and the moderate improving depressed mood class during cycle 3 experienced a significant severity of 4 or higher. During cycle 3 only, the moderate improving depressed mood reported a decrease in the severity of depressed mood as the cycle progressed, but the severity remained at moderate levels. The symptoms of mood disturbance have been reported to increase at initiation of chemotherapy, but generally remain stable during treatment (Nieboer et al., 2005). This suggests that women who report higher levels of depressed mood at the beginning of the cycle maintain this symptom at moderate to severe levels through the end of the cycle. While the 1-class model for anxiety indicated an average baseline severity of 0.74 in cycle 2 and 0.60 in cycle 3, the LGMM found a 2-

class model that fit the data with a consistently mild anxiety class during both cycles (95% of respondents in cycle 2 and 92% in cycle 3) and a consistently moderate anxiety class during cycle 2 (5% of respondents) and a low moderate improving to mild anxiety class during cycle 3 (8% of respondents). Similar to depressed mood, the moderate classes reported a severity of anxiety of greater than 3 across both cycles, with severity levels slightly higher during cycle 2 when compared to cycle 3. Only the low moderate improving to mild anxiety class reported improvement in the severity of anxiety during the first 14 days of chemotherapy.

Recent findings of classes of symptom trajectories are conflicting with the results of this study. Onselen et al. (2012) identified 3 classes of women with sleep disturbance during the 6 months following surgery for breast cancer, a low and high class, but also a decreasing class that represented 5.3% of their sample (n=398). The conflicting findings may be a result of differing instrumentation and timing of measures, where Onselen et al. used a 21-item General Sleep Disturbance Scale measured monthly for 6 months following surgery, as opposed to the single-item severity measured daily over 2 cycles. Additionally, Onselen et al. constrained their models, setting the slope variances to zero to better estimate classes, potentially finding the third, decreasing class not found here. A few recent reports of classes of trajectories of depression and psychological distress in women with breast cancer have found 4 or 5 class models as the best fit (Desheilds, Tibbs, Fan, & Taylor et al., 2006; Dunn et al., 2011; Helgeson, Snyder, & Seltman, 2004; Henselmans et al., 2010; Lam et al., 2010; Wang et al., 2014). Differences in the number of trajectories identified may be due to methodological discrepancies, where, for example, Deshields et al. (2006) used a cut-point placement based on CES-D scores at 3

time points following treatment and Dunn et al. (2015) modeled trajectories based on CES-D scores prior to and monthly for 6 months after surgery for breast cancer. The use of the CES-D cut-points as opposed to the continuous severity single-item measure and the time points measured (every 3 months or monthly) would certainly elicit differing patterns of trajectories when compared to daily measures. Finally, varying analysis methods used to identify classes may have also contributed to inconsistencies in findings.

The primary limitation of this study is related to sample sizing. As previously discussed, a larger sample size may have elicited different results and potentially identified a multisymptom model. Additionally, the sample was fairly homogenous in demographic variables, including marital status and ethnicity. While data were collected from multiple sites across the United States, findings may not generalize to all populations of women receiving initial treatment for breast cancer.

This study was limited by the use of a single-item measure that may be prone to increased measurement error. Although numerous sources cite good reliability and validity with use of single-item measure, some would argue that more than one item is needed in symptom studies (Cleeland & Mendoza, 2011; Mooney et al., 2014). For practical purposes, these measures are useful in symptom studies and data were available for this secondary analysis using single-item measures (Cleeland & Mendoza, 2011; Mooney et al., 2014).

Particular care should be given to the nature of the data in our study and the usefulness of LGMM in modeling symptom trajectories with daily reporting. In our identified models, and given the use of daily symptom severity reporting, it is likely that there is more variability within the classes than the presented growth factors adequately

represent. Additionally, a large number of days where women reported zero severity on symptoms may have decreased the aggregate means for the growth factors and means may not well-represent the actual severity of the symptoms. Caution should be used in considering the existence of the classes identified in our models and the interpretation of the estimated growth parameters.

Conclusions

Results of this study suggest that women receiving chemotherapy for breast cancer experience different, distinct trajectories of the severity of fatigue, disturbed sleep, depressed mood, and anxiety, all symptoms that have been previously reported as distressing and may have a negative effect on outcome measures such as treatment adherence, quality of life, and health during survivorship. At the person-level, patterns emerge where a good number of individuals experience low symptoms, but there are also those at risk for moderate to severe levels. Additionally, regardless of class membership and with the exception of the worsening disturbed sleep classes, the severity of symptoms remained fairly stable or even improved across the cycle of chemotherapy. Clinicians should seek to identify those at risk for moderate or severe symptom trajectories with the awareness that unless there is an intervention, symptoms are likely to continue or possibly escalate through the cycle of chemotherapy. Future research should focus on replication of this hypothesis-generating study, on identifying potential correlates of class membership and outcomes related to class membership to clarify the identification of those individuals who are likely to experience symptoms at a severe level during chemotherapy. Additionally, researchers should consider methodological approaches that

account for a high level of variability in symptom prevalence and severity, using large samples, when applying LGMM.

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CHAPTER 3

ANTECEDENTS, CO-OCCURING SYMPTOMS, AND OUTCOMES OF DISTINCT TRAJECTORIES OF FATIGUE AND DISTURBED SLEEP IN WOMEN WITH BREAST CANCER

Prepared to reformat for submission to *Supportive Care in Cancer*

Abstract

The purpose of this study was to examine if membership in differing symptom subgroups for fatigue and disturbed sleep in women receiving treatment for breast cancer is determined by demographic, clinical, or symptom characteristics.

A secondary analysis was utilized to examine data collected from 166 women undergoing chemotherapy for breast cancer, who self-reported on the severity of 10 symptoms through daily phone calls to an automated system. Independent-samples *t* tests and ANOVA tests of mean difference and chi-square tests of associations among categories were used to distinguish between subgroups of women previously determined to demonstrate distinct trajectories of fatigue and disturbed sleep on antecedents, co-occurring symptoms, and outcome variables.

Participants in this study had a mean age of 52.91 years, were mostly Caucasian (91.46%), and the largest proportion of the sample was diagnosed with Stage II disease (40.36%). No demographic variables were associated with class membership for either fatigue or disturbed sleep. Chemotherapy regimen predicted fatigue severity class, with those women who received a Doxorubicin containing regimen more likely to be in the higher severity classes (cycle 2: $\chi^2 = 7.75$, $p = .02$; cycle 3: $\chi^2 = 8.59$, $p = .01$). Higher severity fatigue class was associated with increased hours lying down during cycle 2 ($F(2,44) = 2.03$, $p = .02$). Membership in higher severity fatigue classes was associated with increased disturbed sleep (cycle 2: $F(2, 162) = 6.03$, $p < .001$; cycle 3: Welch(2, 36) =9.21, $p < .001$), depressed mood (cycle 2: Welch(2, 40) = 8.77, $p < .001$; cycle 3: Welch(2, 34) =5.31, $p = .01$), nausea and vomiting (cycle 2: Welch(2, 41) = 5.95, $p = .01$; cycle 3: Welch(2, 35) = 6.66, $p < .01$), anxiety (cycle 2: Welch(2, 40) = 3.79, $p = .03$;

cycle 3: Welch(2, 35) =3.39, $p < .01$), and trouble thinking (cycle 3: $F(2, 74) = 7.26$, $p < .01$*). Membership in the worsening disturbed sleep class was associated with fatigue (cycle 2: $t(162) = 11.72$, $p < .01$; cycle 3: $t(153) = 4.67$, $p = .03$), depressed mood (cycle 2: Welch $t(27) = 7.37$, $p = .01$), and trouble thinking (cycle 3: $t(75) = -2.02$, $p < .01$). The overall symptom severity during cycle 2 predicted fatigue and disturbed sleep class membership during cycle 3 (fatigue: $F(1,153) = 28.90$, $p < .001$; disturbed sleep: $t(153) = 15.47$, $p < .001$).

While demographic variables did not distinguish class membership for fatigue or disturbed sleep, further study is needed to determine whether genetic or biological factors may. The co-existence of symptoms during chemotherapy may distinguish trajectory classes for fatigue and disturbed sleep. Symptom severity during an earlier cycle predicted class membership for fatigue and disturbed sleep during a subsequent cycle, suggesting that clinicians should be aware that women who experience significant symptoms during an earlier cycle may be at risk for severe symptoms during later cycles.

Introduction

Individual symptoms and symptoms clusters are dynamic and may change over the course of treatment for breast cancer (Langford et al., 2016). Common and debilitating cancer symptoms, including fatigue and disturbed sleep, may be more severe and distressing during active chemotherapy treatment (Langford et al., 2016; Payne, Piper, Rabinowitz, & Zimmerman, 2006).

Fatigue is the most common and a particularly distressing symptom for women receiving chemotherapy for breast cancer (Huang, Chen, Liang, & Miaskowski, 2014). Fatigue may continue through survivorship and can have a negative impact on quality of

life. Importantly, high levels of fatigue may predict shorter recurrence-free and overall survival in breast cancer patients (Groenvold et al., 2007). Additionally, insomnia, poor sleep quality, and increased daytime sleepiness are shown to cause severe distress in patients with breast cancer and are related to increased fatigue (Beck, et al., 2010; Berger & Higginbotham, 2000; Kuo, Chiu, Liao, & Hwang, 2006). Not only are fatigue and sleep disturbance major contributors to decreased quality of life, ability to function, and disease-related interference with employment, but these symptoms may also interrupt treatment and influence treatment effectiveness (Bradley, Neumark, Luo, & Schenk, 2007).

Several demographic and clinical characteristics have been associated with fatigue and disturbed sleep prevalence and severity in women receiving chemotherapy for breast cancer. While age does not appear to relate to fatigue, Beck et al. (2010) and Colagiuri et al. (2011) reported a positive relationship between age and disturbed sleep, where older women experienced increased disturbed sleep during chemotherapy (Browall, Ahlberg, Persson, Karlsson, & Danielson, 2008; deJong, Candel, Schouten, Abu-Saad, & Courtens, 2004; deJong, Kester, Schouten, Abu-Saad, & Courtens, 2006; Goldstein et al., 2012; Jacobsen et al., 1999; Von Ah, Kang, & Carpenter, 2008). While deJong et al. (2004) reported that divorced women were more fatigued than women living with a partner, Huang et al. (2014) found that married women were more fatigued than nonmarried. Additionally, Jacobsen et al. (1999) found no relationship between marital status and fatigue and Colagiuri et al. and Onselen et al. (2012) found no relationship between marital status and disturbed sleep. Employment is not reported to relate to fatigue, but a lack of employment may predict increases in disturbed sleep. Both income

and stage of disease are not reported to relate with fatigue or sleep disturbance in women receiving chemotherapy for breast cancer (Beck et al., 2010; Colagiuri et al., 2011; deJong et al., 2004; Von Ah et al., 2008).

Outcome variables such as decreases in functional status are reported to associate with fatigue and sleep disturbance (Ancoli-Israel et al., 2006; Beck et al., 2010; Berger & Higginbotham, 2000; Colagiuri et al., 2011; Downie, Fan, Houede-tchen, Yi, & Tannock, 2006; Fortner, Stepanski, Wang, Kasprowicz, & Durrance, 2002; Huang et al., 2014; Onselen et al., 2012). Additionally, fatigue and disturbed sleep during chemotherapy for breast cancer have been reported to predict decreases in activity level (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Colagiuri et al., 2011; deJong et al., 2004; Jacobsen et al., 1999).

Fatigue is reported to co-occur with several symptoms, including trouble sleeping (Ancoli-Israel et al., 2006; Bender Ergun, Rosenzweigh Cohen, & Sereika, 2005; Berger, 1998; Berger & Farr, 1999; Berger, Farr, Kuhn, Fischer, & Agrawal, 2007; Berger & Higginbotham, 2000; Berger, Wielgus, Hertzog, Fischer, & Farr, 2010; Bower et al., 2011; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Goldstein et al., 2012; Jacobsen et al., 1999; Kim, Barsevick, Tulman, & McDermott, 2008; Liu et al., 2009; Liu et al., 2012; Onselsen et al., 2012), depressed mood (Ancoli-Israel et al., 2006; Bender et al., 2005; Bower et al., 2011; Byar, Berger, Bakken, & Cetak, 2006; Dragomir & Fodoreanu, 2013; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy et al., 1999; Goldstein et al., 2012; Huang et al., 2014; Jacobsen et al., 1999; Kim et al., 2008; Liu et al., 2009; Nieboer et al., 2005; Prigozin, Uziely, & Musgrave, 2010; Von Ah et al., 2008), anxiety (Bender et al., 2005; Byar et al., 2006; Dragomir & Fodoreanu, 2013;

Prigozin et al., 2010), pain (Bender et al., 2005; Gaston-Johansson et al., 1999; Jacobsen et al., 1999; Kim et al., 2008; Nieboer et al., 2005), nausea (Jacobsen et al., 1999; Miaskowski et al., 2014), and trouble thinking (Bender et al., 2005; Jacobsen et al., 1999; Kim et al., 2008; Merriman et al., 2015). Only Prigozin et al. (2010) did not find a relationship between fatigue and potential co-occurring symptoms of pain, nausea and vomiting, and trouble thinking. Besides the relation to fatigue described earlier, disturbed sleep has been reported to co-occur with depressed mood (Ancoli-Israel et al., 2006; Bender et al., 2005; Berger et al., 2010; Colagiuri et al., 2011; Kim et al., 2008; Liu et al., 2009), anxiety (Bender et al., 2005; Colagiuri et al., 2011), pain (Bender et al., 2005; Fortner et al., 2002; Kim et al., 2008), and trouble thinking (Bender et al., 20052; Kim et al., 2008). Again, Prigozin et al. did not find a strong relationship between disturbed sleep and several symptoms including depressed mood, anxiety, pain, trouble thinking, and nausea and vomiting.

Because of the significance of fatigue and disturbed sleep as debilitating symptoms for women receiving chemotherapy, a greater understanding of the trajectory of the development and progression of these symptoms is needed. Using data across cycle 2 and 3 in women initiating chemotherapy treatment for newly diagnosed breast cancer, we previously identified three patterns of fatigue described by a Latent Growth Mixture Model (LGMM), including those with mild improving fatigue (59% of women in cycle 2 and 64% in cycle 3), low moderate improving to mild fatigue (30% of women in cycle 2 and 25% in cycle 2), and high moderate improving fatigue (11% of women in both cycles). Two patterns of disturbed sleep were described by a LGMM model, including mild improving disturbed sleep (89% of women in cycle 2 and 81% in cycle 3)

and moderate worsening disturbed sleep during cycle 2 (11% of women) and mild worsening disturbed sleep during cycle 3 (19% of women). The purpose of this analysis was to determine if antecedents, co-occurring symptoms, and outcomes are associated with class membership.

Methods

Participants and Setting

This was a secondary analysis of data collected as part of three longitudinal studies that used an automated telephone-linked-care system for monitoring symptoms during chemotherapy. Participants in Study 1 were recruited from four ambulatory clinics in the southeast and western United States. Participants in Study 2 and Study 3 were recruited from two settings in the Midwest and western United States. In both Study 1 and Study 2, participants were assigned to a usual care and a symptom management intervention group, but only those in Study 2 were found to have differences in reported symptoms between the control and intervention groups. Study 3 involved no intervention and no group assignment. All data from eligible participants in Study 1 and Study 3 and those in the usual care group in Study 2 were included in this secondary analysis. Eligibility requirements for this secondary analysis included being a woman diagnosed with breast cancer at initial treatment with chemotherapy, completion of study measures through cycles 2 and 3, and reported data for at least 3 days during each cycle.

From the three parent studies, 259 women were identified as eligible. 93 women were excluded from the secondary analysis because they were either randomized to the intervention group in Study 2 or did not complete study measures through cycles 2 and 3. The total sample for this study was 166 women, 165 who completed 3 days of measures

during cycle 2 and 155 of women who completed 3 days of measures during cycle 3.

Measures

All 3 parent studies used similar instrumentation. Demographic and clinical data were collected at baseline and included age, gender, race/ethnicity, employment status, education, diagnosis, extent of disease, and chemotherapy protocol, whether the participant received a regimen containing Doxorubicin and whether the participant received a regimen containing Taxane separately. The telephone-linked-care automated system is further described by Mooney, Beck, Friedman, Farzanfar, and Wong (2014). During a daily automated phone call, beginning with the first day of chemotherapy and continuing through the cycle, participants were asked "During the past 24 hours did you experience (symptoms)?" Conditional branching was employed so that a no response was scored as zero and a yes response prompted the system to ask the participant to rate the severity of the symptom on a Likert scale of 1 to 10. The use of single-item measures for studying symptoms is considered to have acceptable reliability and validity (Cleeland & Mendoza, 2011; Mooney et al., 2014). Symptoms assessed included fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea/vomiting, sore mouth, and diarrhea across all three parent studies. Two additional symptoms, distress associated with changing appearance and trouble thinking, were assessed in Studies 2 and 3. A subsample, consisting of participants enrolled in those 2 parent studies only, was used in analyses that included those 2 symptoms.

Hours spent lying down was collected daily and employed participants were asked whether they were able to go to work each day whether full or part-time employed. To account for varying cycles lengths among participants, only data from the first 14

days of each cycle were used in the analysis, providing a consistent period of treatment across participants.

This secondary analysis was reviewed by the Institutional Review Board (IRB) at the University of Utah. Subjects were identified only by their original study identification number. All participants signed a written, informed consent upon initiation of participation in the original studies.

Statistical Analysis

The Software Statistical Package for the Social Sciences (SPSS), version 23.0 was used for data management and data analysis. P values less than .05 were considered statistically significant and there was no adjustment for multiple comparisons as this was a hypothesis generating study.

Descriptive statistics and frequency distributions were generated on the sample characteristics. After determining the best model fit for the data, including classes as previously reported, the model-predicted class membership for each individual was obtained using posterior probabilities. While there is uncertainty in the model-predicted class assignment, high entropy and high posterior probabilities in the retained models suggest that model-predicted class assignments could be considered observed variables. Class membership assignment was then used to test for mean differences across the classes using independent-samples *t* tests and ANOVA and tests of associations among categories using chi-square on antecedents, co-occurring symptoms, and outcomes (deJong et al., 2004). Small cell sizes were accounted for with use of the more conservative Fisher's exact chi-square. This technique allowed for tests of associations among categories when cell sizes had an expected frequency of five or less (Green &

Salkind, 2008; Jung & Wickerama, 2008). In cases where classes did not display homogeneity of variance, the Welch statistic, a robust test that allows violation of this assumption, was used (Green & Salkind, 2008). Where appropriate, follow-up post hoc contrasts were conducted to evaluate pairwise differences in class membership on antecedents, co-occurring symptoms, and outcomes. In cases where equal variances were not assumed, the Dunnett's *C* test was used (Green & Salkind, 2008). The analysis proceeded to answer 4 specific aims.

Aim 1 was to determine whether differing symptom trajectory profiles for fatigue and disturbed sleep are associated with variations in demographic and clinical characteristics. Using the trajectory classes for fatigue and disturbed sleep, as previously described, and treating those as observed group variables in each of 2 cycles of treatment (cycle 2 and cycle 3), the association between the classes and age were examined using independent-samples *t* tests and ANOVA and the association between the classes and stage of disease, education, employment, marital status, and chemotherapy regimen were examined using chi-square.

Aim 2 was to determine whether differing symptom trajectory profiles for fatigue and disturbed sleep are associated with variations in outcomes, such as average hours spent lying down and days of missed work. Daily measures of hours spent lying down during the first 14 days of each cycle separately were averaged for each individual for each cycle 2 and 3. Days of missed work during the first 14 days of each cycle separately were summed for all employed participants. To answer this aim, tests of mean differences across the classes were conducted on the outcome using independent-samples *t* tests and ANOVA. Only those participants who were employed were included in the

test of mean differences across the classes for days of missed work.

Aim 3 was to determine whether differing symptom trajectory profiles for fatigue and disturbed sleep are associated with variations in the severity of other symptoms, such as pain, trouble thinking, nausea, depressed mood, and anxiety. Tests of mean differences across classes on the number of moderate to severe days reported for each symptom of interest were conducted using independent-samples *t* tests and ANOVA. Summative scores for each symptom included the number of days subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea and vomiting, and trouble thinking individually within the first 14 days of each cycle. These symptoms were studied because they were both prevalent in the sample and previously reported to relate with fatigue and/or disturbed sleep. These summative scores were then compared to class membership for fatigue and disturbed sleep in cycles 2 and 3 using independent-samples *t* tests and ANOVA.

Aim 4 was to determine whether differing symptom trajectory profiles for fatigue and disturbed sleep during cycle 3 were associated with variations in the overall symptom severity during cycle 2. Overall symptom severity for cycle 2 included the number of days where subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting. These symptoms were studied because they were both prevalent in the sample, with data from all participants, and previously reported to relate with fatigue and/or disturbed sleep. The number of days with moderate to severe symptoms during cycle 2 was then compared to the extracted class membership for fatigue and disturbed sleep in cycle 3 using independent-samples *t* tests and ANOVA.

Results

The sample consisted of 166 women with breast cancer. Demographic and clinical characteristics of the sample are summarized in Table 3.1. Women ranged in age between 24 and 80 years (mean age 52.91, *SD* = 10.8). The majority of women were white (91.46%), married (75%), and not currently working (62.8%). The largest proportion of women were diagnosed with Stage II disease (40.36%) and 75.3% of women in the sample had some education beyond high school.

