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Distinct Trajectories of Fatigue and Sleep Disturbance in Women Receiving Chemotherapy for Breast Cancer

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Abstract

Purpose/Objectives—To examine self-reported severity of fatigue and disturbed sleep experienced daily by women with breast cancer during multiple cycles of chemotherapy, exploring potential classes of women experiencing similar symptom trajectories.

Design—In a secondary analysis, classes of women experiencing similar patterns of fatigue and disturbed sleep were identified.

Setting—Oncology clinics in the United States.

Sample—166 women with breast cancer receiving chemotherapy.

Methods—Severity scores were self-reported daily using an automated system. Classes of fatigue and disturbed sleep severity were identified using latent growth mixture modeling.

Main Research Variables—Fatigue, disturbed sleep, age, stage of disease, education, employment, marital status, chemotherapy regimen, hours lying down, and missed work.

Findings—Three fatigue classes were identified: mild decreasing (59% cycle 2, 64% cycle 3), low moderate decreasing (30% cycle 2, 25% cycle 3), and high moderate decreasing (11% both cycles). Two disturbed sleep classes were identified: mild decreasing (89% cycle 2, 81% cycle 3) and increasing (11% cycle 2, 19% cycle 3). Women in the high moderate decreasing fatigue class

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were more likely to have received doxorubicin (p = 0.02) and spent more hours lying down (p = 0.02).

Conclusions—Patterns of symptom trajectories for fatigue and disturbed sleep were distinguished by baseline symptom severity.

Implications for Nursing—Identification of women at risk for fatigue and disturbed sleep may allow clinicians to intensify symptom management.

Keywords

breast cancer; sleep; fatigue; latent growth mixture modeling; latent class analysis; symptoms

Treatment for breast cancer is associated with toxicities that significantly diminish quality of life, interfere with activity and employment, and interrupt treatment (Bradley, Neumark, Luo, & Schenk, 2007; Cleeland et al., 2003). Considerable evidence suggests variability in symptom trajectories during the course of chemotherapy treatment for breast cancer. However, current evidence has not identified individuals at risk for severe symptom trajectories prior to treatment initiation and symptom escalation (Dodd, Cho, Cooper, & Miaskowski, 2010).

Fatigue and disturbed sleep are common and cause distress in women receiving chemotherapy for breast cancer (Beck et al., 2010; Berger & Higginbotham, 2000; Huang, Chen, Liang, & Miaskowski, 2014; Kuo, Chiu, Liao, & Hwang, 2006). Although fatigue increases with the initiation of treatment, it does not increase with time (Byar, Berger, Bakken, & Cetak, 2006; Jacobsen et al., 1999; Nieboer et al., 2005; Payne, Piper, Rabinowitz, & Zimmerman, 2006). During chemotherapy, the frequency and duration of nighttime awakening and difficulty falling asleep increase and women report the poorest sleep quality on the first night following treatment (Beck et al., 2010; Berger & Higginbotham, 2000; Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002). Several potential antecedents to and outcomes of fatigue and disturbed sleep during chemotherapy have been studied. For example, although age is not reported to relate to fatigue during chemotherapy, older adult women experience increased disturbed sleep (Beck et al., 2010; Browall, Ahlberg, Persson, Karlsson, & Danielson, 2008; Colagiuri et al., 2011; de Jong, Candel, Schouten, Abu-Saad, & Courtens, 2004; de Jong, Kester, Schouten, Abu-Saad, & Courtens, 2006; Goldstein et al., 2012; Jacobsen et al., 1999; Von Ah, Kang, & Carpenter, 2008). Reports of the relationship between marital status and fatigue or disturbed sleep during chemotherapy are conflicting (Colagiuri et al., 2011; de Jong et al., 2004; Huang et al., 2014; Jacobsen et al., 1999; Van Onselen et al., 2012). Income and disease stage are not reported to relate to fatigue or sleep disturbance during chemotherapy for breast cancer (Beck et al., 2010; Colagiuri et al., 2011; de Jong et al., 2004; Von Ah et al., 2008). In addition, fatigue and disturbed sleep may predict decreases in activity level during chemotherapy for breast cancer (Berger, 1998; Berger & Farr, 1999; Berger & Higginbotham, 2000; Colagiuri et al., 2011; de Jong et al., 2004; Jacobsen et al., 1999).