The prevalence of individual symptoms in the sample during the first 14 days of each cycle and the prevalence of moderate/severe levels of symptoms during the first 14 days of each cycle are reported in Table 3.2. The most prevalent symptom was fatigue, followed by disturbed sleep, pain, nausea and vomiting, depressed mood, and anxiety. Diarrhea, trouble thinking, sore mouth, and distress associated with change in appearance were not highly prevalent or highly prevalent at moderate to severe levels.

Aim 1

Results of the tests of mean differences and associations among categories across classes on the demographic variables are presented in Tables 3.3 for the fatigue classes and 3.4 for the disturbed sleep classes. All test results were nonsignificant, with the exception of chemotherapy regimen. Women who received Doxorubicin as part of their chemotherapy regimen were more likely to be in the high moderate improving fatigue class when compared to the mild improving fatigue class in both cycles 2 and 3.

Aim 2

For fatigue and disturbed sleep, the independent-samples *t* tests and ANOVAs for both hours spent lying down and days of missed work were nonsignificant, with the

Table 3.1 Sample Demographic and Clinical Characteristics (*n* =166)

Characteristic	**Mean**	***SD***
Age (in years)	52.90	10.8
Characteristic	***n***	**%**
Ethnicity		
Non-Hispanic	162	97.6%
Hispanic	2	1.2%
Unknown	2	1.2%
Marital Status		
Partnered	123	74.1%
Nonpartnered	41	24.7%
Unknown	2	1.2%
Employment		
Full-time	48	29.2%
Part-time	13	7.8%
Not Employed	103	62.0%
Unknown	2	1.0%
Education Status		
High school	3	22.3%
Some College	52	31.3%
Associate Degree	15	9.0%
Bachelor Degree	36	21.7%
Postgraduate	22	13.2%
Unknown	4	2.5%
Income		
Less than $9,999	8	4.8%
$10,000-29,999	16	9.6%
$30,000-49,000	37	22.3%
$50,000-69,000	20	12.1%
$70,000 or More	57	34.3%
Unknown	10	6.1%
Declined to State	18	10.8%
Stage of Disease		
Stage I	20	12.1%
Stage II	67	40.3%
Stage III	38	22.9%
Stage IV	36	21.7%
Unknown	5	3.0%
Chemotherapy Regimen		
Cyclophosphamide with Doxorubicin	68	41.0%
Docetaxel	23	13.9%
Cyclophosphamide with Methotrexate and 5-FU	16	9.6%
Docetaxel with Carboplatin	13	7.8%
Cyclophosphamide with Docetaxel	12	7.2%
Cyclophosphamide with Doxorubicin and Docetaxel	9	5.4%
Cyclophosphamide with Doxorubicin and 5-FU	6	3.6%
Cyclophosphamide with 5-FU	4	2.4%
Other	15	9.1%

Table 3.2 Symptom Prevalence and Mean Number of Days at Moderate to Severe Levels

Symptom	Cycle	No. (%) of Women Reported Symptom Severity Greater than 0 at Least Once	Mean no. Days (*SD*), Range of Symptom Reported with Severity Greater than 0	No. (%) of Women Reported Symptom Severity Greater than 3 at Least Once	Mean no. Days (*SD*), Range of Symptom Reported with Severity Greater than 3	No. Days (%) Symptom Reported Level 0	No. Days (%) Symptom Reported Level 1-10	No. Days (%) Symptom Reported Level 4-10
Physical Symptoms								
Fatigue [a]	2	153 (92.7%)	7.53 (3.69), 1-14	115 (69.7%)	5.09 (3.47), 1-14	659 (36.4%)	1,152 (63.6%)	585 (32.3%)
	3	148 (94.9%)	7.09 (3.93), 1-14	105 (67.3%)	4.95 (3.70), 1-14	654 (38.4%)	1,050 (61.6%)	520 (30.5%)
Disturbed Sleep [a]	2	126 (76.4%)	3.63 (2.56), 1-13	103 (62.4%)	2.87 (2.07), 1-13	1,354 (74.8%)	457 (25.2%)	296 (16.3%)
	3	110 (70.5%)	3.40 (2.64), 1-13	85 (54.5%)	2.46 (1.76), 1-11	1,330 (78.1%)	374 (21.9%)	209 (12.3%)
Pain [a]	2	124 (75.2%)	4.55 (3.20), 1-14	75 (45.5%)	3.51 (2.95), 1-13	1,247 (68.9%)	564 (31.1%)	263 (14.5%)
	3	104 (66.7%)	5.16 (3.74), 1-14	66 (42.3%)	4.15 (3.33), 1-14	1,167 (68.5%)	537 (31.5%)	274 (16.1%)
Nausea and Vomiting [a]	2	116 (70.3%)	3.90 (2.92), 1-13	78 (47.3%)	2.66 (2.28), 1-11	1,359 (75.0%)	542 (29.9%)	208 (11.5%)
	3	111 (71.2%)	4.05 (3.31), 1-14	63 (40.4%)	3.14 (2.63), 1-12	1,254 (73.6%)	450 (26.4%)	198 (11.6%)
Diarrhea [a]	2	69 (41.8%)	2.13 (1.53), 1-8	30 (18.2%)	1.83 (0.87), 1-4	1,664 (91.9%)	147 (8.1%)	55 (3.0%)
	3	49 (31.4%)	2.63 (1.82), 1-10	23 (14.7%)	2.17 (1.53), 1-6	1,575 (92.4%)	129 (7.6%)	49 (2.9%)
Sore Mouth [a]	2	68 (41.2%)	3.62 (2.34), 1-11	38 (23.0%)	3.11 (2.29), 1-10	1,565 (86.4%)	246 (13.6%)	118 (6.5%)
	3	68 (43.6%)	3.32 (2.61), 1-13	38 (24.4%)	2.66 (2.72), 1-13	1,478 (86.7%)	216 (12.7%)	91 (5.3%)
Trouble Thinking [b]	2	46 (27.9%)	2.67 (1.97), 1-11	28 (17.0%)	2.50 (2.19), 1-10	884 (93.2%)	64 (6.8%)	37 (3.9%)
	3	31 (19.9%)	3.26 (2.11), 1-9	21 (13.5%)	1.95 (1.07), 1-5	776 (94.1%)	46 (5.6%)	20 (2.4%)
Appearance [b]	2	38 (23.0%)	3.32 (2.57), 1-12	25 (15.2%)	3.16 (2.37), 1-9	882 (93.0%)	66 (7.0%)	42 (4.4%)
	3	15 (9.6%)	3.27 (3.97), 1-13	10 (6.4%)	3.50 (4.50), 1-12	801 (97.1%)	24 (2.9%)	17 (2.1%)
Mood Disturbance Symptoms								
Depressed Mood [a]	2	99 (60.0%)	3.60 (3.21), 1-13	70 (42.4%)	3.23 (2.84), 1-12	1,455 (80.3%)	356 (19.7%)	226 (12.5%)
	3	83 (53.2%)	3.47 (3.11), 1-14	55 (35.3%)	2.87 (2.86), 1-13	1,416 (83.1%)	288 (16.9%)	158 (9.3%)
Anxiety [a]	2	77 (46.7%)	3.34 (3.17), 1-13	47 (28.5%)	2.91 (2.83), 1-11	1,544 (85.3%)	267 (14.7%)	147 (8.2%)
	3	62 (39.7%)	3.56 (3.62), 1-13	40 (25.6%)	2.65 (2.56), 1-9	1,483 (87.0%)	221 (13.0%)	106 (6.2%)

[a] *n*=165, cycle 2; *n*=156, cycle 3; 1811(78.4%) days reported cycle 2, 1704(78.0%) days reported cycle 3; 499(21.6%) days missing cycle 2, 480(22.0%) days missing cycle 3
[b] *n*=84, cycle 2; *n*=75, cycle 3; 948 (80.6%) days reported cycle 2, 825 (79.6%) days reported cycle 3; 228 (19.4%) days missing cycle 2, 211 (20.4%) days missing cycle 3

Table 3.3 Tests of Mean Differences and Associations Among Categories for Antecedents and Outcomes of Fatigue Class Membership

Characteristic		Mild Improving	Low Moderate Improving to Mild	High Moderate Improving	Omnibus Test
		Cycle 2			
Age (in years)		51.79 (10.70)	53.56 (10.20)	57.51 (11.76)	$F(2, 159) = 2.35$, $p = .10$
Education					
	Less than high school	4 (4.3%)	1 (2.0%)	1 (5.3%)	$\chi^2 = 2.16$, $p = .99$
	High school	20 (21.5%)	8 (16.3%)	3 (15.8%)	
	Undergraduate	57 (61.3%)	33 (67.3%)	13 (68.4%)	
	Postgraduate	12 (12.9%)	7 (14.3%)	2 (10.5%)	
Marital Status					
	Married	72 (75.8%)	37 (75.5%)	13 (68.4%)	$\chi^2 = 1.54$, $p = .85$
	Not Married	23 (24.2%)	12 (24.5%)	6 (31.6%)	
Employment					
	Employed	32 (33.7%)	22 (44.9%)	6 (31.6%)	$\chi^2 = 2.91$, $p = .58$
	Not Employed	63 (66.3%)	27 (55.1%)	13 (68.4%)	
Stage					
	I	13 (14.1%)	5 (10.0%)	2 (30.5%)	$\chi^2 = 4.60$, $p = .80$
	II	34 (37.0%)	25 (50.0%)	8 (42.1%)	
	III	24 (26.1%)	10 (20.0%)	4 (63.2%)	
	IV	21 (22.8%)	10 (20.0%)	5 (26.3%)	
Doxorubicin					
	Yes	41 (46.6%)	27 (57.4%)	14 (82.4%)	$\chi^2 = 7.75$, $p = .02$*
	No	47 (53.4%)	20 (52.6%)	3 (17.6%)	
Taxane					
	Yes	34 (38.6%)	14 (29.2%)	3 (17.6%)	$\chi^2 = 3.01$, $p = .22$
	No	54 (61.4%)	33 (70.2%)	14 (82.4%)	
Hours Spent Lying Down		10.00 (2.54)	10.79 (2.64)	12.36 (3.77)	$F(2, 44) = 2.03$, $p = .02$*
Days Missed Work (n=20)		1.9 (1.52)	3.13 (2.03)	2.5 (2.12)	$F(2, 17) = 1.05$, $p = .37$

Table 3.3 continued

Characteristic		Mild Improving	Low Moderate Improving to Mild	High Moderate Improving	Omnibus Test
		Cycle 3			
Age (in years)		52.9 (10.31)	52.53 (12.00)	54.13 (12.00)	$F(2, 150) = 0.13$, $p = .88$
Education					
	Less than high school	3 (3.2%)	1 (2.6%)	1 (5.6%)	$\chi^2 = 3.47$, $p = .75$
	High school	20 (21.5%)	5 (5.1%)	5 (27.8%)	
	Undergraduate	58 (62.4%)	26 (66.7%)	10 (55.6%)	
	Postgraduate	12 (12.9%)	7 (17.9%)	2 (11.1%)	
Marital Status					
	Married	69 (72.6%)	29 (74.4%)	15 (83.3%)	$\chi^2 = 0.78$, $p = .74$
	Not Married	26 (27.4%)	10 (25.6%)	3 (16.7%)	
Employment					
	Employed	36 (37.9%)	15 (41.0%)	7 (38.9%)	$\chi^2 = 0.06$, $p = 1.00$
	Not Employed	59 (62.1%)	24 (59.0%)	11 (61.1%)	
Stage					
	I	11 (11.3%)	6 (15.8%)	0 (0.0%)	$\chi^2 = 7.69$, $p = .25$
	II	37 (38.1%)	20 (52.6%)	9 (47.4%)	
	III	27 (27.8%)	5 (13.2%)	6 (33.3%)	
	IV	22 (22.7%)	7 (18.4%)	3 (16.7%)	
Doxorubicin					
	Yes	45 (46.9%)	22 (57.9%)	15 (83.3%)	$\chi^2 = 8.59$, $p = .01$*
	No	51 (53.1%)	16 (42.1%)	3 (16.7%)	
Taxane					
	Yes	38 (39.6%)	11(28.9%)	2 (11.1%)	$\chi^2 = 6.06$, $p = .05$
	No	58 (60.4%)	27 (71.1%)	16 (88.9%)	
Hours Spent Lying Down		10.44(2.94)	10.71 (2.51)	10.05 (2.51)	$F(2, 150) = 0.35$, $p = .70$
Days Missed Work (n=27)		1.33(1.50)	1.43(1.72)	2.20(1.65)	$F(2, 24) = 0.51$, $p = .61$

*$p<.05$

Table 3.4 Tests of Mean Differences and Associations Among Categories for Antecedents and Outcomes of Disturbed Sleep Class Membership

		Cycle 2		
Characteristic		**Mild Improving**	**Moderate Worsening**	**Omnibus Test**
Age (in years)		53.06 (10.63)	52.03 (11.54)	$t(159) = 0.19$, $p = .66$
Education				
	Less than high school	6 (4.4%)	0 (0.0%)	$\chi^2 = 1.08$, $p = .94$
	High school	26 (19.3%)	4 (16.0%)	
	Undergraduate	85 (63.0%)	18 (72.0%)	
	Postgraduate	18 (13.3%)	3 (12.0%)	
Marital Status				
	Married	104 (75.9%)	17 (68.0%)	$\chi^2 = 1.01$, $p = .61$
	Not Married	33 (24.1%)	8 (32.0%)	
Employment				
	Employed	48 (35.3%)	11 (44.0%)	$\chi^2 = 0.87$, $p = .64$
	Not Employed	88 (64.7%)	14 (56.0%)	
Stage				
	I	14 (10.4%)	6 (24.0%)	$\chi^2 = 3.80$, $p = .40$
	II	57 (42.2%)	10 (40.0%)	
	III	33 (24.4%)	4 (16.0%)	
	IV	31 (23.0%)	5 (20.0%)	
Doxorubicin				
	Yes	68 (53.1%)	14 (58.3%)	$\chi^2 = 0.22$, $p = .66$
	No	60 (46.9%)	10 (41.7%)	
Taxane				
	Yes	44 (34.4%)	7 (29.2%)	$\chi^2 = 0.25$, $p = .65$
	No	84 (65.6%)	17 (70.8%)	
Hours Spent Lying Down		10.66 (2.59)	9.87 (3.88)	$t(28.1) = 0.98$, $p = .33$
Days Missed Work (n=20)		2.44 (1.93)	2.50 (1.29)	$t(18) = 0.00$, $p = .95$

Table 3.4 continued

Cycle 3				
Characteristic		**Mild Improving**	**Mild Worsening**	**Omnibus Test**
Age (in years)		52.79 (10.95)	52.70 (9.18)	$t(150) = 0.00$, $p = .97$
Education				
	Less than high school	5 (11.1%)	1 (5.9%)	$\chi^2 = 2.31$, $p = .62$
	High school	26 (57.8%)	2 (11.8%)	
	Undergraduate	12 (26.7%)	12 (70.6%)	
	Postgraduate	2 (4.4%)	2 (11.8%)	
Marital Status				
	Married	103 (76.3%)	11 (61.1%)	$\chi^2 = 2.25$, $p = .41$
	Not Married	32 (23.7%)	7 (38.9%)	
Employment				
	Employed	53 (39.3%)	7 (38.9%)	$\chi^2 = 0.29$, $p = 1.00$
	Not Employed	82 (60.7%)	11 (61.1%)	
Stage				
	I	17 (12.7%)	2 (11.1%)	$\chi^2 = 1.83$, $p = .77$
	II	58 (43.3%)	7 (38.9%)	
	III	32 (23.9%)	3 (16.7%)	
	IV	27 (20.1%)	6 (33.3%)	
Doxorubicin				
	Yes	72 (53.3%)	10 (58.8%)	$\chi^2 = 0.18$, $p = .67$
	No	63 (46.7%)	7 (41.2%)	
Taxane				
	Yes	44 (32.6%)	7 (41.2%)	$\chi^2 = 0.50$, $p = .59$
	No	91 (67.4%)	10 (58.8%)	
Hours Spent Lying Down		10.69 (2.74)	9.65 (3.23)	$t(150) = 1.48$, $p = .14$
Days Missed Work (n=27)		1.50(1.71)	1.60(1.52)	$t(25) = 0.01$, $p = .91$

*$p<.05$

exception of hours spent lying down during cycle 2 (see Tables 3.3 and 3.4). During cycle 2, the number of hours spent lying down was statistically significantly higher in the high moderate improving fatigue class when compared to the mild improving fatigue class ($p = .02$). Although not statistically significant in the ANOVA, examination of days missed work within each class for fatigue across both cycles suggests an upward trend in class mean, as days missed work increased with fatigue class severity.

Aim 3

Class membership for fatigue and disturbed sleep was compared with the number of moderate to severe days of individual symptoms using independent-samples *t* tests and ANOVA and results are presented in Tables 3.5 and 3.6. Women in the high moderate improving fatigue class reported a greater number of days with moderate to severe disturbed sleep ($p < .01$* in cycle 2 and $p < .01$* in cycle 3) and nausea and vomiting ($p < .01$* in cycle 2 and $p < .01$*in cycle 3) during both cycles and anxiety ($p = .03$*) and depressed mood ($p < .01$*) during only cycle 2 when compared to women in the mild improving fatigue class. Women in the high moderate improving fatigue class also reported a statistically significantly greater number of days with moderate to severe depressed mood ($p = .001$*, $p = .010$*) during both cycles when compared to women in the low moderate improving to mild fatigue class. Additionally, women in the low moderate improving to mild fatigue latent trajectory class reported a statistically significantly greater number of days with moderate to severe disturbed sleep ($p < .01$*, $p < .01$*) when compared to women in the mild improving fatigue class during both cycles. Women in the low moderate improving to mild fatigue class also reported a greater number of days with moderate to severe pain ($p = .02$*) when compared to women in the

Table 3.5 95% Confidence Intervals of Pairwise Differences Among the Mean Number of Days with Moderate to Severe Symptoms for Fatigue Class Membership

Fatigue Class	Mean Days	*SD*	Mild Improving	Low Moderate	*p* omnibus test
Cycle 2					
Anxiety					Welch(2, 40) = 3.79, $p = .03$*
Mild Improving	.49	1.13			
Low Moderate	.64	1.52	-.74 to .44		
High Moderate	3.10	4.14	.18 to 5.05**	-.01 to 4.94	
Depressed Mood					Welch(2, 40) = 8.77, $p < .001$*
Mild Improving	.74	1.66			
Low Moderate	1.54	2.38	-.11 to 1.71		
High Moderate	4.11	3.77	1.12 to 5.61**	.21 to 4.92**	
Disturbed Sleep					$F(2, 162) = 6.03$, $p < .001$*
Mild Improving	1.34	1.83			
Low Moderate	2.24	2.33	-1.76 to -.04**		
High Moderate	2.89	2.58	-2.79 to -.31**	-1.98 to .67	
Pain					Welch(2, 61) = 4.64, $p = .02$*
Mild Improving	1.34	2.62			
Low Moderate	2.38	2.87	-.13 to 2.21		
High Moderate	0.79	1.55	-1.66 to .55	.26 to 2.93**	
Nausea and Vomiting					Welch(2, 41) = 5.95, $p = .01$*
Mild Improving	0.83	1.47			
Low Moderate	1.42	2.32	-1.46 to .28		
High Moderate	3.00	2.87	.45 to 3.88**	-.28 to 3.44	
Trouble Thinking					$F(2, 80) = .37$, $p = .69$
Mild Improving	0.89	1.80			
Low Moderate	0.82	1.63			
High Moderate	0.00	0.00			

Table 3.5 continued

Fatigue Class	Mean Days	*SD*	Mild Improving	Low Moderate	*p* omnibus test
Cycle 3					
Anxiety					Welch(2, 35) =3.39, $p < .01$*
Mild Improving	0.38	1.18			
Low Moderate	0.92	2.09	-.32 to 1.41		
High Moderate	1.38	2.73	-.22 to 3.13**	-.93 to 2.75	
Depressed Mood					Welch(2, 34) =5.31, $p = .01$*
Mild Improving	0.58	1.35			
Low Moderate	1.28	2.87	-.46 to 1.87**		
High Moderate	1.02	3.11	-3.74 to .64	.34 to 4.16	
Disturbed Sleep					Welch(2, 36) =9.21, $p < .001$*
Mild Improving	0.85	1.26			
Low Moderate	1.92	1.77	.32 to 1.83**		
High Moderate	2.83	2.92	.20 to 3.77**	-.98 to 2.80	
Pain					Welch(2, 36) =2.73, $p = .08$
Mild Improving	1.29	2.26			
Low Moderate	2.33	3.22			
High Moderate	3.17	4.94			
Nausea and Vomiting					Welch(2, 35) = 6.66, $p < .01$*
Mild Improving	0.73	1.38			
Low Moderate	1.49	2.36	-.23 to 1.73		
High Moderate	3.78	3.90	.66 to 5.43**	-.24 to 4.82	
Trouble Thinking					$F(2, 74) = 7.26$, $p < .01$*
Mild Improving	0.35	0.92			
Low Moderate	1.50	1.24	-2.16 to -.14*		
High Moderate	0.53	1.03	-.96 to .86	-2.39 to .19	
Total Cycle 2 Days Moderate or Severe Symptoms					$F(1,153) = 28.90$, $p < .001$*
Mild Improving	7.43	8.40			
Low Moderate	14.00	8.01	2.78 to 10.37*		
High Moderate	22.89	9.75	10.32 to 20.60**	3.18 to 14.60**	

*$p<.05$ for omnibus test
** The difference in means is significant at the .05 significance using Dunnett's *C* procedure.

Table 3.6 Tests of Mean Differences for Co-occurring Symptoms With Disturbed Sleep Class Membership

Disturbed Sleep Class	Mean Days	*SD*	*p* omnibus test
Cycle 2			
Fatigue			$t(162) = 11.72, p < .01$*
Mild Improving	3.16	3.52	
Moderate Worsening	5.84	4.08	
Depressed Mood			Welch $t(27) = 7.37, p = .01$*
Mild Improving	1.07	2.01	
Moderate Worsening	3.12	3.69	
Anxiety			$t(162) = 2.66, p = .11$
Mild Improving	0.73	1.86	
Moderate Worsening	1.44	2.65	
Pain			$t(162) = 0.10, p = .75$
Mild Improving	1.58	2.55	
Moderate Worsening	1.76	3.23	
Nausea and Vomiting			$t(162) = 0.96, p = .33$
Mild Improving	1.20	1.93	
Moderate Worsening	1.64	2.71	
Trouble Thinking			$t(80) = 0.07, p = .79$
Mild Improving	0.84	1.79	
Moderate Worsening	1.00	1.32	
Cycle 3			
Fatigue			$t(153) = 4.67, p = .03$*
Mild Improving	3.12	3.66	
Mild Worsening	5.17	4.67	
Depressed Mood			Welch $t(18.3) = 3.97, p = .06$
Mild Improving	0.82	1.88	
Mild Worsening	2.50	3.50	
Anxiety			Welch $t(18.5) = 2.68, p = .12$
Mild Improving	0.56	1.55	
Mild Worsening	1.61	2.66	
Pain			$t(152) = .47, p = .49$
Mild Improving	1.71	2.99	
Mild Worsening	2.22	2.98	
Nausea and Vomiting			$t(153) = 1.76, p = .19$
Mild Improving	1.19	2.22	
Mild Worsening	1.94	2.65	
Trouble Thinking			$t(75) = -2.02, p < .01$*
Mild Improving	0.46	1.00	
Mild Worsening	1.33	1.21	
Total Cycle 2 Days Moderate or Severe Symptoms			$t(153) = 15.47, p < .001$*
Mild Improving	9.80	9.44	
Mild Worsening	19.11	9.53	

*$p<.05$

high moderate improving fatigue class. Finally, women in the low moderate improving to mild fatigue class reported a greater number of days with moderate to severe trouble thinking ($p < .01$*) during cycle 3 only when compared to women in the mild improving fatigue class.

Compared to their counterparts with mild improving disturbed sleep, the moderate worsening disturbed sleep trajectory class experienced statistically significantly more days with moderate to severe fatigue ($p < .01$*) and depressed mood ($p = .01$*) in cycle 2 and the mild worsening disturbed sleep trajectory class experienced statistically significantly more days with moderate to severe fatigue *(*$p = .03$*) and trouble thinking ($p < .01$*) during cycle 3. There was no association between membership in the worsening disturbed sleep trajectory class and nausea and vomiting, pain, or anxiety during either cycle.

Aim 4

For both fatigue ($F(1,153) = 28.90$, $p<.001$*) and disturbed sleep ($F(1, 153) = 15.47$, $p<.001$*), the overall symptom severity in cycle 2, the total number of days where subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting, was associated with class membership in cycle 3 (see Tables 3.5 and 3.6). For fatigue, means for the mild improving fatigue class (7.43, $SD = 8.40$), low moderate improving to mild fatigue class (14.00, $SD = 8.01$), and high moderate improving fatigue class (22.89, $SD = 9.75$) suggest that those in the low moderate improving to mild and high moderate improving classes for fatigue in cycle 3 had statistically higher overall symptom severity in cycle 2 when compared to the mild improving fatigue class. Additionally, those in the high moderate improving class for

fatigue in cycle 3 had statistically higher overall symptom severity in cycle 2 when compared to the low moderate improving to mild class. Means for the mild improving disturbed sleep class (9.80, *SD* = 9.44) and mild worsening disturbed sleep class (19.11, *SD* = 9.53) suggest that those in the mild worsening class during cycle 3 reported statistically higher overall symptom severity in cycle 2 when compared to the mild improving class.

Discussion

Identifying longitudinal patterns of symptoms is important because it can elucidate factors that contribute to distinct symptom trajectories. Various demographic and clinical characteristics were examined as possibly distinguishers of fatigue and disturbed sleep class membership. None of the demographic or clinical characteristics were found to be associated with fatigue or disturbed sleep class membership, with the exception of chemotherapy regimen. Our findings are consistent with several reports that age and fatigue are not related (Browall et al., 2008; deJong et al., 2004; deJong et al., 2006; Goldstein et al., 2012; Jacobsen et al., 1999; Von Ah et al., 2008). Although Beck et al. (2010) and Colagiuri et al. (2011) found a relationship between age and disturbed sleep, this relationship was not found in our sample, similar to findings reported by Browall et al. (2008) and Onselen et al. (2012). Reports of the relationship between marital status and fatigue are inconsistent, where deJong et al. (2004) reported that divorced women were more fatigued than women living with a partner, and Huang et al. (2013) found that married women were more fatigued than nonmarried. In our sample, there was no relationship between marital status and fatigue, similar to findings reported by Jacobsen et al. (1999). The lack of relationship between marital status and disturbed sleep is similar to the findings of Colagiuri et al. and Onselen et al. While our finding

that employment status does not predict fatigue is supported in the literature, Onselen et al. found an association between unemployment and disturbed sleep that we did not find in our sample (deJong et al., 2004; deJong et al., 2006; Huang et al., 2014). The lack of association between stage of disease and either fatigue or disturbed sleep has been previously reported (Beck et al., 2010; Colagiuri et al., 2011; deJong et al., 2004; Jacobsen et al., 1999; Onselen et al., 2012; Von Ah et al., 2008). Inconsistencies between our findings of the relationship between demographic and clinical characteristics and fatigue and disturbed sleep class membership may be related to a lack of sample variation on these demographics and a relatively small sample size in the present study. Further research is needed to explore other personal characteristics that might be associated with distinct classes for fatigue and disturbed sleep, including molecular and genetic determinants (Cleeland et al., 2003; Miaskowski et al., 2014).

Women in this sample who received Doxorubicin as part of their chemotherapy regimen were more likely to be in the high moderate improving fatigue class when compared to the mild improving fatigue class. The effects of chemotherapy type on fatigue severity have been reported with inconsistent findings. Berger (1998) and Berger and Farr (1999) found that levels of fatigue 48 hours after each of the first 3 chemotherapy treatments were not significantly different when comparing cohorts of women who received CMF, Doxorubicin with Cyclophosphamide, and CAF. deJong et al. (2006) reported significant differences in the course of fatigue between those receiving CMF and those receiving Doxorubicin, with fatigue peaking at a later time for those receiving Cyclophosphamide. In the present study, while Doxorubicin did have a significant effect on fatigue class membership, it is unknown if that effect is dose-

dependent or related to other agents received in combination with Doxorubicin. Across the sample, more than 12 different chemotherapy combinations were reported, making it difficult to adequately address the question of how chemotherapy affected class membership. Regardless, with the effect of Doxorubicin on fatigue class found here, further study is needed to determine whether the use of Doxorubicin alone or in combination with other specific agents places women at risk for higher fatigue.

While days of missed work was not significantly associated with class membership, examination of the mean days of missed work for the three classes of fatigue severity suggests an upward trend in the number of days missed as fatigue severity increases (see Table 3.2). Unfortunately, because only 37.2% of the sample was employed, there were only 20 participants for cycle 2 and 27 participants for cycle 3 with data available for days of missed work. A larger cohort of employed participants may have revealed a significant relationship between fatigue severity class and days of missed work.

Increased hours spent lying down was associated with membership in the high moderate improving fatigue class (mean hours = 12.36, *SD* = 3.77) when compared to the mild improving fatigue class (mean hours = 10.00, *SD* = 2.54) during cycle 2 only. This is consistent with other studies which have found that higher fatigue is associated with lower activity levels (Berger & Farr, 1999; Berger & Higginbotham, 2000; deJong et al., 2004; Downie et al., 2006). However, the upward trend and statistical association of hours spent lying down and fatigue severity class was not seen during cycle 3. Further examination with larger samples may better highlight this association.

Severity class membership for both fatigue and disturbed sleep was related to the

presence of other symptoms at moderate to severe levels. In both cycles, the number of days of moderate to severe levels of disturbed sleep was increased for those in the low moderate improving to mild and high moderate improving classes for fatigue when compared to those in the mild improving class for fatigue. Several studies have reported a positive relationship between fatigue and sleep disturbance (Berger & Farr, 1999; Berger & Higginbotham, 2000; Bower et al., 2011; Broeckel et al., 1998; Jacobsen et al., 1999; Liu et al., 2009; Onselen et al., 2012). Liu et al. (2012) found that fatigue significantly related to sleep problems, but also that women with poor sleep during chemotherapy were already experiencing disturbed sleep at baseline and that sleep disturbance did not increase during chemotherapy while fatigue did. This is consistent with findings in this sample, where women in both the low moderate improving to mild and high moderate improving fatigue classes experienced a similar number of days with moderate to severe disturbed sleep that was statistically different from the mild improving fatigue severity class. The significant relationship between fatigue and sleep disturbance suggests a synergistic effect that warrants further study.

Fatigue class membership was also significantly related to the number of days with moderate to severe depressed mood in both cycles, with women in the high moderate improving fatigue class experiencing the most days of moderate to severe depressed mood. The mean days of moderate to severe depressed mood was particularly high during cycle 2 in the high moderate improving fatigue class (mean = 4.11 days, *SD* = 3.77) when compared to both the mild improving fatigue class (mean = .74 days, *SD* = 1.66) and the low moderate improving to mild fatigue class (mean = 1.54 days, *SD* = 2.38). The mean days for depressed mood at moderate to severe levels in the high

moderate improving fatigue class (mean = 1.02 days, *SD* = 3.11) was significantly decreased when compared to the low moderate improving to mild fatigue class (mean = 1.28 days, *SD* = 2.87) in cycle 3, although with a smaller mean difference. It is unknown whether individuals with increased depressed mood during cycle 2 sought and were provided treatment that may have alleviated the number of days they experienced moderate to severe days of depressed mood during cycle 3. Several studies have reported on a significant relationship between fatigue and depression during chemotherapy and the possible existence of a symptom cluster including both fatigue and depression with other symptoms, such as disturbed sleep and pain (Ancoli-Israel et al., 2006; Bender et al., 2005; Bower et al., 2011; Byar et al., 2006; Dragomir & Fodoreanu, 2013; Gaston-Johansson et al., 1999; Goldstein et al., 2012; Huang et al., 2014; Jacobsen et al., 1999; Kim et al., 2008; Liu et al., 2009; Nieboer et al., 2005; Prigozin et al., 2010; Von Ah et al., 2008).

There was also a positive relationship between the number of days with moderate to severe depressed mood and moderate worsening disturbed sleep class membership during cycle 2, suggesting women experienced both depressive symptom and sleep symptoms concurrently. Others have found depressive symptoms predict or are positively related to difficulty with sleeping (Ancoli-Israel, 2006; Bender et al., 2005; Berger et al., 2010; Colagiuri et al., 2011; Kim et al., 2008; Liu et al., 2009). Colagiuri et al. (2011) suggest that there may be a reciprocal relationship between sleep difficulty and depressive symptoms, where sleep difficulty may results from increased depressive symptoms and/or sleep difficulty may lead to increasing depressive symptoms. Not surprisingly, disturbed sleep and depression have been identified in a symptom cluster,

along with fatigue and pain, in women undergoing treatment for breast cancer (Dodd, Cho Cooper, & Miaskowski, 2010; Liu et al., 2009).

In both cycles, the number of days with moderate to severe nausea and vomiting was increased in the high moderate improving fatigue class when compared to the mild improving fatigue class. While those in the mild improving fatigue class experienced less than one day with moderate to severe nausea and vomiting, those in the high moderate improving fatigue class experienced 3 to 4 days of nausea and vomiting at moderate to severe levels. There are several reports of a positive association between fatigue and chemotherapy-induced nausea and vomiting during treatment for cancer, even with use of appropriate antiemetic therapies (Jacobsen et al., 1999; Miaskowski et al., 2014; Osoba et al., 1997; Poon et al., 2013). Poon et al. (2013) found that individuals who suffer from fatigue are 1.57 times less likely to have good control over chemotherapy-induced nausea and vomiting. While the biological mechanism that supports this relationship is not well-understood, it is possible that cytokine induction and dysregulation of neurotransmitters may contribute to the development of both symptoms simultaneously (Poon et al., 2013). Regardless of the etiology, individuals who suffer from higher levels of nausea and vomiting during chemotherapy may be at risk for increased fatigue severity.

During cycle 2, the number of days with moderate to severe levels of anxiety were increased for those in the high moderate improving fatigue class (mean = 3.11 days, *SD* = 4.14) when compared to those in the mild improving fatigue class (mean = .49 days, *SD* = 1.13). This relationship was not found during cycle 3, where the number of days with moderate to severe levels of anxiety had decreased to an average of 1.38 (*SD* = 2.28) for those in the high moderate improving fatigue class. Fatigue and anxiety are reported

to co-occur in women with breast cancer (Bender et al., 2005; Byar et al., 2006; Dragomir & Fodoreanu, 2013; Prigozin et al., 2010). It is unknown whether individuals who were experiencing anxiety in cycle 2 sought and received treatment and thus manifested reduced anxiety during subsequent cycles or if anxiety declines as treatment progresses and the associated stress and uncertainty diminish as the nervousness surrounding unknown expectations decreases. Previous reports suggest that anxiety is persistent during treatment with chemotherapy in women with breast cancer, but may be highest before the first chemotherapy infusion (Bistrup et al., 2015; Lim, Devi, & Ang, 2011). Future research may investigate whether anxiety diminishes, even slightly, over time through each cycle of chemotherapy or whether the difference in anxiety between cycles 2 and 3 was unique to our sample.

We were surprised to observe that pain was statistically significantly more severe for those in the low moderate improving to mild fatigue class, as compared to those in the high moderate improving or mild improving fatigue classes. It is unknown why this was found in our sample, although pain and fatigue are reported to co-occur in women with breast cancer (Bender et al., 2005; Gaston-Johansson et al., 1999; Jacobsen et al., 1999; Kim et al., 2005; Nieboer et al., 2005).

Trouble thinking was significantly related to fatigue and disturbed sleep class during cycle 3 only. This is consistent with others' findings that cognitive function is related to fatigue and disturbed sleep during treatment with chemotherapy. The lack of association among these symptoms during cycle 2 may relate to the smaller, subsample of data used in this analysis, as not all women in our sample reported on severity of trouble thinking (Bender et al., 2005; Jacobsen et al., 1999; Kim et al., 2008; Merriman et al.,

2015).

Increases in overall symptom severity during cycle 2 predicted a higher severity class for fatigue and disturbed sleep during cycle 3. Several studies have reported on the consistency of individual symptoms and symptom clusters over multiple cycles of chemotherapy (Jacobsen et al., 1999; Liu et al., 2009; Payne et al., 2006; Savard et al., 2009; Tchen et al., 2003). The findings of this study indicate that women who experience significant symptom severity during cycle 2 may be at risk for increased severity of fatigue and disturbed sleep during cycle 3.

There were some limitations to this study. Because this was a secondary analysis of existing data, a number of variables were not fully explored, including co-morbidities or significant medical history, symptom management strategies, and fatigue-associated factors, such as nutritional status, cachexia, and daily activity or exercise. Additionally, reports of disturbed sleep were based on subjective report, without objective measures for study. Finally, the sample was fairly homogenous in demographic variables, including marital status and ethnicity. Findings may not generalize to other populations of women receiving initial chemotherapy treatment for breast cancer.

Caution should be used in interpreting our results with regards to the model identified class and extracted predicted class memberships. Given the use of daily symptom severity reporting to define our symptom trajectory classes, it is likely there is more variability around the parameter means than what is described in the models. Predicted class memberships are based on probabilities, and while treated as observed variables in the reported analyses, are truly unobserved variables.

The use of a single-item measure for symptom severity has certain limitations,

including the risk for increased measurement error when compared to measures using multiple items. Single-items measures are practical and useful in the clinical setting and have reported good reliability and validity (Cleeland & Mendoza, 2011; Mooney et al., 2014).

Conclusions

While few demographic or clinical factors were associated with fatigue and disturbed sleep trajectory classes, the presence of other symptoms at moderate to severe levels was associated with membership in higher fatigue and disturbed sleep classes. There was a trend towards an association between membership in the high moderate improving fatigue class and more hours spent lying down and more days of missed work. Overall symptom severity in cycle 2 may predict both fatigue and disturbed sleep class membership in cycle 3. Clinicians need to be aware that women who present with significant symptoms during an early cycle of chemotherapy are at risk for continued severity of fatigue and disturbed sleep in subsequent cycles. Interventions aimed at reducing symptoms may have an impact on activity level and ability to continue employment, as well as reduction of symptoms during future cycles of chemotherapy and into survivorship. Further study is needed to determine whether higher severity of fatigue and disturbed sleep can predict poorer outcomes related inactivity and loss of employment. Additionally, future studies might explore the long-term relationship between overall symptom severity during earlier cycles of chemotherapy and class membership during later cycles of chemotherapy. Finally, well-designed longitudinal studies are needed to determine if there are genetic or molecular markers that may be associated with fatigue or disturbed sleep class membership.

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CHAPTER 4

ANTECEDENTS, CO-OCCURING SYMPTOMS, AND OUTCOMES OF DISTINCT TRAJECTORIES OF THE SYMPTOMS OF MOOD DISTURBANCE IN WOMEN WITH BREAST CANCER

Prepared to reformat for submission to *Psycho-Oncology*

Abstract

The purpose of this study was to examine if membership in differing trajectory classes for depressed mood and anxiety during chemotherapy for breast cancer is determined by demographic, clinical, or symptom characteristics.

A secondary analysis was utilized to explore data collected from 166 women who self-reported on the severity of 10 symptoms through daily phone calls to an automated system while undergoing chemotherapy for breast cancer. Tests of mean differences were used to distinguish between classes with previously identified distinct trajectories of depressed mood and anxiety on demographic, clinical, and symptom variables.

Participants in this study had a mean age of 52.91 years, were mostly Caucasian (91.46%), and the largest proportion of the sample was diagnosed with Stage II disease (40.36%). During cycle 3, for both depressed mood (cycle 3: $\chi^2 = 7.21$, $p < .01$), and anxiety (cycle 3: $\chi^2 = 4.53$, $p = .04$), women who received Doxorubicin were more likely to be in the higher severity classes. Additionally, for anxiety during cycle 3, women with no college experience were more likely to be in the moderate class ($\chi^2 = 9.70$, $p = .03$). Membership in the moderate severity class for anxiety was associated with increased hours spent lying down during cycle 2 ($t(162) = -2.21$, $p = .03$). Membership in the moderate severity anxiety class was associated with fatigue (cycle 2: $t(162) = 18.99$, $p < .001$; cycle 3: $t(153) = 18.14$, $p < .001$), disturbed sleep (cycle 3: $t(153) = 14.39$, $p < .001$), and depressed mood (cycle 2: Welch $t(8.27) = 18.46$, $p < .01$; cycle 3: Welch $t(12.14) = 16.76$, $p < .01$). Membership in the moderate severity depressed mood class was associated with fatigue (cycle 2: $t(162) = 9.02$, $p < .01$), disturbed sleep (cycle 3: $t(153) = 6.31$, $p = .01$), anxiety (cycle 2: Welch $t(24.3) = 11.76$, $p < .01$; cycle 3: Welch

$t(8.1) = 8.95$, $p = .02$), and nausea and vomiting (cycle 2: Welch $t(26.9) = 2.68$, $p < .01$; cycle 3: $t(153) = 4.23$, $p = .04$). The summative number of days with moderate to severe total symptoms during cycle 2 was associated with a higher severity class membership during cycle 3 for both depressed mood ($t(153) = 16.40$, $p < .001$) and anxiety ($t(153) = 21.85$, $p < .001$).

Clinicians should be aware that chemotherapy regimen and the presence of other symptoms is associated with depressed mood and anxiety during chemotherapy for breast cancer. Additionally, higher severity of psychological symptoms during early cycles may continue during subsequent cycles and warrant early intervention to decrease psychological distress.

Background

There is an abundance of literature supporting a high prevalence of disturbing symptoms during chemotherapy in women with breast cancer. Among these highly prevalent symptoms are depression (24-54%) (Bower et al., 2011; Gaston-Johansson, Fall-Dickson, Bakow, & Kennedy, 1999; Kim, Barsevick, Tulman, & McDermott, 2008; Liu et al., 2009; So et al., 2009) and anxiety (6-74%) (Bender, Ergun, Rosenzweigh, Cohen, & Sereika, 2005; Browall, Persson, Ahlberg, Karlsson, & Danielson, 2009; So et al., 2009). Depression and anxiety are more common in oncology patients than in the general population and are often assessed together and referred to as psychological distress (Gold et al., 2016). Mood disturbance may be related to anxiety, diagnostic testing, worries about disease progression, concern about an inability to perform usual functions, and concerns about the future (Gaston-Johansson et al., 1999). Chemotherapy may reduce a patient's ability to function both physically and cognitively and increase

morbidity, leading to increased psychological distress (Gaston-Johansson et al., 1999). Additionally, increases in mood disturbance may be associated with shorter recurrence-free periods and overall survival in survivors of breast cancer (Groenvold et al., 2007). Worth noting is evidence that mood disturbance in oncology patients may result in treatment non-adherence, increased time in the hospital, impairment in quality of life, poor prognosis, and increased mortality (Gold et al., 2016; Jones et al., 2015; Mitchell et al., 2011).