The current study was framed by the Dynamic Symptoms Model, which describes the complex nature and longitudinal trajectory of the symptom experience, incorporating the

potential for distinct patterns of symptom change with time that may be preceded by antecedent variables and may influence outcomes (Brant, Dudley, Beck, & Miaskowsi, 2016). Consistent with the model, the current study includes specific antecedents (demographic and clinical variables), growth parameters of the symptom experience, and consequences (days of missed work and hours spent lying down). Advances in longitudinal statistical modeling have allowed for newer methodologic approaches to studying classes of symptom trajectories, identifying homogeneous classes of people who share common symptom trajectories. Several investigators have applied subgroup analyses to symptom data for women with breast cancer during various stages of the disease, but only one report of classes of disturbed sleep trajectories and no reports of classes of fatigue trajectories were found in the literature (Dunn et al., 2011; Lam et al., 2010; Langford et al., 2016; Van Onselen et al., 2012).

The purpose of the current study was to examine self-reported severity of fatigue and disturbed sleep experienced daily by women with breast cancer during multiple cycles of chemotherapy and to explore potential classes of women experiencing similar symptom trajectories. The specific aims were to (a) determine the distinct trajectory classes associated with the severity of fatigue and disturbed sleep reported by women undergoing cycles 2 and 3 of chemotherapy for breast cancer, (b) determine if class membership is determined by various antecedent variables, and (c) determine if class membership is associated with days of missed work and hours spent lying down. Understanding trajectories of symptoms may elucidate common etiologies, which may inform the development of targeted symptom interventions.

Methods

Participants and Setting

The current 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. Studies 1 and 2 tested the use of an automated system for monitoring and managing symptoms during chemotherapy. Study 3 was an observational study using the same automated system for data collection. A detailed description of the sampling procedures for the parent studies and automated system are provided elsewhere (Mooney, Beck, Friedman, Farzanfar, & Wong, 2014; Mooney et al., 2017).

For study 1, participants were recruited from Cancer Centers of the Carolinas in Greenville, South Carolina, and Intermountain Hematology/Oncology Associates, Wasatch Hematology/Oncology Associates, and Huntsman Cancer Institute, all in Salt Lake City, Utah. For study 2, participants were recruited from Huntsman Cancer Institute and Vanderbilt University Medical Center in Nashville, Tennesee. For study 3, participants were recruited from Huntsman Cancer Institute. Eligibility requirements for this analysis included being a woman diagnosed with breast cancer at initial treatment with chemotherapy, completing study measures through cycles 2 and 3, and reporting data for at least three days during each cycle to allow for application of the analytic methods. Women receiving radiation therapy or biotherapy agents were excluded. Although participants were randomly assigned to a usual care group or a symptom management intervention group in study 1 and 2, differences were

found in reported symptoms between groups in study 2 only. Therefore, data collected from eligible participants randomized to the control group in study 2 and data from all eligible participants in studies 1 and 3 were used in this secondary analysis. Cycles 2 and 3 were examined because symptom data were collected during only these cycles in study 1. To accommodate for varying cycle lengths, only data from the first 14 days of each cycle were included.

The original sampling frame consisted of 259 women with breast cancer who were pooled from the three parent studies. 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 (cycle 2) and 155 (cycle 3) completed measures on at least three days, which was sufficient to apply the analytic methods using Monte Carlo estimation (Muthén & Muthén, 2000).

Measures

Demographic and disease-related data (age, stage of disease, education, employment, marital status, and chemotherapy regimen) were collected at study entry from the participants and their medical record. Participants called the automated system daily to report the presence and severity of fatigue and disturbed sleep, using single-item indicators, with acceptable reliability and validity (Cleeland & Mendoza, 2011; Mooney et al., 2014). Modeled after common symptom assessment tools, the automated system employed conditional branching such that participants were first asked, “During the past 24 hours did you experience (symptoms)?” A “yes” response yielded a question asking the participant to score the symptom severity using a Likert-type scale, with scores ranging from 1 (low) to 10 (high). Participants also reported hours spent lying down; employed participants reported whether they were able to go to work each day.

Procedures

All parent studies and this secondary analysis were approved by the University of Utah Institutional Review Board. Participants were identified only by their original study identification number. All participants signed a written, informed consent to participate in the original parent studies, which included language giving permission for the data collected to be used in additional scientific investigations.

Statistical Analysis

Mplus, version 6.0, was used for mixture model analyses, and SPSS®, version 23.0, was used for data management and analysis of demographic and clinical variables. The data were cleaned and transformed to a person–period data set, containing a participant identifier, a time indicator (time of measurement), outcome variables (symptom scores for each symptom on a Likert-type scale ranging from 0–10), and correlate variables (demographic and disease-related variables, hours spent lying down, and days of missed work). Alpha was set at 0.05, and no adjustments were made for multiplicity in this exploratory study. Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores.