Mood disturbance has been associated with previous treatment for mood disturbance, lack of an intimate confiding relationship, younger age, and stressful non-cancer life experiences (Burgess et al., 2005; Dunn et al., 2011; Gold et al., 2016). Depressed mood and anxiety in women with breast cancer are often associated with the presence of other symptoms in symptom clusters, such as fatigue, cognitive impairment, pain, sleep disturbance, and hot flashes (Berger & Higginbotham, 2000; Berger, Wielgus, Hertzog, Fischer, & Farr, 2010; Bower et al., 2011; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Gaston-Johansson, Fall-Dickson, Bakow, & Kennedy, 1999; Jacobsen et al., 1999; Kim, Barsevick, Tulman, & McDermott, 2008; Liu et al., 2009; So et al., 2009; Tchen et al., 2003). These symptom cluster studies often involve a cross-sectional design and include symptoms in a cluster based on prevalence, as opposed to severity or distress, using mostly variable-oriented analysis methods.

More recently, seven reported studies have included a subgroup analysis of classes of women with breast cancer experiencing similar trajectories of mood disturbance and potential correlates of class membership (Bistrup et al., 2015; DeShields, Tibbs, Fan, & Taylor, 2006; Dunn et al., 2011; Helgeson, Snyder, & Seltman, 2004;

Henselmans et al., 2010; Lam et al., 2012; Lam, Shing, Bonanno, Mancini, & Fielding, 2014; Wang, Chang, Chen, Chen, & Hsu, 2014). These reports have identified 3-5 classes with distinct trajectories of mood disturbance across various time-points in the breast cancer treatment spectrum. Potential correlates of class membership included quality of life and state/trait anxiety measures, younger age, type of surgery, employment, education, and social support (Bistrup et al., 2015; DeShields et al., 2006; Dunn et al., 2011; Helgeson et al., 2004; Henselmans et al., 2010; Lam et al., 2012; Lam et al., 2014; Wang et al., 2014). Importantly, while longitudinal in design, each of studies evaluated symptoms of psychological distress and correlates at specific time-points, ranging from 3-7 times over 6-55 months, but did not examine the patterns that begin during chemotherapy treatment.

Given the significant burden of treatment-associated symptoms, and their association with inferior long-term outcomes relative to adherence, functional status, employment and mortality, identification of those at risk for moderate to severe levels of mood disturbance during chemotherapy treatment for breast cancer is important (Gold et al., 2016; Jones et al., 2015; Mitchell et al., 2011). Using Latent Growth Mixture Modeling (LGMM), we previously observed two distinct patterns of depressed mood; the majority (91% of respondents in cycle 2 and 94% in cycle 3) with a minimal level of depressed mood and a small class with a moderate level of depressed mood (9% of respondents in cycle 2 and 6% in cycle 3). Two latent trajectories of anxiety were also revealed using a LGMM model, including a minimal anxiety class (95% of respondents in cycle 2 and 92% in cycle 3) and a moderate anxiety class (5% of respondents in cycle 2 and 8% in cycle 3). The purpose of this analysis was to determine if antecedents, co-

occurring symptoms, and outcomes are associated with class membership for the mood disturbance responses of depressed mood and anxiety.

Methods

Participants and Setting

Data from 3 longitudinal studies that utilized the automated telephone-linked-care system for data collection were used in this secondary analysis. Participants were recruited from 6 settings, including clinics in the southeast, western, and midwestern United States. Studies 1 and 2 were both randomized clinical trials and Study 3 involved no intervention or study group assignment. While in both Study 1 and Study 2, participants were assigned to a usual care and a symptom management intervention group, only those in Study 2 were found to have differences in reported symptoms between the groups. All data from eligible participants in Study 1 and Study 3 and those in the usual care group in Study 2 were included in this secondary analysis. Across all 3 parent studies, data were available for cycle 2 and cycle 3. Eligibility requirements for this secondary analysis included being a woman diagnosed with breast cancer beginning initial treatment with chemotherapy and completed study measures through cycle 2 and cycle 3.

A cohort of 259 women with a breast cancer diagnosis and receiving initial treatment with chemotherapy were pooled from the three parent studies. Of these, 80 women who were randomized to the intervention group for Study 2 along with 13 women who did not complete study measures through cycles 2 and 3 were excluded. A total sample of 166 women completed study measures through cycles 2 (n=165) and 3 (n=155) on at least 3 days were included in this secondary analysis.

Measures

All 3 parent studies utilized similar instrumentation. Demographic and disease-related data were collected at baseline and included age, gender, race/ethnicity, employment status, education, extent of disease and details of the chemotherapy protocol. Single-item indicators were used to assess each symptom. Conditional branching was used, where participants were asked, "During the past 24 hours did you experience (symptoms)?" A no response was scored as zero and a yes response elicited further questioning using a 1 to 10 Likert scale for the severity of that particular symptom. The investigator-developed instrument is further described by Mooney, Beck, Friedman, Farzanfar, and Wong (2014). Symptoms assessed included fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea/vomiting, sore mouth, and diarrhea across all three parent studies. Two additional symptoms, distress associated with changing appearance and trouble thinking, were assessed in Studies 2 and 3. A subsample was used in analyses that included those 2 symptoms, consisting of participants enrolled in those 2 parent studies only.

Daily hours spent lying down and whether or not employed participants were able to attend work were collected. To account for varying cycle lengths, only data from the first 14 days of each cycle were included in the analyses.

Study Procedures

This study was reviewed by Institutional Review Board (IRB) at the University of Utah. All participants signed a written, informed consent upon enrollment in the parent studies.

Statistical Analysis

The Software Statistical Package for the Social Sciences (SPSS), version 23.0 was used for data management and data analysis. P values less than .05 were considered statistically significant and because this was a hypothesis-generating study, there was no adjustment for multiplicity.

Descriptive statistics and frequency distributions were generated on the sample characteristics. Using the models previously described for depressed mood and anxiety in both cycles, the model predicted class membership was obtained for each individual on each symptom during each cycle using posterior probabilities. While there is uncertainty in predicted class membership, the entropy and posterior probabilities as previously reported for our models suggest a strong model fit and predicted class membership was treated as an observed variable for the purposes of this analysis (Jung & Wickerama, 2008). Class membership assignment was then used to test for mean differences and associations among the categories across the classes on antecedents, co-occurring symptoms, and outcomes. Fisher's exact chi-square was used to account for small cell sizes, a conservative test that allows for tests of associations among categories when cell sizes had an expected frequency of five or less. In cases where classes did not display homogeneity of variance, the Welch statistic, a robust test that allows violation of this assumption, was used. The analysis proceeded to answer four specific aims.

Aim 1 was to determine whether differing symptom trajectory profiles for depressed mood and anxiety are associated with variations in demographic and clinical characteristics. After establishing the classes for the severity of each individual symptom in each cycle, age, stage of disease, education, employment, marital status, and

chemotherapy regimen were compared to class membership across the classes for depressed mood and anxiety for each cycle using chi-square (stage of disease, education, employment, marital status, and chemotherapy regimen) and independent-samples *t* tests (age). Because of the large diversity of chemotherapy regimens and the sample size, it was not statistically possible to interpret comparison between the individual regimens. Instead, tests were conducted on two agents of interest, whether or not women received Doxorubicin as part of their regimen and whether or not women received a Taxane as part of their regimen.

Aim 2 was to determine whether differing symptom trajectory profiles for depressed mood and anxiety are associated with variations in outcome measures, such as average hours spent lying down and days of missed work. Daily measures of hours spent lying down were averaged for each individual for each cycle 2 and 3. Days of missed work were summed for all employed participants for each cycle 2 and 3. To answer this aim, tests of mean differences across the classes were conducted on the outcome variables using independent-samples *t* tests. Only those participants who were employed were included in the test of mean differences across the classes for days of missed work.

Aim 3 was to determine whether differing symptom trajectory profiles for depressed mood and anxiety are associated with variations in the severity of other symptoms, such as fatigue, disturbed sleep, pain, nausea and vomiting, and trouble thinking. These symptoms were studied because they were both prevalent in the sample and previously reported to relate with depressed mood and/or anxiety. Tests of mean differences across classes on the number of moderate to severe days reported for each symptom of interest were conducted using independent-samples *t* tests. Summative

scores for each symptom included the number of days subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea, and trouble thinking within the first 14 days of each cycle. These summative scores were then compared to class membership for depressed mood and anxiety in cycles 2 and 3 using independent-samples *t* tests.

Aim 4 is to determine whether differing symptom trajectory profiles for depressed mood and anxiety during cycle 3 are associated with variations in the overall symptom severity during cycle 2. Overall symptom severity for cycle 2 included the number of days where subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting. These symptoms were studied because they were both prevalent in the sample, with data from all participants, and previously reported to relate with depressed mood and/or anxiety. The total number of moderate to severe days was then compared to the extracted class membership for depressed mood and anxiety in cycle 3 using independent-samples *t* tests.

Results

A total of 166 women with breast cancer participated in the study. Subject demographic and clinical characteristics are summarized in Table 4.1. Women ranged in age from 24 to 80 years (mean age = 52.91, *SD* = 10.8). Most women were White (91.46%), married (75%), and not currently working (62.8%). The majority of the sample had some education beyond high school (75.3%) and 40.36% of women in the sample were diagnosed with Stage II breast cancer. Participants received over 12 different regimens of chemotherapy during the study period. The prevalence of symptoms within the sample across both cycles is presented in Table 4.2. Fatigue was

Table 4.1 Sample Demographic and Clinical Characteristics (*n* =166)

Characteristic	**Mean**	***SD***
Age (in years)	52.90	10.8
Characteristic	***n***	**%**
Ethnicity		
Non-Hispanic	162	97.6%
Hispanic	2	1.2%
Unknown	2	1.2%
Marital Status		
Partnered	123	74.1%
NonPartnered	41	24.7%
Unknown	2	1.2%
Employment		
Full-time	48	29.2%
Part-time	13	7.8%
Not Employed	103	62.0%
Unknown	2	1.0%
Education Status		
High school	3	22.3%
Some College	52	31.3%
Associate Degree	15	9.0%
Bachelor Degree	36	21.7%
Postgraduate	22	13.2%
Unknown	4	2.5%
Income		
Less than $9,999	8	4.8%
$10,000-29,999	16	9.6%
$30,000-49,000	37	22.3%
$50,000-69,000	20	12.1%
$70,000 or More	57	34.3%
Unknown	10	6.1%
Declined to State	18	10.8%
Stage of Disease		
Stage I	20	12.1%
Stage II	67	40.3%
Stage III	38	22.9%
Stage IV	36	21.7%
Unknown	5	3.0%
Chemotherapy Regimen		
Cyclophosphamide with Doxorubicin	68	41.0%
Docetaxel	23	13.9%
Cyclophosphamide with Methotrexate and 5-FU	16	9.6%
Docetaxel with Carboplatin	13	7.8%
Cyclophosphamide with Docetaxel	12	7.2%
Cyclophosphamide with Doxorubicin and Docetaxel	9	5.4%
Cyclophosphamide with Doxorubicin and 5-FU	6	3.6%
Cyclophosphamide with 5-FU	4	2.4%
Other	15	9.1%

Table 4.2 Symptom Prevalence and Mean Number of Days at Moderate to Severe Levels

Symptom	Cycle	No. (%) of Women Reported Symptom Severity Greater than 0 at Least Once	Mean no. Days (*SD*), Range of Symptom Reported with Severity Greater than 0	No. (%) of Women Reported Symptom Severity Greater than 3 at Least Once	Mean no. Days (*SD*), Range of Symptom Reported with Severity Greater than 3	No. Days (%) Symptom Reported Level 0	No. Days (%) Symptom Reported Level 1-10	No. Days (%) Symptom Reported Level 4-10
Physical Symptoms								
Fatigue [a]	2	153 (92.7%)	7.53 (3.69), 1-14	115 (69.7%)	5.09 (3.47), 1-14	659 (36.4%)	1152 (63.6%)	585 (32.3%)
	3	148 (94.9%)	7.09 (3.93), 1-14	105 (67.3%)	4.95 (3.70), 1-14	654 (38.4%)	1050 (61.6%)	520 (30.5%)
Disturbed Sleep [a]	2	126 (76.4%)	3.63 (2.56), 1-13	103 (62.4%)	2.87 (2.07), 1-13	1354 (74.8%)	457 (25.2%)	296 (16.3%)
	3	110 (70.5%)	3.40 (2.64), 1-13	85 (54.5%)	2.46 (1.76), 1-11	1330 (78.1%)	374 (21.9%)	209 (12.3%)
Pain [a]	2	124 (75.2%)	4.55 (3.20), 1-14	75 (45.5%)	3.51 (2.95), 1-13	1247 (68.9%)	564 (31.1%)	263 (14.5%)
	3	104 (66.7%)	5.16 (3.74), 1-14	66 (42.3%)	4.15 (3.33), 1-14	1167 (68.5%)	537 (31.5%)	274 (16.1%)
Nausea and Vomiting [a]	2	116 (70.3%)	3.90 (2.92), 1-13	78 (47.3%)	2.66 (2.28), 1-11	1359 (75.0%)	542 (29.9%)	208 (11.5%)
	3	111 (71.2%)	4.05 (3.31), 1-14	63 (40.4%)	3.14 (2.63), 1-12	1254 (73.6%)	450 (26.4%)	198 (11.6%)
Diarrhea [a]	2	69 (41.8%)	2.13 (1.53), 1-8	30 (18.2%)	1.83 (0.87), 1-4	1664 (91.9%)	147 (8.1%)	55 (3.0%)
	3	49 (31.4%)	2.63 (1.82), 1-10	23 (14.7%)	2.17 (1.53), 1-6	1575 (92.4%)	129 (7.6%)	49 (2.9%)
Sore Mouth [a]	2	68 (41.2%)	3.62 (2.34), 1-11	38 (23.0%)	3.11 (2.29), 1-10	1565 (86.4%)	246 (13.6%)	118 (6.5%)
	3	68 (43.6%)	3.32 (2.61), 1-13	38 (24.4%)	2.66 (2.72), 1-13	1478 (86.7%)	216 (12.7%)	91 (5.3%)
Trouble Thinking [b]	2	46 (27.9%)	2.67 (1.97), 1-11	28 (17.0%)	2.50 (2.19), 1-10	884 (93.2%)	64 (6.8%)	37 (3.9%)
	3	31 (19.9%)	3.26 (2.11), 1-9	21 (13.5%)	1.95 (1.07), 1-5	776 (94.1%)	46 (5.6%)	20 (2.4%)
Appearance [b]	2	38 (23.0%)	3.32 (2.57), 1-12	25 (15.2%)	3.16 (2.37), 1-9	882 (93.0%)	66 (7.0%)	42 (4.4%)
	3	15 (9.6%)	3.27 (3.97), 1-13	10 (6.4%)	3.50 (4.50), 1-12	801 (97.1%)	24 (2.9%)	17 (2.1%)
Mood Disturbance Symptoms								
Depressed Mood [a]	2	99 (60.0%)	3.60 (3.21), 1-13	70 (42.4%)	3.23 (2.84), 1-12	1455 (80.3%)	356 (19.7%)	226 (12.5%)
	3	83 (53.2%)	3.47 (3.11), 1-14	55 (35.3%)	2.87 (2.86), 1-13	1416 (83.1%)	288 (16.9%)	158 (9.3%)
Anxiety [a]	2	77 (46.7%)	3.34 (3.17), 1-13	47 (28.5%)	2.91 (2.83), 1-11	1544 (85.3%)	267 (14.7%)	147 (8.2%)
	3	62 (39.7%)	3.56 (3.62), 1-13	40 (25.6%)	2.65 (2.56), 1-9	1483 (87.0%)	221 (13.0%)	106 (6.2%)

[a] *n*=165, cycle 2; *n*=156, cycle 3; 1811(78.4%) days reported cycle 2, 1704(78.0%) days reported cycle 3; 499(21.6%) days missing cycle 2, 480(22.0%) days missing cycle 3
[b] *n*=84, cycle 2; *n*=75, cycle 3; 948 (80.6%) days reported cycle 2, 825 (79.6%) days reported cycle 3; 228 (19.4%) days missing cycle 2, 211 (20.4%) days missing cycle

the most prevalent symptom, followed by disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting.

Aim 1

Results of the tests of mean differences and associations among categories across classes on the demographic variables are presented in Table 4.3 for the depressed mood classes and Table 4.4 for the anxiety classes. Only the comparison of education to class membership for anxiety during cycle 3 and the comparison of whether or not women received Doxorubicin were related to class membership for both depressed mood and anxiety during cycle 3. In this cycle only, high school graduates were more likely to be in the moderate anxiety class and those with an undergraduate degree were more likely to be in minimal anxiety class. Also, those in the moderate severity class for both symptoms were more likely to have received Doxorubicin. All respondents in the moderate severity class for depressed mood during cycle 3 received Doxorubicin and 83.3% of respondents in the moderate class for anxiety during cycle 3 received Doxorubicin.

Aim 2

For both symptoms, the *t* tests for both hours spent lying down and days of missed work were nonsignificant (see Tables 4.3 and 4.4), with the exception of hours spent lying down and anxiety class membership during cycle 2. Women in the moderate anxiety class reported statistically significantly higher average daily hours spent lying down when compared to women in the minimal anxiety class during cycle 2 ($p = .03$*).

Table 4.3 Tests of Mean Differences and Associations Among Categories for Antecedents and Outcomes of Depressed Mood Class Membership

Characteristic		Consistently Mild	Consistently Low Moderate	Omnibus Test
Cycle 2				
Age (in years)		52.29 (11.01)	50.66 (8.95)	$t(159) = 1.23$, $p = .27$
Education				
	Less than high school	6 (4.4%)	0 (0.0%)	
	High school	25 (18.4%)	5 (20.8%)	$\chi^2 = 0.88$, $p = .98$
	Undergraduate/Technical School	88 (64.7%)	16 (66.7%)	
	Postgraduate	17 (12.5%)	3 (12.5%)	
Marital Status				
	Married	105 (76.1%)	16 (66.7%)	$\chi^2 = 1.27$, $p = .50$
	Not Married	33 (23.9%)	8 (33.3%)	
Employment				
	Employed	54 (39.1%)	6 (25.0%)	$\chi^2 = 1.88$, $p = .46$
	Not Employed	84 (60.9%)	18 (75.0%)	
Stage				
	I	15 (11.0%)	5 (20.8%)	$\chi^2 = 2.43$, $p = .64$
	II	58 (42.6%)	9 (37.5%)	
	III	31 (22.8%)	6 (25.0%)	
	IV	32 (23.5%)	4 (16.7%)	
Doxorubicin				
	Yes	63(47.7%)	7(35.0%)	$\chi^2 = 1.13$, $p = .34$
	No	69(52.3%)	13(65.0%)	
Taxane				
	Yes	43(32.6%)	8(40.0%)	$\chi^2 = .43$, $p = .61$
	No	89(67.4%)	12(60.0%)	
Hours Spent Lying Down		10.57 (2.63)	10.33 (3.82)	$t(27) = 0.30$, $p = .77$
Days Missed Work (n=20)		2.28 (1.81)	4.0 (0.00)	$t(18) = 1.73$, $p = .21$

Table 4.3 continued

Characteristic		Consistently Mild	Consistently Low Moderate	Omnibus Test
Cycle 3				
Age (years)		52.73 (10.97)	53.56 (10.73)	$t(150) = 0.05$, $p = .82$
Education				
	Less than high school	5 (3.5%)	0 (0.0%)	
	High School	24 (16.9%)	3 (33.3%)	$\chi^2 = 2.01$, $p = .68$
	Undergraduate/Technical School	94 (66.2%)	5 (55.6%)	
	Postgraduate	19 (13.4%)	1 (11.1%)	
Marital Status				
	Married	109 (75.7%)	5 (55.6%)	$\chi^2 = 2.55$, $p = .32$
	Not Married	35 (24.3%)	4 (44.4%)	
Employment				
	Employed	57 (39.6%)	3 (33.3%)	$\chi^2 = 0.78$, $p = 1.00$
	Not Employed	87 (60.4%)	6 (66.7%)	
Stage				
	I	19 (13.3%)	0 (0.0%)	$\chi^2 = 1.58$, $p = 0.84$
	II	60 (42.0%)	5 (55.6%)	
	III	33 (23.2%)	2 (22.2%)	
	IV	31 (21.8%)	2 (22.2%)	
Doxorubicin				
	Yes	74(51.4%)	8(100.0%)	$\chi^2 = 7.21$, $p < .01$*
	No	70(48.6%)	0(0.0%)	
Taxane				
	Yes	50 (34.7%)	1(12.5%)	$\chi^2 = 1.68$, $p = .27$
	No	94 (65.3%)	7(87.5%)	
Hours Spent Lying Down		10.59 (2.72)	10.24 (4.15)	$t(150) = 0.36$, $p = .72$
Days Missed Work (n=27)		1.56(1.71)	1.00(0.00)	$t(25) = 0.21$, $p = .65$

Table 4.4 Tests of Mean Differences and Associations Among Categories for Antecedents and Outcomes of Anxiety Class Membership

Characteristic		Consistently Mild	Consistently Moderate	Omnibus Test
Cycle 2				
Age (in years)		52.53 (10.72)	59.13 (9.76)	$t(159) = 3.25$, $p = .07$
Education				
	Less than high school	5 (3.3%)	1 (11.1%)	
	High school	26 (17.2%)	4 (44.4%)	$\chi^2 = 6.45$, $p = .13$
	Undergraduate/Technical School	99 (65.6%)	4 (44.4%)	
	Postgraduate	21 (13.9%)	0 (0.0%)	
Marital Status				
	Married	114 (74.5%)	7 (77.8%)	$\chi^2 = 0.73$, $p = 1.00$
	Not Married	39 (25.5%)	2 (22.2%)	
Employment				
	Employed	60 (39.2%)	0 (0.0%)	$\chi^2 = 6.76$, $p = .05$
	Not Employed	93 (60.8%)	9 (100.0%)	
Stage				
	I	20 (13.2%)	0 (0.0%)	$\chi^2 = 4.21$, $p = .36$
	II	65 (43.0%)	2 (14.3%)	
	III	33 (21.9%)	3 (21.4%)	
	IV	33 (21.9%)	9 (64.3%)	
Doxorubicin				
	Yes	76 (52.8%)	6 (75.0%)	$X^2 = 1.51$, $p = .29$
	No	68 (47.2%)	2 (25.0%)	
Taxane				
	Yes	49 (34.0%)	2 (25.0%)	$\chi^2 = 0.28$, $p = .72$
	No	95 (66.0%)	6 (75.0%)	
Hours Spent Lying Down		10.41 (2.77)	12.53 (3.03)	$t(162) = -2.21$, $p = .03$*
Days Missed Work (n=20)		2.45 (1.79)	0 (0.00)	

Table 4.4 continued

Characteristic		Consistently Mild	Low Moderate to Mild	Omnibus Test
Cycle 3				
Age (years)		52.69 (10.90)	53.87 (8.73)	$t(150) = .13$, $p = .72$
Education				$\chi^2 = 9.70$, $p = .03$*
	Less than high school	4 (2.9%)	1 (7.7%)	
	High school	22 (15.8%)	5 (38.5%)	
	Undergraduate/Technical School	95 (68.3%)	5 (38.5%)	
	Postgraduate	18 (12.9%)	2 (15.4%)	
Marital Status				$\chi^2 = 3.52$, $p = .24$
	Married	107 (76.4%)	7 (53.8%)	
	Not Married	33 (23.6%)	6 (46.2%)	
Employment				$\chi^2 = 3.90$, $p = .15$
	Employed	56 (39.7%)	4 (33.3%)	
	Not Employed	85 (60.3%)	8 (66.7%)	
Stage				$\chi^2 = 2.85$, $p = .58$
	I	19 (13.7%)	0 (0.0%)	
	II	60 (43.2%)	5 (38.5%)	
	III	31 (22.3%)	4 (30.8%)	
	IV	29 (20.9%)	4 (30.8%)	
Doxorubicin				$\chi^2 = 4.53$, $p = .04$*
	Yes	72 (51.4%)	10 (83.3%)	
	No	68 (48.6%)	2 (16.7%)	
Taxane				$\chi^2 = 1.67$, $p = .23$
	Yes	49(35.0%)	2(16.7%)	
	No	91(65.0%)	10(83.3%)	
Hours Spent Lying Down		10.44 (2.75)	11.87(3.20)	$t(150) = -1.77$, $p = .08$
Days Missed Work (n=27)		1.46(1.67)	2.00(1.73)	$t(25) = 0.28$ $p = .60$

Aim 3

Results of the independent samples *t* tests comparing class membership with the number of moderate to severe days of individual symptom are presented in Tables 4.5 and 4.6. Women in the moderate depressed mood class reported a statistically significantly greater number of days with moderate to severe fatigue ($p < .01$*), anxiety ($p < .01$*), and nausea and vomiting ($p = .04$*) during cycle 2 and disturbed sleep ($p = .01$*), anxiety ($p = .02$*), and nausea and vomiting ($p = .04$*) during cycle 3 when compared to women in the minimal depressed mood class. Pain and trouble thinking were not related to depressed mood class membership. Women in the moderate anxiety class reported statistically significantly greater number of days with moderate to severe fatigue ($p < 001$*) and depressed mood ($p < .01$*) during cycle 2 and fatigue ($p < 001$*), disturbed sleep ($p < .01$*), and depressed mood ($p < .01$*) during cycle 3 when compared to women in the low anxiety class. Pain, nausea and vomiting, and trouble thinking were not associated with anxiety class membership.

Aim 4

For both depressed mood ($F(1,153) = 16.404$, $p < 001$*) and anxiety ($F(1, 153) = 21.849$, $p < 001$*), the overall symptom severity in cycle 2, the total number of days where subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting was associated with class membership in cycle 3. For depressed mood, means for the minimal (10.12, $SD = 9.47$) and moderate (23.22, $SD = 8.61$) classes suggest that those in the moderate class for depressed mood during cycle 2 reported statistically higher overall symptom severity in cycle 2 when compared to the minimal class. Similarly, means for the minimal (9.82, $SD = 9.24$) and moderate (22.38,

Table 4.5 Tests of Mean Differences for Co-occurring Symptoms With Depressed Mood Class Membership

Depressed Mood Class	Mean Days	*SD*	Omnibus Test
Cycle 2			
Fatigue			$t(162) = 9.02, p < .01$*
Consistently Mild	3.21	3.53	
Consistently Low Moderate	5.63	4.20	
Disturbed Sleep			$t(162) = 0.99, p = .32$
Consistently Mild	1.74	2.15	
Consistently Low Moderate	2.21	2.17	
Anxiety			Welch $t(24.3) = 11.76, p < .01$*
Consistently Mild	0.49	1.38	
Consistently Low Moderate	2.92	3.43	
Pain			$t(162) = 0.50, p = .48$
Consistently Mild	1.66	2.75	
Consistently Low Moderate	1.25	1.96	
Nausea and Vomiting			Welch $t(26.9) = 2.68, p < .01$*
Consistently Mild	1.13	1.90	
Consistently Low Moderate	2.08	2.75	
Trouble Thinking			$t(80) = 0.49, p = .49$
Consistently Mild	0.82	1.73	
Consistently Low Moderate	1.33	1.97	
Cycle 3			
Fatigue			Welch $t(8.5) = 8.49, p = .06$
Consistently Mild	3.13	3.63	
Consistently Low Moderate	2.20	5.20	
Disturbed Sleep			$t(153) = 6.31, p = .01$*
Consistently Mild	1.26	1.79	
Consistently Low Moderate	2.78	1.20	
Anxiety			Welch $t(8.1) = 8.95, p = .02$*
Consistently Mild	0.46	1.22	
Consistently Low Moderate	4.33	3.87	
Pain			$t(153) = 0.05, p = .83$
Consistently Mild	1.78	2.98	
Consistently Low Moderate	1.56	3.25	
Nausea and Vomiting			$t(153) = 4.23, p = .04$*
Consistently Mild	1.18	2.23	
Consistently Low Moderate	2.78	2.64	
Trouble Thinking			
Consistently Mild	0.53	1.03	
Consistently Low Moderate	0.00	0.00	
Total Cycle 2 Days Moderate/Severe Symptoms			$t(153) = 16.40, p < .001$*
Consistently Mild	10.12	9.46	
Consistently Low Moderate	23.22	8.61	

Table 4.6 Tests of Mean Differences for Co-occurring Symptoms With Anxiety Class Membership

Anxiety Class	Mean Days	*SD*	Omnibus Test
Cycle 2			
Fatigue			$t(162) = 18.99, p < .001$*
Consistently Mild	3.28	3.54	
Consistently Moderate	8.56	3.36	
Disturbed Sleep			$t(162) = 0.19, p = .66$
Consistently Mild	1.79	2.15	
Consistently Moderate	2.11	2.26	
Depressed Mood			Welch $t(8.27) = 18.46, p < .01$*
Consistently Mild	1.08	2.01	
Consistently Moderate	6.44	3.71	
Pain			$t(162) = 0.32, p = .57$
Consistently Mild	1.63	2.69	
Consistently Moderate	1.11	2.03	
Nausea and Vomiting			$t(162) = 1.20, p = .28$
Consistently Mild	1.23	2.03	
Consistently Moderate	2.00	2.60	
Trouble Thinking			
Consistently Mild	.86	1.75	
Consistently Moderate	.00	.00	
Cycle 3			
Fatigue			$t(153) = 18.14, p < .001$*
Consistently Mild	2.98	3.62	
Low Moderate to Mild	7.46	3.82	
Disturbed Sleep			$t(153) = 14.39, p < .001$*
Consistently Mild	1.19	1.71	
Low Moderate to Mild	3.08	1.80	
Depressed Mood			Welch $t(12.14) = 16.76, p < .01$*
Consistently Mild	.59	1.14	
Low Moderate to Mild	5.69	4.48	
Pain			$t(153) = 0.34, p = .56$
Consistently Mild	1.73	2.91	
Low Moderate to Mild	2.23	3.83	
Nausea and Vomiting			$t(153) = 2.94, p = .09$
Consistently Mild	1.18	2.23	
Low Moderate to Mild	2.31	2.59	
Trouble Thinking			$t(75) = -1.35, p = .18$
Consistently Mild	.51	1.03	
Low Moderate to Mild	1.50	.71	
Total Cycle 2 Days Moderate/Severe Symptoms			$t(153) = 21.85, p < .001$*
Consistently Mild	9.82	9.24	
Low Moderate to Mild	22.38	9.65	

SD = 9.65) classes suggest that those in the moderate class for anxiety during cycle 2 reported statistically higher overall symptom severity in cycle 2 when compared to the minimal class.

Conclusions

Identifying factors that contribute to symptom trajectories allows clinicians to target those at risk for increased symptom experiences during chemotherapy. Various demographic and clinical characteristics were examined as possibly distinguishers of depressed mood and anxiety class membership. None of the demographic or clinical characteristics were found to be associated with depressed mood or anxiety class membership, with the exception of education. During cycle 3, women with no college experience were likely to be in the moderate anxiety class when compared to women with a college degree. This finding, in combination with findings reported by Lam et al. (2010) of an association between education and psychological distress trajectory, suggest that higher education may be protective against anxiety during chemotherapy treatment. While several studies have correlated younger age with higher mood disturbance, a relationship between age and class membership was not found in this sample (DeSheilds et al., 2006; Dunn et al., 2011; Gold et al., 2016; Lam et al., 2010). Importantly, during cycle 3, women in the moderate class for both depressed mood and anxiety were more likely to have received Doxorubicin as part of their chemotherapy regimen than not. One explanation for this may be that women who received Doxorubicin also reported higher levels of fatigue (see previous reports). Given a known relationship between fatigue and mood disturbance (Berger & Farr, 1999; deJong, Kester, Schouten, Abu-Saad, & Courtens, 2006), it would stand to reason that if receipt of Doxorubicin is correlated with

fatigue, it would also correlate with symptoms of mood disturbance.

While stage of disease was not associated with class membership for anxiety in either cycle, examination of the moderate anxiety class for both cycles revealed that all women in this class reported Stage II or greater disease. Worries about disease progression and concerns about the future are reported to relate to mood disturbance, but, in our study, particularly to anxiety, as the moderate depressed mood did not trend with the same relation to stage of disease (Gaston-Johansson et al., 1999). Unfortunately, we were underpowered to test differences among the classes in disease stage. In a larger sample, with a greater class count for the moderate anxiety class, these subtle differences may have been statistically different.

During cycle 2 only, women in the consistently moderate anxiety class reported statistically significant greater average daily hours spent lying down (mean hours = 12.53, *SD* = 3.03) when compared to women in the consistently mild anxiety class (mean hours = 10.41, *SD* = 2.77). No reports were found where differences in activity level or resting hours were compared with severity of anxiety during treatment for breast cancer and it is unknown why this difference among the classes was not found during cycle 3 in our sample.

None of the other demographic or clinical variables were associated with class membership in this sample. There are a couple of possible explanations for this. First, the number of women who experienced a moderate to severe trajectory for depressed mood (9% of respondents in cycle 2 and 6% in cycle 3) and anxiety (5% of respondents in cycle 2 and 8% of respondents in cycle 3) was low. Additionally, more half of the women in the sample did not experience even a single day of either symptom.

Henselmans et al. (2010) also found a large group of women who experienced no mood disturbance during chemotherapy, suggesting that not all women, or even a great percentage of women experience these symptoms. In our sample, in particular, the low class counts for the moderate trajectory classes for depressed mood and anxiety may have decreased the power and ability to detect differences among the classes on these potential correlate variables. Second, class trajectories may be predicted by variables other than demographic and clinical determinants, such as genetic and molecular factors. Cleeland et al. (2003) and Miaskowski et al. (2014) propose that a lack of association between demographic characteristics and symptom presentation may be related to a possible relationship between biologic mechanisms and genetic and epigenetic determinants with symptom experience rather than demographic and clinical determinants. Further study is needed to determine whether these variables may distinguish class membership for symptoms of mood disturbance.

Membership in the moderate latent classes for both depressed mood and anxiety was overwhelmingly related to fatigue. This is not surprising, as fatigue has been associated with symptoms of mood disturbance in both cross-sectional correlation and symptom cluster studies (Bender et al., 2005; Gaston-Johansson, 1999; Kim et al., 2008; Liu et al., 2009; Savard et al., 2009; So et al., 2009; Von Ah, Kang, & Carpenter, 2008). The finding that increases in the severity of disturbed sleep is associated with depressed mood and anxiety during cycle 3 is consistent with reports that sleep difficulty and depression and anxiety are associated and may cluster (Colagiuri et al., 2011; Onselen et al., 2012).

While nausea and vomiting has been associated with anxiety, that relationship

was not found in our sample (Poon et al., 2013). One explanation may be that the relationship between anxiety and nausea reported by Poon et al. (2013), was specific to anticipatory anxiety measured prior to receiving chemotherapy, not a trajectory of anxiety over the course of chemotherapy. While the results of this study are congruent with those reported by Osoba et al. (1997), the data we had do not allow for exploration of specific types of nausea, including anticipatory or delayed nausea. Interestingly, nausea and vomiting was increased for those in the moderate depressed mood class during both cycles. To our knowledge, this finding has not been reported in women with breast cancer, but suggests that mood disturbance may be associated with physical symptoms, such as nausea and vomiting.

In our study, as within other studies, we found a close relationship between the symptoms of mood disturbance. The relationship between both symptoms of mood disturbance is well studied (Colagiuri et al., 2011; Dunn et al., 2011; Gold et al., 2016; Lam et al., 2012). Gold et al. (2016) report on a collective of combined anxiety and depression syndrome (CADS), suggesting that these symptoms often occur together and that elucidating etiology for one symptom may explain the other and developing interventions aimed at managing one, may assist in management of the other.

Increases in overall symptom severity during cycle 2 were associated with membership in the moderate class for both depressed mood and anxiety. This finding is consistent with several studies that have reported on the consistency of individual symptoms and symptom clusters over multiple cycles of chemotherapy (Jacobsen et al., 1999; Liu et al., 2009; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Savard et al., 2009; Tchen et al., 2003). Importantly, clinicians must be aware that women who

experience significant symptom severity during cycle 2 may be at risk for increased severity in the symptoms of mood disturbance during cycle 3. Early intervention may improve long-term symptom experiences during chemotherapy.

A major limitation of this study is a lack of data for several relevant variables of interest, including history of psychological illness or distress and comorbidities. One of the strongest correlates of symptoms of mood disturbance during cancer treatment is a history of psychological illness, poor coping, or distress prior to initiation of treatment (Gold et al., 2016). Because of the nature of our study, data for these variables were unavailable and psychological history could not be controlled for.

Another limitation is the relatively homogenous sample in marital status (74.1% married). It is unknown whether married women receive more support than nonmarried and potentially influenced the degree to which symptoms of mood disturbance were experienced. Of the reviewed literature, only Helgeson et al. (2004) reported on social support as a predictive correlate of trajectories of psychological adjustment. Further study is needed with diverse samples to determine whether marital status and/or social support can explain differences in the trajectories of mood disturbance.

The use of a single-item measure for symptom severity has limitations, including the risk for increased measurement error when compared to measures using multiple items. Single-items measures are useful in the clinical setting for practical purposes and have reported good reliability and validity (Cleeland, Fisch, & Dunn, 2011; Mooney et al., 2014).

Caution should be used in interpreting our results with regards relative to extracted predicted class memberships. Given the use of daily symptom severity

reporting to define our symptom trajectory classes, there may be more variability within the classes around the parameter estimates than what is described in the models. In addition, predicted class memberships are based on probabilities, and while treated as observed variables in these analyses, care should be used to over-extend the interpretation.

Future research should focus on the identification of potential correlates for class membership, including genetic and molecular determinants. Additionally, results of this study should be replicated in larger samples to determine whether these same classes are consistent and if, with larger class counts, correlates and long-term outcomes may be attributed to class membership. Clinicians should have awareness that symptoms of mood disturbance may co-occur and may relate to fatigue, disturbed sleep, and nausea and vomiting. Interventions should be developed to assist women with symptoms of mood disturbance throughout chemotherapy, targeting those women at who report symptoms of mood disturbance early in a cycle of chemotherapy.

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CHAPTER 5

DISCUSSION AND CONCLUSIONS

Introduction

Women with breast cancer undergoing treatment with chemotherapy experience persistent symptoms related to both tumor and treatment (Kim, Barsevick, Tulman, & McDermott, 2008; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Wood, Nail, Gilster, Winters, & Elsea, 2006). The change in the presence and severity of a symptom over time, or the trajectory of the symptom, is dynamic throughout the course of treatment and survival (Payne, 2002). General symptoms, such as fatigue, disturbed sleep, depressed mood, and anxiety, are particularly distressing, as the specific etiology is often unknown, making it difficult for healthcare providers to manage (Kim, McGuire, Tulman, & Barsevick, 2005; National Comprehensive Cancer Network, 2010; Ware, Kosinski, & Keller, 1996). The existence of these symptoms during treatment is also related to inferior outcomes, including decreases in functional status, reduced occupational functioning, treatment nonadherence, increased hospitalization and, during survival, increased recurrence and mortality (Beck et al., 2010; Cleeland et al., 2000; Lee et al., 2004).

Previous studies have identified that the challenges of studying symptoms include difficulty separating tumor burden effects or disease-related symptoms from treatment-related effects, obtaining serial samples in repeated measures or longitudinal designs, and

controlling for confounding variables, such as comorbidities and medications (Wood et al., 2006). Previous studies of symptoms experienced by women with breast cancer undergoing chemotherapy have focused on the prevalence of symptoms, as opposed to the severity of symptoms. Additionally, theoretically important time points, such as baseline, nadir, and end of cycle, are often used for data collection, ignoring the potentially dynamic existence of symptoms on a daily basis. Understanding the severity of symptoms, as they exist on a daily basis, and the correlates of daily symptom experiences, will assist clinicians in identifying women who may be at risk for symptom development or increased symptom severity prior to or during early cycles of chemotherapy. Those women at highest risk for elevated symptom burden may be targeted for self-management support, pharmacological intervention, and more intensive provider surveillance during chemotherapy to improve outcomes, and address issues such as treatment adherence, functional losses, and increased rates of hospital admission.

The objectives of this study were to identify subgroups of women experiencing similar symptom trajectories while undergoing chemotherapy for breast cancer and to determine if demographic, clinical, and symptom variables are associated with specific symptom classes.

Sample

This was a secondary analysis of pooled data collected as part of two longitudinal, randomized controlled trials that tested the use of an automated telephone-linked-care system for monitoring symptoms and intervening in the presence of symptoms during chemotherapy: "Telephone-linked Care for Cancer Symptoms Management (TLC-Chemo Alert)," which was funded by the NIH/DHHS (R01 CA89474 Mooney PI) and

"Symptom Care at Home (SCH)," which was funded by the NIH/DHHS (R01 CA120558 Mooney, PI). Additionally, data were included from a nonrandomized, longitudinal study utilizing the same automated telephone-linked-care system for data collection of the presence of symptoms during chemotherapy: "Symptom Care by Phone (SCP2)" (Mooney, PI).

The sample consisted of 166 women, ages 18 and older, diagnosed with breast cancer and undergoing initial treatment with cycles 2 and 3 of chemotherapy. Women were primarily middle-aged (mean age 52.91 years, *SD* = 10.8), mostly White (91.46%), mostly married (75%), and mostly not employed (62.8%). Women in the sample received any of 12 different chemotherapy regimens consisting of differing combinations and dosing of chemotherapy agents, such as Adriamycin with Cyclophosphamide (41.7%), Docetaxel or Paclitaxel alone (12.8%), Cyclophosphamide with 5Flourouracil (12.8%), Cyclophosphamide with Docetaxel (7.1%), Docetaxel with Adriamycin and Cyclophosphamide (5.1%), Docetaxel with Carboplatin (7.7%), Adriamycin with Cyclophosphamide and 5Flourouracil (3.8%), and others (6.4%). Eighty-two (52.6%) women received Doxorubicin as part of their regimen and 51 (32.7%) women received Paclitaxel or Docetaxel.

Study Findings

The first aim of this study was to determine the trajectory classes reflecting the severity of 10 symptoms (fatigue, pain, disturbed sleep, depressed mood, anxiety, nausea and vomiting, diarrhea, distress about appearance changes, sore mouth, and trouble thinking) reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer. Specific research questions were the following: 1) What are the trajectories of

the severity of individual symptoms reported by women undergoing chemotherapy for breast cancer during cycle 2 and during cycle 3? 2) What are the trajectory classes, if any, associated with the severity of individual symptoms reported by women undergoing chemotherapy for breast cancer during cycle 2 and cycle 3? 3) Do the trajectory classes associated with the severity of individual symptoms differ between cycle 2 and cycle 3 of chemotherapy? Symptoms were measured by self-report on a 0-10 response scale, daily during cycle 2 and cycle 3 of breast cancer treatment with chemotherapy. To accommodate for varying cycle lengths, only the first 14 days of symptom reports during each cycle were used for the analysis of symptom trajectories.

Common symptoms, with their prevalence (i.e., occurring at least once) during cycle 2 and cycle 3, included fatigue (prevalence of 92.7% and 94.9%), disturbed sleep (prevalence of 76.4% and 70.5%), depressed mood (prevalence of 60% and 53.2%), anxiety (prevalence of 46.7% and 39.7%), pain (prevalence of 75.2% and 66.7%), and nausea and vomiting (prevalence of 70.3% and 71.2%). Sore mouth (prevalence of 41.2% and 43.6%), distress associated with change in appearance (prevalence of 23% and 9.6%), diarrhea (prevalence of 41.8% and 31.4%), and trouble thinking (prevalence of 27.9% and 19.9%) were less prevalent. All 10 individual symptoms were modeled over 14 days of each cycle in a 1-class model and then latent class mixture models of distinct patterns of variation over time were evaluated for each symptom. These models defined classes of women who experienced a similar symptom trajectory over the first 14 days of each cycle of chemotherapy. Of the 10 symptoms, latent classes were recovered for fatigue, disturbed sleep, depressed mood, and anxiety. Of the remaining symptoms, trouble thinking was the only symptom with a 2-class model without significant

warnings, but with low class counts. For the other 5 symptoms, there were warnings in the output that indicated the multiclass models were not trustworthy. Exploration of further multiclass models for these 6 symptoms in this sample was terminated with the 2-class solution. We were likely underpowered to detect latent classes for these six symptoms and it is possible that in a larger sample, multiclass models might have been retained. During both cycles of treatment, a majority of respondents reported a severity of zero for many of the symptoms, including sore mouth, trouble thinking, diarrhea, and distress associated with change in appearance. These symptoms were reported on fewer days overall during cycle 2 and cycle 3 and may have limited the ability to recover classes. Logically, it may be that latent classes with homogenous trajectories for these symptom were not recovered because these symptoms were simply not reported frequently enough to model multiple homogenous trajectories. Less prevalent symptoms may be better studied using cross-sectional designs or modeling data from specific theoretically relevant time-points when the symptom is expected to be present.

Fatigue was the symptom with the greatest prevalence (92.7% during cycle 2 and 94.9% during cycle 3) and 67.3% of women during cycle 2 and 69.7% of women during cycle 3 reported a moderate to severe level of fatigue at least once during each cycle. A 3-class model provided the best fit to the data with acceptable fit indices and class proportions. This model reflected three distinct trajectories: mild improving, low moderate improving to mild, and high moderate improving fatigue severity. Fatigue severity improved across the first 14 days of each cycle for all classes. While the majority of subjects were in the mild improving fatigue class (59% for cycle 2 and 64% for cycle 3), those in both the low moderate improving to mild and high moderate

improving fatigue classes reported persistent fatigue during both cycles. In both cycles, 11% of respondents were in the high moderate improving fatigue class. Additionally, the growth factors and visualization of the trajectories over the two cycles of chemotherapy, suggests that fatigue in cycle 2 did not differ in pattern during cycle 3, similar to previously reported findings of fatigue patterns over multiple courses of chemotherapy (Berger, 1998; Jacobsen et al., 1999).

Disturbed sleep was highly prevalent (70.5% during cycle 2 and 76.4% during cycle 3) and at moderate to severe levels (62.4% during cycle 2 and 54.5% during cycle 3) in the sample. A two-class model was described that included the following classes: mild improving disturbed sleep during both cycles and moderate worsening disturbed sleep (11% of respondents) during cycle 2 and mild worsening disturbed sleep (19% of respondents) during cycle 3. Only those women in the worsening disturbed sleep classes had an increase in severity during the 14 days. This suggests that identification of women at risk for disturbed sleep early in the course of treatment, and subsequent intervention, may improve sleep later in the course of treatment.

The prevalence of depressed mood (53.2% during cycle 2 and 60% during cycle 3) and anxiety (39.7% during cycle 2 and 46.7% during cycle 3) was similar to previously reported findings (Bower et al., 2011; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Kim et al., 2008; Liu et al., 2009; So et al., 2009). Depressed mood and anxiety were also prevalent at moderate to severe levels in the sample (42.4% during cycle 2 and 35.3% during cycle 3, 28.5% during cycle 2 and 25.6% during cycle 3, respectively). Two-class models were retained for both depressed mood and anxiety. A consistently mild depressed mood class during both cycles (91% of respondents in

cycle 2 and 94% in cycle 3) and a consistently moderate depressed mood class (6% of respondents) during cycle 2 and a moderate improving depressed mood class (9% of respondents) during cycle 3 were identified. While the mean severity in the consistently mild depressed mood classes was less than 1 over both cycles, the mean severity in the consistently moderate and moderate improving depressed mood classes were 4 or higher across both cycles. During cycle 3, these women experienced a slight improvement in depressed mood, but remained with moderate severity. Symptoms of mood disturbance have been reported to increase from baseline, but generally remain stable over time (Nieboer et al., 2005). Our findings suggest that women who report a higher severity of depressed mood early in a cycle of chemotherapy may retain the symptom throughout the cycle of chemotherapy. A 2-class model was retained for anxiety that fit the data with consistently mild anxiety classes during both cycles (92% of respondents in cycle 2 and 95% in cycle 3) and a consistently moderate anxiety class (5% of respondents) during cycle 2 and a low moderate improving to mild anxiety class (8% of respondents) during in cycle 3. Similar to depressed mood, the mean daily severity in the moderate anxiety class was greater than 3 across both cycles, with mean severity levels slightly higher during cycle 2 when compared to cycle 3.

While not large, a group of women existed in our sample who experienced fatigue, disturbed sleep, depressed mood, and anxiety at moderate to severe levels during chemotherapy treatment. The growth factors and visualization over the two cycles of chemotherapy are presented in see Table 5.1. Only fatigue is reported in the literature having similar patterns over multiple courses of chemotherapy (Berger, 1998; Jacobsen et al., 1999). Patterns of disturbed sleep, depressed mood, and anxiety are not well-studied

Table 5.1 Growth Factor Means and Predicted Frequencies for Each Class

Class	Intercept	Slope	Quadratic Term	Class Count
Fatigue				
	Cycle 2			
Mild Improving	2.25*	-0.26*	0.01*	97.94
Low Moderate Improving to Mild	3.21*	0.32	-0.03*	51.46
High Moderate Improving	5.66*	0.34	0.01	18.26
	Cycle 3			
Mild Improving	1.76*	-0.12	0.00	106.24
Low Moderate Improving to Mild	2.52*	0.65*	-0.06*	41.50
High Moderate Improving	5.43*	0.60*	-0.06*	18.26
Disturbed Sleep				
	Cycle 2			
Mild Improving	1.74*	-0.20*	0.01	145.85
Moderate Worsening	3.76*	-0.28	0.03	18.15
	Cycle 3			
Mild Improving	0.87*	-0.07	0.00	133.65
Mild Worsening	1.66*	0.14	0.00	31.35
Depressed Mood				
	Cycle 2			
Consistently Mild	0.78*	-0.04	0.00	148.50
Consistently Moderate	4.04*	0.22	-0.01	14.85
	Cycle 3			
Consistently Mild	0.27	0.13	-0.01	155.10
Moderate Improving	4.82*	0.23	-0.02*	9.90
Anxiety				
	Cycle 2			
Consistently Mild	0.69*	-0.10*	0.01*	156.75
Consistently Moderate	4.90*	0.03	0.00	8.25
	Cycle 3			
Consistently Mild	0.34*	-0.03	0.00	156.75
Low Moderate Improving to Mild	3.53*	0.17	-0.02	8.25

*$p<.05$

over multiple cycles of chemotherapy. However, even the reports of fatigue are based on a single aggregate trajectory and further study is needed to discover whether individuals differ in their class membership across multiple cycles of chemotherapy. Cross-tabulations and Chi square were used to compare whether extracted predicted class memberships varied within individuals between cycle 2 and cycle 3 for these four symptoms of interest. Of those in the mild improving fatigue class during cycle 2, 6.8% moved to the low moderate improving to mild fatigue class and 1.1% moved to the high moderate improving fatigue class during cycle 3. Of those in the low moderate improving to mild fatigue class during cycle 2, 25% moved to the mild improving fatigue class and 18.8% moved to the high moderate improving fatigue class during cycle 3. Of those in the high moderate improving fatigue class during cycle 2, 22.2% moved to the mild improving fatigue class and 33.3% moved to the low moderate improving to mild fatigue class during cycle 3. Of those in the mild improving disturbed sleep class during cycle 2, 6.9% moved to the mild worsening disturbed sleep class during cycle 3 and 64% moved from the moderate worsening disturbed sleep class during cycle 2 to the mild improving disturbed sleep class during cycle 3. There was no movement from the consistently mild depressed mood class to the moderate improving depressed mood class between cycles, but 57.1% of those in the consistently moderate depressed mood class during cycle 2 moved to the consistently mild depressed mood class during cycle 3. Finally, while only 5.4% of those in the consistently mild anxiety class during cycle 2 moved to the low moderate improving to mild anxiety class during cycle 3, 37.5% of those in the low moderate improving to mild anxiety class during cycle 2 moved to the consistently mild anxiety class during cycle 3. The moderate sample size in this study,

and more importantly, the small class counts for the moderate and severe symptom classes across all four symptoms make it difficult to tease out potential moderating factors for class movement, such as age, stage of disease, or chemotherapy regimen. Additionally, because this was a secondary analysis, data related to symptom management strategies used during cycle 2 could not be controlled for to adjust a study of class movement. Research is needed, with larger samples, to determine if these patterns of movement do exist and potential correlates of movement between classes. Possible methods include both visualization and statistical repeated-measures longitudinal analysis.

The second aim was to identify multisymptom trajectory classes of women undergoing cycles 2 and 3 of chemotherapy for breast cancer. A multisymptom model was not identified in this sample. Because individual symptom multiclass models were not retained for trouble thinking, sore mouth, distress with changing appearance, diarrhea, nausea and vomiting, or pain, these symptoms were excluded from a multisymptom model analysis. Even with only including symptoms with retained multiclass models, a multisymptom model using fatigue, disturbed sleep, depressed mood, and anxiety was likely underpowered given the modest sample size and large variability in the number of days with reported symptoms. There are two likely explanations for this lack of findings. First, it is possible that a model explaining the trajectory of multiple symptoms in women receiving chemotherapy for breast cancer does not exist. However, this is unlikely, as several recent reports suggest that symptoms may exist in combination during chemotherapy and individuals may be at risk for these concurrent symptoms (Bender, Ergun, Rosenzweigh, Cohen, & Sereika, 2005; Berger &

Farr, 1999; Berger & Higginbotham, 2000; Bower et al., 2011; Broekel, Jacobsen, Horton, Balducci, & Lyman, 1998; Jacobsen et al., 1999; Byar, Berger, Bakken, & Cetek, 2006; Dodd, Cho, Cooper, & Miaskowski, 2010; Gaston-Johannson et al., 1999; Liu et al., 2009; Liu et al., 2012; Molassiotis, Yam, Yung, Chan, & Mok, 2002; Osoba et al., 1997; Poon et al., 2013; So et al., 2009). These studies report the existence of concurrent symptoms among those symptoms that are more commonly prevalent, such as fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea and vomiting. In our sample, there was marked within-class variability in the growth factor parameters. While a mixture distribution may well represent the diversity in these symptoms, we did not have the sample size needed to recover classes. Future designs may be more successful with larger samples and the addition of model constraints to address these highly variable symptom experiences and increase statistical power.

With the second aim unanswered, an exploratory analysis was undertaken to determine whether various demographic, clinical, and symptom characteristics were predictive of class membership for each individual symptom of fatigue, disturbed sleep, depressed mood, and anxiety. Aim three was to determine if demographic, clinical and symptom variables predict membership in distinct individual symptom trajectory classes. The specific research question was the following: To what extent are differing symptom trajectory profiles associated with variations in age, chemotherapy regimen, stage of disease, marital status, employment, education, and the presentation of other symptoms at moderate to severe severity?

For all four symptoms, univariate tests of mean differences among classes on demographic variables were not statistically significant, except for chemotherapy

regimen and education. For fatigue, depressed mood, and anxiety, women who received Doxorubicin as part of their chemotherapy regimen were more likely to be in the higher severity classes. These findings cannot be verified with previous reports, as the effect of chemotherapy type on symptom presentation is understudied and inconsistently reported in the literature (Berger, 1998; Berger & Farr, 1999; DeJong, Kester, Schouten, Abu-Saad, & Courtens, 2006). Across the sample, more than 12 different chemotherapy combinations were reported, making it difficult to adequately address the question of how chemotherapy regimen was associated with class membership. Further study is needed to determine whether the use of Doxorubicin places women at risk for higher fatigue, depressed mood, and anxiety and whether this effect is dose-dependent or related to other agents received in combination with Doxorubicin. Additionally, for anxiety, women with no college education were more likely to be in the moderate symptom severity class when compared to women with a college degree. This finding, in combination with previous reports, suggests that higher educational attainment may be associated with lower anxiety during chemotherapy, although further research is needed to replicate these observations (Lam et al., 2010).

Inconsistencies between our findings and previously reported findings of the relationship between demographic and clinical characteristics and symptoms may be related to limited variability in the sample with respect to demographic characteristics, and the relatively small sample size in the present study. The number of women who were predicted in the higher severity classes for all symptoms was low and this may have decreased the power to detect differences among the classes on these variables. Further research is needed to explore other personal characteristics that might be associated with

distinct symptom classes.

Membership in higher fatigue classes was associated with increased number of days of moderate to severe disturbed sleep, depressed mood, nausea and vomiting, anxiety, and trouble thinking. The relationship between fatigue and disturbed sleep is not surprising and is consistent with previous reports (Berger & Farr, 1999; Berger & Higginbotham, 2000; Bower et al., 2011; Broekel et al., 1998; Jacobsen et al., 1999; Liu et al., 2009; Onselen et al., 2012). Similarly, an increase in the number of days with moderate to severe fatigue was associated with membership in the moderate severity class for both depressed mood and anxiety. Relationships among depressive symptoms, trouble sleeping, psychological distress, and fatigue have been reported by other investigators (Bender et al., 2005; Byar et al., 2006; Dodd et al., 2010; Gaston-Johannson et al., 1999; Kim et al., 2008; Liu et al., 2009; Niebor et al., 2005; So et al., 2009; Von Ah & Carpenter, 2008). The finding that there is an association between sleep and mood disturbances during cycle 3 is consistent with observations about the co-occurrence of sleep difficulties, anxiety and depressed mood (Colagiuri et al., 2011; Onselen, Cooper et al., 2012). Additionally, the number of days with moderate to severe levels of nausea and vomiting was increased in the severe fatigue class when compared to the minimal fatigue class. There are several reports of a positive association between fatigue and chemotherapy-induced nausea and vomiting, even with use of appropriate anti-emetics (Molassiotis et al., 2002; Osoba et al., 1997; Poon et al., 2013). In addition, the relationships between both fatigue and disturbed sleep with trouble thinking has been previously reported (Bender et al., 2005).

The number of days with moderate to severe depressed mood and anxiety were

associated with the moderate severity class for anxiety and depressed mood, respectively. The relationship between both symptoms of mood disturbance is well studied and commonly known as co-occurrence of anxiety and depressive symptoms or CADS (Colagiuri et al., 2011; Dunn et al., 2011; Gold et al., 2016; Lam, Shing, Bonanno, Mancini, & Fielding, 2012). The co-existence of these symptoms suggests that etiology for one may explain the other and developing interventions aimed at managing one may assist in management of the other. Unfortunately, data for several potential moderators of class membership for depressed mood and anxiety were not available on participants in this sample, including history of mood disturbance, measures of trait anxiety, and baseline measures of psychological health. Future research should attempt to capture the potential relationship between depressed mood and anxiety and class membership for these co-existing symptoms.

Finally, for all four symptoms, across both cycles, the total number of days with moderate to severe symptoms, including fatigue, disturbed sleep, depressed mood, anxiety, nausea and vomiting, and pain during cycle 2, was associated with a higher severity class membership during cycle 3. This suggests that the overall symptom experience during an earlier cycle may predict the occurrence of fatigue, disturbed sleep, depressed mood, and anxiety during a later cycle. These results suggest that individuals with an increased overall symptom experience during an early cycle of chemotherapy may be targeted for increased symptom management in an effort to improve the symptom experience during subsequent cycles.

Aim four was to determine if distinct symptom trajectory classes were associated with change in functional status from cycle 2 to cycle 3, days of missed work, and hours

spent lying down during cycles 2 and 3 of chemotherapy for breast cancer. The specific research question for this aim was the following: To what extent are differing symptom trajectory profiles associated with variations in change in functional status, days of missed work, and hours spent lying down as reported by women undergoing chemotherapy for breast cancer?

We could not evaluate the association between change in functional status and latent class membership because of a large amount of missing data, and thus a change score for functional status could only be calculated for 12 women.

Potential consequences of latent class membership for fatigue, disturbed sleep, depressed mood, and anxiety were studied and included average daily hours spent lying down and days of missed work. Results of the significant outcomes are presented in Tables 5.2 and 5.3. For fatigue, women in the high moderate improving class reported an average of 12.36 hours spent lying down, which was statistically significantly higher when compared to women in the mild improving class who reported an average of 10 hours spent lying down during cycle 2. This is consistent with other studies that have found that higher fatigue is associated with lower activity levels (Berger & Farr, 1999; Berger & Higginbotham, 2000; deJong, Cantel, Shouten, Abu-Saad, & Courtens, 2004; Downie, Fan, Houede-tchen, Yi, & Tannock, 2006). However, in cycle 3, there was no association between hours spent lying down and fatigue class membership, and the mean hours spent lying down were nearly identical across the three fatigue classes. Further examination with larger samples may better highlight this association. During cycle 2 only, women in the consistently moderate anxiety class, as compared to women in the consistently mild anxiety class, reported higher average daily hours spent lying down

Table 5.2 Outcomes of Fatigue Class Membership

Outcome	**Mild Improving Mean Hours/Days *(SD)***	**Low Moderate Improving to Mild Mean Hours/Days *(SD)***	**High Moderate Improving Mean Hours/Days *(SD)***	**ANOVA**
		Cycle 2		
Hours Spent Lying Down	10.00 (2.54)	10.79 (2.64)	12.36 (3.77)	$F(2, 44) = 2.03$, $p = .02$*
Days Missed Work (n=20)	1.9 (1.52)	3.13 (2.03)	2.5 (2.12)	$F(2, 17) = 1.05$, $p = .37$
		Cycle 3		
Hours Spent Lying Down	10.44 (2.94)	10.71 (2.51)	10.05 (2.51)	$F(2, 150) = 0.35$, $p = .70$
Days Missed Work (n=27)	1.33 (1.50)	1.43 (1.72)	2.20 (1.65)	$F(2, 24) = 0.51$, $p = .61$

Table 5.3 Outcomes of Anxiety Class Membership

Cycle 2			
Outcome	**Consistently Mild Mean Hours *(SD)***	**Consistently Moderate Mean Hours *(SD)***	**Independent-Samples *t* test**
Hours Spent Lying Down	10.41 (2.77)	12.53 (3.03)	$t(162) = -2.21$, $p = .03$*
Cycle 3			
Outcome	**Consistently Mild Mean Hours *(SD)***	**Low Moderate Improving to Mild Mean Hours *(SD)***	**Independent-Samples *t* test**
Hours Spent Lying Down	10.44 (2.75)	11.87 (3.20)	$t(150) = -1.77$, $p = .08$

(mean hours 12.53 vs. 10.41). No prior research has identified an association between inactivity and anxiety.

All other tests of mean differences among the classes on the outcomes for hours spent lying down and days of missed work were nonsignificant. While the omnibus test was nonsignificant during both cycles, the mean days of missed work increased as fatigue severity class increased. Unfortunately, only 37.2% of the sample was employed either part or full-time and we were statistically underpowered to detect differences in missed work days among the fatigue latent classes. The relationships between fatigue and days of missed work deserves exploration in a cohort with more employed participants.

Limitations

While LGMM is a useful technique for identifying subgroups of individuals who experience similar symptom trajectories, there are inherent limitations, including the assumption that classes represent unobserved population subgroups (Colder et al., 2002; Ialongo, 2010; Sterba & Bauer, 2010). This is particularly problematic in cases with small sample sizes, a large number of assessments or measurement time points, and highly variable data. Care should be taken to consider whether the size and nature of the data allowed the researcher to find multiple classes when they actually exist (Ialongo, 2010). While several subgroups were identified in this analysis of symptoms reported by women with breast cancer, the existence of latent class subgroups should not be over-interpreted. Ialongo (2010) suggests five steps that can be utilized to build the case for the existence of latent class subgroups, including providing a rationale for the chosen statistical approach, using substantive theory to hypothesize about subgroup existence, testing antecedents and consequences to group membership, comparing alternative

models, and considering sample size and the nature of the data. These five steps are discussed in relation to our findings below.

Providing Rationale for Approach

Our selected approach for modeling the daily symptom reports was LGMM, which is well suited for symptom studies, where longitudinal patterns are of interest and models can identify homogeneous subgroups of individuals with similar symptom experiences. The categorical latent variables correspond to the person-oriented component in that they represent a category or class that describes subgroups of individuals who are relatively homogeneous within that class and are heterogeneous across classes (Muthen & Muthen, 2000). LGMM also allows estimation of the relationship between class membership and antecedent or outcome variables (Muthen & Muthen, 2000). A limitation of LGMM is the requirement for multiple measurement time points, with at least 4 or 5 time points preferred (Muthen & Muthen, 2000). With this, comes the requirement for larger sample sizes to achieve adequate statistical power and allow for the assumed attrition rates. While there is no general rule for determining sample size applicable to all situations in growth modeling, the Monte Carlo method has been recommended. Assuming data are missing at random, the Monte Carlo method, which does consider the number of measurement time points, estimated a sample size requirement of between 150 and 250 participants for our study. Our sample size of 166 women was therefore at the lower limit of those estimates, adequate, but given the nature of symptom data, where some symptoms are highly variable among women and across days and other symptoms are often reported at a severity of zero, and the use of a large number of measurement time points, where we included data from 14 daily reports, a

larger sample size would provide greater power to support our confidence in the existence of the identified latent classes. In addition, greater power, through a larger sample size, may have allowed us to conclude that there were only single-class models for the 6 symptoms where we were unable to identify multiclass models.

Use of Substantive Theory

Substantive theory assists in building the case for the existence of subgroups (Ialongo, 2010). Comparison of our results to the few other studies reporting symptom trajectory subgroups revealed conflicting findings and therefore do not help to confirm our subgroup findings. Several recent studies of the symptoms of mood disturbance and one study of disturbed sleep where growth mixture techniques were used, identified models with a greater number of classes when compared to our findings (Bistrup et al., 2015; Dunn et al., 2015; Gold et al., 2016; Helgeson et al., 2004; Henselmans et al., 2010; Lam et al., 2010; Onselen et al., 2012; Wang et al., 2014). Differing findings among these subgroup studies and our study may be attributed to differing sample demographic and clinical characteristics, differing measurement time points, and differences in the instruments used to measure varying symptoms. Additional research employing these kinds of longitudinal latent variable methods is warranted to better understand the trajectory of symptoms experienced during breast cancer.

Tests of Antecedents and Consequences

Testing whether theoretically relevant covariates predict class membership probabilities and establishing the predictive value of classes can reassure researchers of the existence of classes (Ialongo, 2010). Certainly, the identification of antecedents to class membership and outcomes of class membership within our sample strengthens the

argument for the existence of the identified classes, although these associations were limited to chemotherapy regimen, education, and hours spent lying down and were not all replicated during both cycles. In addition, the identification of co-occurring symptoms within classes supports the existence of the identified classes. The use of covariates as evidence of class existence is particularly relevant when the associated antecedents, co-occurring symptoms, and outcomes are reported to relate to fatigue, disturbed sleep, depressed mood, or anxiety in the literature. For example, we found that women in the low moderate improving to mild anxiety class during cycle 3 had lower educational attainment. Consistent with these observations, Lam et al. (2010) noted that education was protective against psychological distress. In this case, our finding was consistent with previous reports and serves as a support for the existence of the latent classes for anxiety we identified. However, some of our significant associations have not been well-studied and could not be substantiated in the published literature. For example, we found that women in the consistently moderate anxiety class during cycle 2 reported higher average daily hours spent lying down when compared to women in the consistently mild anxiety class. However, no reports were found in the literature where differences in activity level or resting hours were associated with the severity of anxiety during treatment, and we were unable to verify our finding with those of previous studies. Here, our significant association between an outcome and class membership for anxiety is not as helpful in supporting the existence of the latent classes. There were several non-significant associations in our sample that have been reported to exist in the literature, including the reported relationship between age and disturbed sleep. Additionally, some of our significant associations were not supported in the literature, where findings are

either conflicting or are inconsistently reported. For example, we found that women in the higher severity classes for fatigue, depressed mood, and anxiety were more likely to have receiving Doxorubicin as part of their chemotherapy regimen. Unfortunately, we were unable to verify these findings with previous reports, as the effect of chemotherapy type on symptom presentation is understudied and inconsistently reported. Again, our finding of an association between an antecedent and class membership for fatigue, depressed mood, and anxiety was not supported in the literature, and is not as helpful in building confidence towards the existence of the identified latent classes. One possibility is that differences between our findings and those previously reported may be related to our small sample size and resultant low statistical power, or to low proportions in some of the classes. For example, Table 5.4 presents the model predicted class counts for the identified latent classes of fatigue, disturbed sleep, depressed mood, and anxiety. The class proportions are low in the higher severity classes for all symptoms, and particularly for the symptoms of mood disturbance. Tests of between-group differences among the classes may have had attenuated power, resulting in differences between our results and those reported by other investigators. As such, there remains the possibility that the classes we identified do not completely represent the symptom trajectories experienced during cycles 2 and 3 of treatment for breast cancer. The findings reported here should not be over-interpreted, and continued study of this important aspect of the treatment experience is warranted.

Comparing Alternative Models

Comparing the results of an alternative modeling approach and model fit can also be used to build a stronger case for subgroup existence. A unique feature of LGMM is

Table 5.4 Class Counts for Fatigue, Disturbed Sleep, Depressed Mood, and Anxiety

Class	Class Count
Fatigue	
Cycle 2	
Mild Improving	97.94
Low Moderate Improving to Mild	51.46
High Moderate Improving	18.26
Cycle 3	
Mild Improving	106.24
Low Moderate Improving to Mild	41.50
High Moderate Improving	18.26
Disturbed Sleep	
Cycle 2	
Mild Improving	145.85
Moderate Worsening	18.15
Cycle 3	
Mild Improving	133.65
Mild Worsening	31.35
Depressed Mood	
Cycle 2	
Consistently Mild	148.50
Consistently Moderate	14.85
Cycle 3	
Consistently Mild	155.10
Moderate Improving	9.90
Anxiety	
Cycle 2	
Consistently Mild	156.75
Consistently Moderate	8.25
Cycle 3	
Consistently Mild	156.75
Low Moderate Improving to Mild	8.25

that this method uses a formal statistical procedure to test whether the hypothesized trajectories actually emerge from the data rather than assume the existence of a particular number of trajectories or classes (Andruff, Carraro, Thompson, Gaudreau, & Louvet, 2009). The simplest assumption, a single-class model, was hypothesized first. Classes were added to the model to determine the solution, or the number of classes, that best fit the data. Intercepts, slopes, and possibly quadratic or cubic functions were determined for each class. In our study, multiple model fit indices guided the determination of the number of classes retained. Of primary interest were the Bayesian Information Criterion (BIC) and entropy, along with the Akaike Information Criterion (AIC), Bootstrapped Likelihood Ratio Test (BLRT), and the Vuong-Lo-Mendell-Rubin Test (VLMR). The BIC was used to evaluate improvement in model fit as additional classes were added. Smaller BIC values suggested a better model fit (Colder et al., 2002; Muthen & Muthen, 2000). If the addition of a class resulted in a reduction in the BIC value relative to the BIC from the previous model (without the added class), then the new model was considered an improvement and the model was retained. The addition of classes continued until the BIC did not decrease with the addition of a class. Additionally, entropy was used to evaluate the probabilities of membership in each class for each individual. Entropy is a summary measure of classification accuracy based on these probabilities that ranges from 0 to 1.0 (Colder et al., 2002). The closer entropy values are to 1.0, the better the classification. Model selection was determined by multiple additional criteria, including the "K" versus "K-1" class models to determine whether a model with K classes fit the data better than a model with "K-1" classes using the parametric bootstrapped likelihood ratio (BLRT) and Vuong-Lo-Mendell-Rubin

Likelihood Ratio Tests (VLMR) (Dunn et al., 2011; Jung & Wickerama, 2008; Nylund, Asparouhov, et al., 2007; Nylund, Bellmore, et al., 2007). Finally, to determine the best-fitting model, the distribution of subjects in each class (class proportions) were examined, and the class-specific trajectories were graphed and visually inspected to determine if the predicted trajectories were clinically meaningful and theoretically interpretable (Onselen, et al., 2012). The retained models were those that produced the best fit indices relative to the other tested models, with class proportions of greater than 5% of the sample. For fatigue, the 3-class model was retained because it produced a lower BIC and higher entropy when compared to the 2-class model, but was more parsimonious and clinically relevant when compared to the 4-class model during both chemotherapy treatment cycles. Additionally, one of the classes in the 4-class model during treatment cycle 3 had class proportions of less than 5%. For disturbed sleep, depressed mood, and anxiety, 2-class models were retained because the 3-class models had class counts of 5% or less for at least one class. Use of model fit indices for selecting the best fitting model in comparison to other models helps to strengthen our confidence in the existence of the identified classes.

Considering Sample Size and the Nature of the Data

In our study, steps were taken to build the case for subgroup existence in our sample, including use of parsimony and substantive theory as well as use of model fit indicators, but the sample size and nature of the data available limit the usefulness of LGMM. This study was limited in sample size to the participants in the primary studies who met the criteria for this secondary analysis. Certainly a larger sample size would be useful for identifying greater variety of growth trajectories and determining the reliability

and stability of class definitions (Colder et al., 2002). This may be especially true in cases of relatively low base rate outcomes, such as rarer symptoms or symptoms often reported at a severity level of zero (Ialongo, 2010). While our sample of 166 women was minimally acceptable to apply LGMM for subgroup identification, the degree of variability in women's symptom trajectories potentially warranted a larger sample to identify classes that could be described with confidence.

Particular care should be given to the nature of the data in our study and the usefulness of LGMM in modeling symptom trajectories with daily reporting. In our identified models, and given the use of daily symptom severity reporting, it is likely that there is more variability within the classes than the presented growth factors adequately represent. As an example of this, examination of spaghetti plots of a random sample of 10 women drawn from each of the severity classes for fatigue during cycle 2 demonstrates the degree of variability and inability to visually discern patterns among women with predicted membership in the same classes (see Figure 5.1). Additionally, because symptoms peak and ebb, there was a large number of days where women reported zero severity on symptoms. The reliance on aggregated means with many daily reports of zero may have decreased the aggregate means for the growth factors and therefore may not well-represent the actual severity pattern of the symptoms (see Table 5.5). Examination of a random sample of 10 women predicted in each of the fatigue severity classes (see Figure 5.2-5.4) during cycle 2 demonstrates the effect of the days with zero severity on the fitted line plots for individuals. The prevalence of days with zero severity on the reported symptom may reduce the overall mean severity for individual days, which would then decrease the aggregate means for the class parameters.

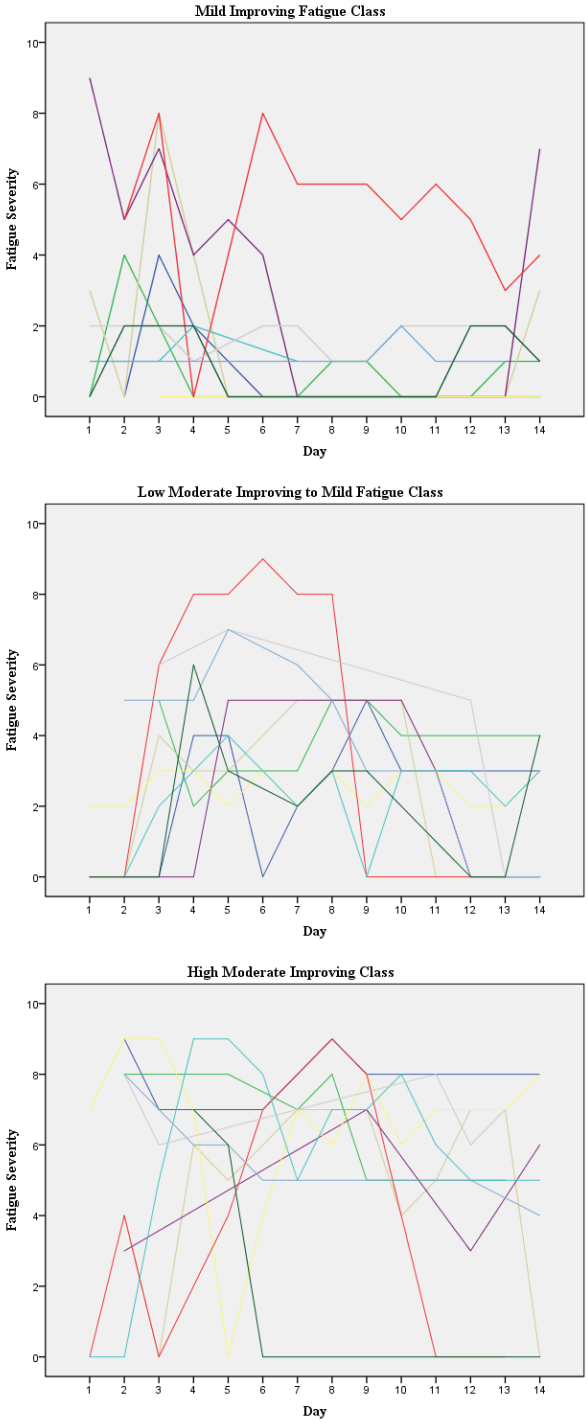

Figure 5.1 Spaghetti plots demonstrating high variability in trajectories of fatigue across 3 severity classes and the effect of days with zero level severity on the fitted line plot for individuals.

Table 5.5 Number of Days Symptoms Reported at Various Severity Levels

Symptom	Cycle	No. Days (%) Symptom Reported Level 0	No. Days (%) Symptom Reported Level 1-10	No. Days (%) Symptom Reported Level 4-10
Fatigue [a]	2	659 (36.4%)	1152 (63.6%)	585 (32.3%)
	3	654 (38.4%)	1050 (61.6%)	520 (30.5%)
Disturbed Sleep [a]	2	1354 (74.8%)	457 (25.2%)	296 (16.3%)
	3	1330 (78.1%)	374 (21.9%)	209 (12.3%)
Pain [a]	2	1247 (68.9%)	564 (31.1%)	263 (14.5%)
	3	1167 (68.5%)	537 (31.5%)	274 (16.1%)
Nausea and Vomiting [a]	2	1359 (75.0%)	542 (29.9%)	208 (11.5%)
	3	1254 (73.6%)	450 (26.4%)	198 (11.6%)
Diarrhea [a]	2	1664 (91.9%)	147 (8.1%)	55 (3.0%)
	3	1575 (92.4%)	129 (7.6%)	49 (2.9%)
Sore Mouth [a]	2	1565 (86.4%)	246 (13.6%)	118 (6.5%)
	3	1478 (86.7%)	216 (12.7%)	91 (5.3%)
Trouble Thinking [b]	2	884 (93.2%)	64 (6.8%)	37 (3.9%)
	3	776 (94.1%)	46 (5.6%)	20 (2.4%)
Appearance [b]	2	882 (93.0%)	66 (7.0%)	42 (4.4%)
	3	801 (97.1%)	24 (2.9%)	17 (2.1%)
Depressed Mood [a]	2	1455 (80.3%)	356 (19.7%)	226 (12.5%)
	3	1416 (83.1%)	288 (16.9%)	158 (9.3%)
Anxiety [a]	2	1544 (85.3%)	267 (14.7%)	147 (8.2%)
	3	1483 (87.0%)	221 (13.0%)	106 (6.2%)

[a] 1811(78.4%) days reported cycle 2, 1704(78.0%) days reported cycle 3; 499(21.6%) days missing cycle 2, 480(22.0%) days missing cycle 3

[b] 948 (80.6%) days reported cycle 2, 825 (79.6%) days reported cycle 3; 228 (19.4%) days missing cycle 2, 211 (20.4%) days missing cycle 3

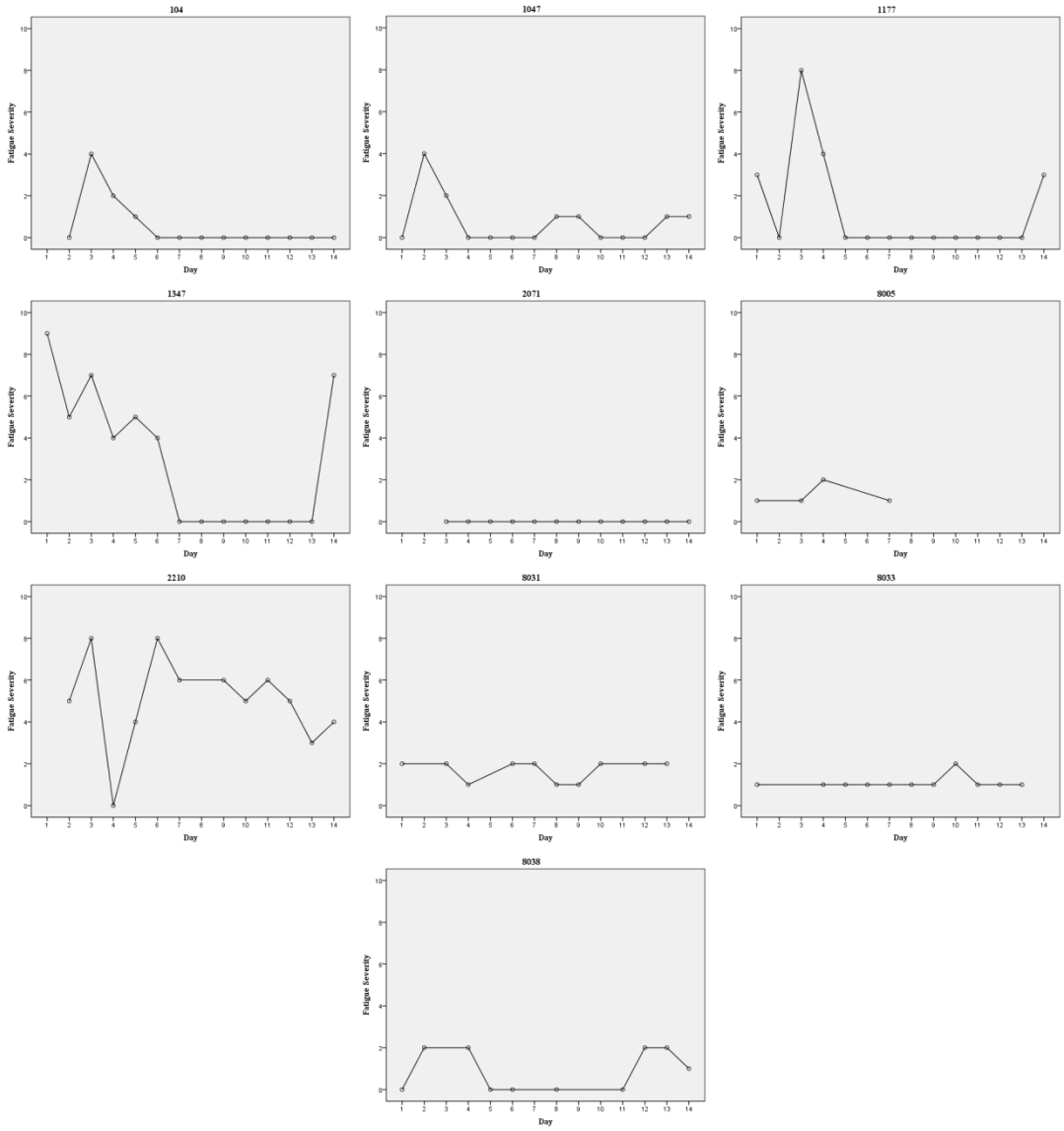

Figure 5.2 Fitted line plots for random sample of 10 women in the mild improving fatigue class during cycle.

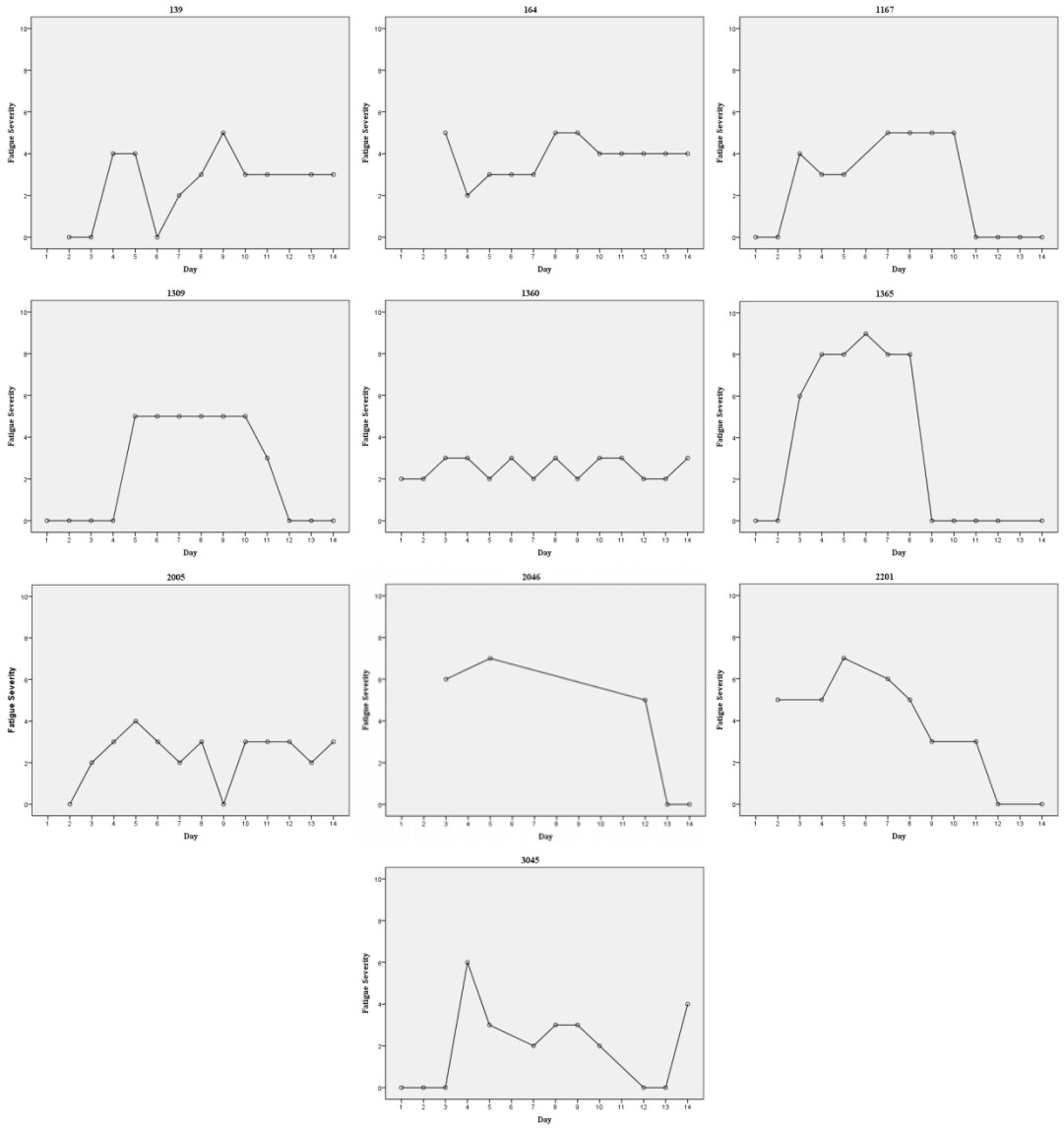

Figure 5.3 Fitted line plots for random sample of 10 women in the low moderate improving to mild fatigue class during cycle 2.

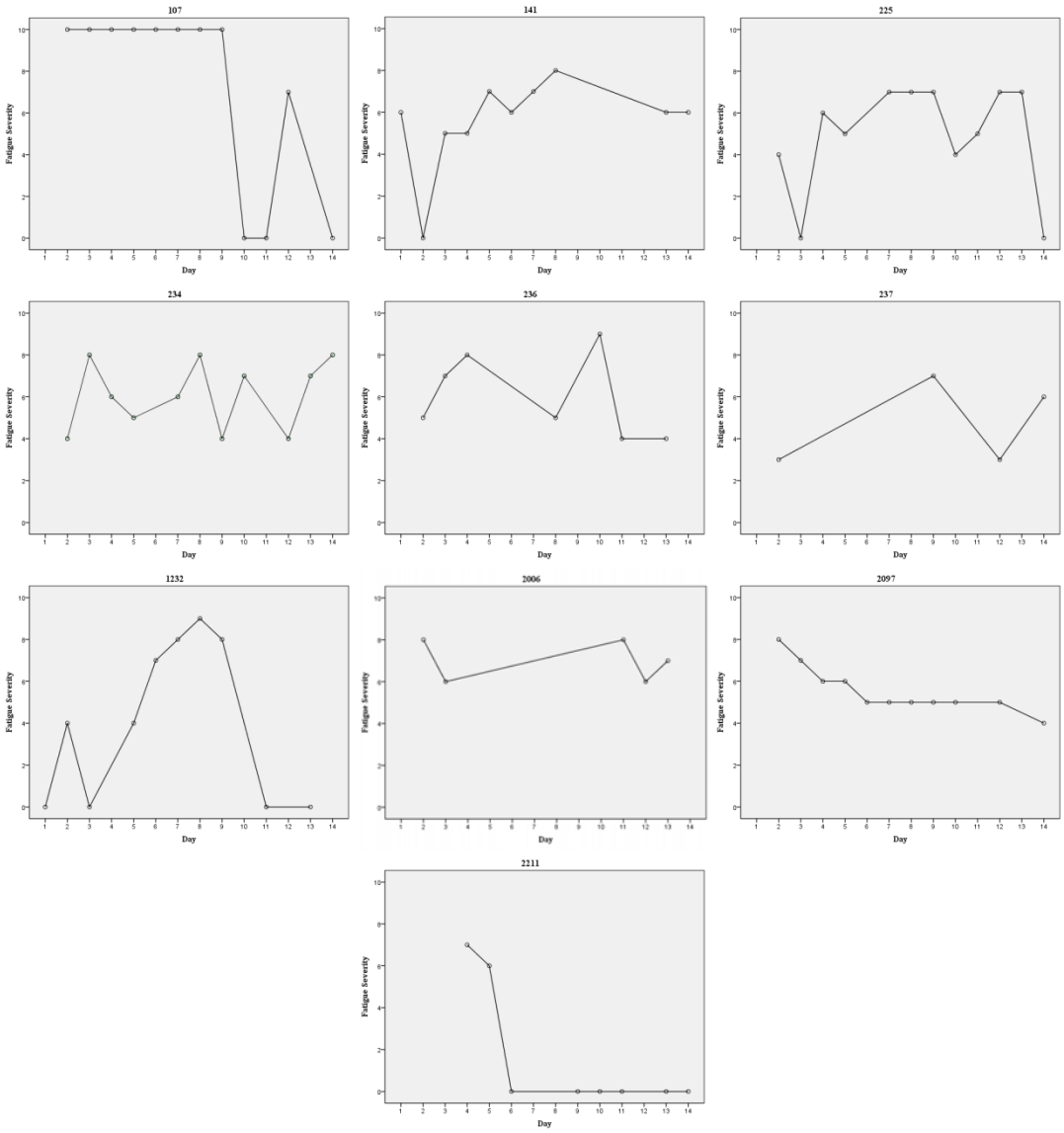

Figure 5.4 Fitted line plots for random sample of 10 women in the high moderate improving fatigue class during cycle 2.

The result would be to systematically underestimate symptom severity.

Naming of the classes in our models was qualitatively achieved using visualization of the mean class trajectories. Class names were based on common category nomenclature for symptom severity, none (0), mild (0-3), moderate (4-7), and severe (7-10) for the intercept and a description of the slope and quadratic terms, whether consistent, improving, or worsening within the same severity threshold or moving between categories. These labels might be misleading as average severities were influenced by the zero severity reports and this impact is greater in symptoms that occur less frequently. Trajectories that varied greater than one severity degree during the 14 days were considered to be improving or worsening, depending on their directionality. If the change moved to a differing severity category, it was indicated in the name. Examination of the standard errors for the parameter estimates in our models revealed large confidence intervals in many cases, indicating the range of possible values that were likely to include the population parameter. In cases where the range included the possibility of zero, those growth parameters were considered not statistically significant. For example, during cycle 2, the slopes for both the low moderate improving to mild fatigue class and the high moderate improving classes were nonsignificant (see Table 5.6). However, visualization of the trajectories revealed an improvement in the severity of fatigue during the chemotherapy cycle (see Figure 5.5). Here, improvement was indicated in the class names, even with confidence intervals suggesting a range of values that could include zero. Caution should be considered in determining the validity and statistical significance of the growth parameters and in the methods used for naming the classes where the standard errors are large and confidence intervals include zero.

Table 5.6 Growth Factors and 95% Confidence Intervals for Fatigue During Cycle 2

Fatigue Class	Intercept (SE), 95% CI	Slope (SE), 95% CI	Quadratic Term (SE), 95% CI
Mild Improving	2.25 (.29)*, [2.82, 1.68]	-0.26 (0.08)*, [-0.10, -0.42]	0.01 (0.01)*, [0.02, 0.00]
Low Moderate Improving to Mild	3.21 (0.52)*, [4.23, 2.18]	0.32 (0.17), [.66, -0.02]	-0.03 (0.01)*, [-0.01, 0.06]
High Moderate Improving	5.66 (0.73)*, [7.09, 4.24]	0.34 (0.21), [0.75, -0.07]	-0.03 (0.02)*, [-0.00, -0.06]

*$p < .05$

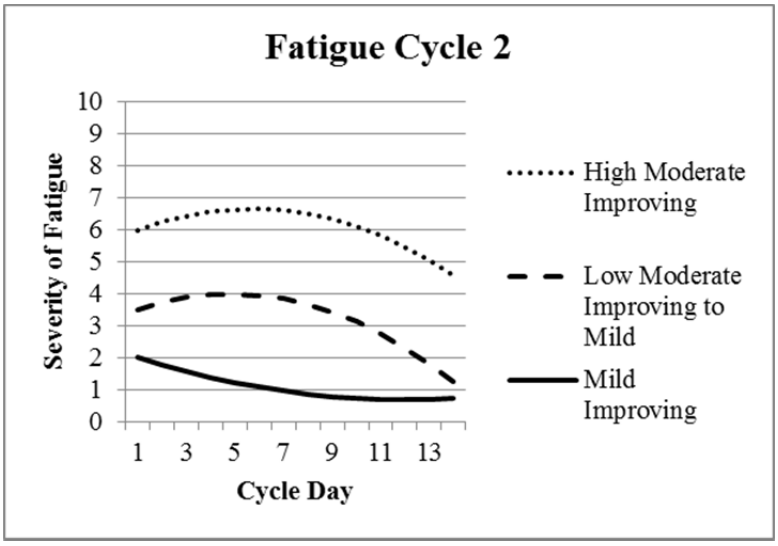

Figure 5.5 Trajectory of fatigue classes during cycle 2.

Of additional concern is the nature of the data collection procedures with regards to the days where all symptoms were reported at a severity of zero. For all days, women had the option of reporting that they had no symptoms in a single response measure. This allowed women to be compliant in calling and indicate quickly no symptoms, but there remains the possibility that women used this option when they may have been experiencing symptoms, wanted to comply with the daily calling, but only had time for a brief call. Table 5.7 provides an example of the number of days where 30 women, taken as random samples of 10 women from each fatigue class during, reported zero on fatigue during cycle 2, the number of days where women reported zero on all symptoms using the single response option compared to the number of days where fatigue was scored as zero while other symptoms were reported individually at severities above zero. From this random subsample, it does appear that there were days where women used the single response score to indicate a fatigue severity of zero, and it is possible that in some cases, this response may not have accurately reflected the symptom severity, but rather the need to shorten the call length. Caution should be used when interpreting the results of our study, especially with regards to the number of days women reported zero severity and the effect of those zeros on the symptom trajectories and parameter means.

Limitations related to sample size and the nature of our data result because this was a secondary data analysis using previously collected data. We were constrained in sample size to those women who met the inclusion criteria and were available for this secondary analysis. Additionally, the sample was fairly homogenous in ethnicity and marital status, possibly limiting the generalizability of the findings. Several variables, which may have informed the analysis and interpretation of the analysis, were

Table 5.7 Example of Days With Reported Zero Severity on Fatigue for Random Sample of 10 Women From Each Fatigue Severity Class During Cycle 2

Fatigue Class Random Sample (*n*=30)	**Total Days Zero on All Symptoms (Single Score)**	**Total Days Zero on Fatigue (Reported Severity on Some Other Symptom)**	**Total Days Zero on Fatigue (Total)**
Mild Improving	17	38	55
Low Moderate Improving to Mild	13	21	34
High Moderate Improving	9	7	16

unavailable, including history of psychological illness or distress, comorbidities, and the use symptom management strategies.

Reported chemotherapy regimens varied in cycle length and dosing. For consistency in capturing the symptom trajectories over a similar period of time for each participant, only data collected during the first 14 days of each cycle were included in the analysis. While this limits the interpretability of the results to the first 14 days of each cycle, it does capture acute phase following chemotherapy administration and only negates the period of time where symptoms may return to a precycle baseline in cases of longer cycles. In addition, some women may have received weekly chemotherapy treatments, which means they potentially received two doses of chemotherapy during the 14 day period of interest. Future work should focus on capturing the entire cycle of chemotherapy, regardless of length, to determine whether and how these symptoms trajectories differ among the classes within and after the first 14 days.

Given the limitations of LGMM, particularly with reference to our sample size and the nature of our data, care should be given in the interpretation of our findings and the application to further research and practice. A next step would certainly involve consideration of other analytic methods for describing the variation in symptom trajectories among women receiving chemotherapy for breast cancer. Other potentially useful methods may include visualization and pattern-based methods and less-restrictive variable-oriented methods such as Latent Growth Curve Modeling, which is used to model quantitative individual differences in developmental change, but does not predict class existence (Sterba & Bauer, 2010). Additionally, Latent Class Growth Analysis may be useful, where associations among repeated measures using multiple class-specific

trajectories are identified, but without variability within the classes (Sterba & Bauer, 2010). Finally, attempts to replicate the findings of our study using LGMM, should consider larger sample sizes to strengthen the confidence in the existence of latent trajectory classes, expecting large variability among the reported symptom severities.

Recommendations for Future Research

This study contributes to a growing body of cancer-related symptom literature, including the development of a person-focused nursing symptom science congruent with person-centered nursing practice (Henly, Wyman, & Findorff, 2011). A unique contribution of this study is the modeling of change over time, using a health trajectory perspective that is dynamic, idiographic, and person focused (Henly et al., 2011). Additionally, this study tested for associations between various theoretically relevant variables and latent class membership for fatigue, disturbed sleep, depressed mood, and anxiety. Given the limitations described above with regards to the usefulness of LGMM and cautions related to sample size and the nature of the data, future research should first seek to determine whether LGMM is the best method for describing patterns of change in symptom presentation where daily severity data are available and many days are reported as mild or zero severity for many symptoms. While we were unable to identify subgroup models for many of the individual symptoms, these symptoms were still present in our sample and warrant discussion in the symptom literature. Methods that include visualization of the data may assist in better understanding the unique patterns with which many symptoms present. Building off the reported findings of this study, future research should focus on determining whether these classes are replicable and stable across multiple cycles beyond cycle 2 and 3 and continuing to study potential correlates,

covariates, or long-term outcomes of class membership, including genetic and molecular factors.

Although we were able to find changes in class membership between cycles, because of methodological limitations, including sample size, we were unable to test for factors unique to those who switched class. Methodological advancements are needed to better understand this phenomenon, with the possible use of visual techniques and advanced statistical methods. Future research should consider varying methods for studying movers and stayers between consecutive cycles of chemotherapy.

This study utilized constructs shared across four symptom theories: the multiplicative nature of symptoms and the existence of antecedents and consequences to the symptoms (Barsevick, 2007; Cleeland et al., 2003; Dodd et al., 2001; Parker, Kimble, Dunbar, & Clark, 2005). In addition, this study assumed that symptoms co-occur in individuals in such a way that those individuals can be subclassified based on their unique symptom trajectories. Potential covariates of class membership were studied, including various demographic and clinical factors. While symptoms did, in fact, co-occur throughout both cycles of chemotherapy in ways unique to the symptom class, the theorized antecedents did not associate with class membership in most cases.

Unfortunately, we were unable to describe a multisymptom latent class model in this sample. Future work should focus on the co-existence of multiple symptoms, attempting to understand the etiological pathways that lead to multisymptom presentation. When designing studies using complex longitudinal data, care should be taken to ensure the sample size accommodates for rare events and variability in severity presentation among highly prevalent symptoms and the ability to test for the existence of

multisymptom trajectory classes. Accounting for these issues in symptom reporting may include methodological considerations such as the use of measures of prevalence versus severity or distress and the use of unique statistical methods for analysis, including visualization, growth modeling with constraints, and cluster analysis.

For all four symptoms, there were differences in class membership based on the presence of other symptoms at moderate to severe levels, suggesting a co-occurrence or co-existence of symptoms. It is unknown whether these symptoms develop as a result of class membership or if class membership is predictive of symptom presentation. One possible explanation for the co-existence of multiple symptoms is that interindividual variability in symptom expression may be related to genetic and molecular factors. This would also explain the lack of relationship between the classes we identified and demographic and clinical factors, where those demographic and clinical factors do not adequately explain genetic differences among individuals (Miaskowski et al., 2014). There is significant evidence to support the role of cytokines and inflammation in symptom production. Cleeland et al. (2003) suggest the concept of sickness behavior, which has been demonstrated in animal models, as an explanation for disease-related symptom presentation. Sickness behavior in animals includes many symptoms that are similar to those experienced by cancer patients. Proinflammatory cytokines, including interleukin -1, tumor necrosis factor-alpha, IFN-alpha, and IL-2, trigger cascade responses that produce symptoms, such as pain, fatigue, cognitive impairment, psychosis, and depressed mood. Clinical evidence suggests that symptoms experienced during cancer treatment may be mediated by cytokines acting on the central and peripheral nervous system. Future research efforts need to combine longitudinal measures of

multiple symptoms in a variety of cancer populations with biologic markers of symptom mechanisms simultaneously collected. Potential associations between symptoms presentation can then be studied, including the possibility that specific biomarkers will correlate with symptom class membership.

Through furthering our understanding of symptom presentation in this unique patient population, we can begin to develop and study potential symptom management strategies to support those who fall into the higher symptom severity classes and those who move into the higher symptom severity classes from a lower class during a previous cycle. We can develop the evidence-base needed to understand women who may be at risk for higher severity of symptoms during chemotherapy and identify factors that may allow early intervention, including education, monitoring, and pharmacological management as needed. By identifying women who may be at increased risk for higher severity of symptoms during chemotherapy and managing those symptoms as appropriate, those women may avoid poor outcomes known to be associated with increased symptom presentation, such as decreases in functional status, loss of employment and productivity, problems with treatment adherence, use of emergency room and hospitalization, and poor outcomes through survivorship (Beck et al., 2010; Bradley, Neumark, Luo, & Schenk, 2007; Byar et al., 2006; Cleeland et al., 2000).

Recommendations for Clinical Practice

The findings of this study suggest that clinical practice must incorporate assessment and management of multiple symptoms early during the course of chemotherapy. Forty-one percent of women reported fatigue at moderate to severe levels, 11% of women reported disturbed sleep at moderate to severe levels, 9% of

women reported depressed mood at moderate to severe levels, and 5% of women reported anxiety at moderate to severe levels during cycle 2. Thirty-six percent of women reported fatigue at moderate to severe level, 19% of women reported disturbed sleep at moderate to severe levels, 6% of women reported depressed mood at moderate to severe levels, and up to 8% of women reported anxiety at moderate to severe levels during cycle 3. Recognizing the existence of a percentage of women who experience individual symptoms at moderate to severe levels across multiple cycles of chemotherapy is important, as not all women will need the same level of symptom management. Of importance, the identified trajectory classes suggest that women who report an initial value of moderate or greater severity of fatigue, disturbed sleep, depressed mood, or anxiety may continue with the symptom at some severity. Many of the classes showed an improvement in trajectory, but not always to a mild level. In addition, the worsening disturbed sleep class trajectories suggest that these women, who reported an initial severity of moderate level, experienced an increase in the symptom during the 14 days. Clinicians should be aware that women who report an initial symptom severity on the 1st day of chemotherapy at moderate to severe levels may benefit from increased symptom surveillance and management. This small percentage of women who reported symptoms at moderate to severe levels were at increased risk for development of a variety of co-existing symptoms, including fatigue, disturbed sleep, depressed mood, anxiety, nausea, and pain. Additionally, these women may have been at increased risk for poorer outcomes, including decreased activity and missed work. Understanding that the presence of severe symptoms during cycle 2 may predict symptom presentation during cycle 3 points to the importance of symptom management during early cycles of

chemotherapy. Practitioners need to assess for and be aware of symptoms early in the course of chemotherapy, as the results of this study suggest that symptoms persist from one cycle to the next. Patient and caregiver education should be directed at not only self-care and pharmacological management strategies but also at recognizing and reporting the existence of symptoms to practitioners. Additionally, practitioners need to be aware that symptoms often co-occur and that the dynamic process of multiple symptoms may be influenced by management of a single symptom. Symptom management, as derived from the evidence-base, needs to be aimed at those women most at-risk for the development of significant symptom severity.

Summary

Results of this study add to our knowledge of the symptoms experienced by women undergoing chemotherapy treatment for breast cancer. This study demonstrates that symptoms are highly prevalent, often at moderate to severe levels and that symptom trajectories are dynamic. Additionally, this study points to the existence of distinct classes of women who experience moderate to severe levels of fatigue, disturbed sleep, depressed mood, and anxiety. While the majority of women experience low to moderate levels of symptoms, a small, but significant percentage of women experience symptoms at moderate to severe levels throughout two cycles of chemotherapy. While demographic factors were not related to symptom trajectory class, the type of chemotherapy and the presence of other symptoms was. Finally, higher overall symptom severity during cycle 2 predicted the presence of individual symptoms at moderate to severe levels during cycle 3. Further research is needed to support the existence of these classes, with larger samples and over additional chemotherapy cycles. Exploration of movers and stayers in

class membership across multiple cycles is needed. Further examination of co-existing symptoms over multiple cycles of chemotherapy, using longitudinal data reporting on the severity of symptoms in needed. Future research designs may consider the usefulness of LGMM in capturing the dynamic nature of the symptom experience, with inherent limitations and the potential to underestimate symptom severity.

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