Latent growth mixture modeling (LGMM) allows for the identification of discrete classes of individuals based on common trajectories 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 (Muthén & Muthén, 2000). Using LGMM, an initial one-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 with its own set of parameter values (intercept and slope) (Singer & Willett, 2003). Missing data were accommodated through use of a full information maximum likelihood method. Stepwise models were evaluated on multiple fit indices, including the Bayesian information criterion (BIC) and entropy, with smaller BIC and entropy close to 1 indicating a better model fit (Colder, Campbell, Ruel, Richardson, & Flay, 2002; Jung & Wickerama, 2008; Muthén & Muthén, 2000). In addition, the best-fitting model was examined for the number of participants in each class (greater than 5% of the sample) and graphed visually to determine if the predicted trajectories were clinically and theoretically relevant (Jung & Wickerama, 2008).

After determining the best model fit for the data, the model-predicted class membership for each individual was obtained using posterior probabilities. Although the model-predicted class assignment is uncertain, high entropy and high posterior probabilities suggest that model-predicted class assignments could be considered observed variables. Model-predicted class memberships then were used to test for differences among the classes on antecedents and consequences of class membership. Chi-square was used to test for associations among categories across classes in antecedents (stage of disease, education, employment, marital status, and chemotherapy regimen). Independent-samples t tests and analysis of variance (ANOVA) were used to test for differences between the classes in age and outcomes (hours spent lying down and days of missed work) (de Jong et al., 2004). 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. Small cell sizes, with an expected frequency of five or less, were accounted for with use of the more conservative Fisher's exact chi-square (Green & Salkind, 2008). In cases for which 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 and outcomes. In cases for which equal variances were not assumed, Dunnett's C test was used (Green & Salkind, 2008).

Results

Patient demographic and clinical characteristics are summarized in Table 1. Participants ranged in age from 24–80 years ($\overline{\mathrm{X}}=52.9\ \mathrm{years}$, SD = 10.8). Most participants were White, married, and unemployed. The largest proportion of the sample was diagnosed with stage II disease and had some education beyond high school. Women in the sample received any of 12 different chemotherapy regimens. Daily call compliance was 78.4% (cycle 2) and 78% (cycle 3). The prevalence of fatigue and disturbed sleep and the percentage of days reported

with severity of 0, severity of 1–10, and severity of 4–10 (moderate to severe levels) are reported in Table 2.

Multiclass latent growth mixture models were evaluated for fatigue and disturbed sleep, and fit indices are presented in Table 3. Intercept, slopes, and quadratic terms are presented in Table 4, and trajectory graphs are presented in Figure 1. 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 term. For fatigue, a three-class solution was selected during both cycles. Most women were in the mild decreasing fatigue class (59% for cycle 2, 64% for cycle 3), with a low fatigue severity level at day 1 of each cycle ($\overline{X}=2.25$, SD = 0.29; $\overline{X}=1.76$, SD = 0.24). Individuals in the low moderate decreasing fatigue class (30% for cycle 2, 25% for cycle 3) had a moderate fatigue severity level at day 1 of each cycle ($\overline{X}=3.21$, SD = 0.52; $\overline{X}=2.52$, SD =0.39), and individuals in the high moderate decreasing fatigue class had a high moderate level of fatigue at day 1 ($\overline{X}=5.66$, SD = 0.73; $\overline{X}=5.43$, SD = 0.51), maintaining that level through day 5, and then had a slight decline in fatigue to day 14 of each cycle. In both cycles, 11% of participants were in the high moderate fatigue class.

For disturbed sleep, two classes were identified during each cycle. Most participants were in the mild decreasing disturbed sleep classes (89% for cycle 2, 81% for cycle 3) and had a low severity of disturbed sleep at day 1 ($\overline{X}=1.74$, SD = 0.2; $\overline{X}=0.87$, SD = 0.13) for each cycle and remained stable during the 14 days. A smaller percentage of participants were in the moderate increasing (cycle 2) and mild increasing (cycle 3) disturbed sleep classes (11% in cycle 2, 19% in cycle 3), with a higher severity of disturbed sleep at cycle day 1 in both cycles ($\overline{X}=3.76$, SD = 1.05; $\overline{X}=1.66$, SD = 0.49) that increased during the 14 days.

Results of the tests of differences and associations among categories across classes on the demographic variables are presented in Table 5 for the fatigue classes and Table 6 for the disturbed sleep classes. All tests were nonsignificant, except for chemotherapy regimen. Women who received doxorubicin were more likely to be in the high moderate decreasing fatigue class when compared to the mild decreasing fatigue class in both cycles 2 (χ^2= 7.75, p = 0.02) and 3 (χ^2 = 8.59, p = 0.01).

Independent-samples t tests and ANOVAs for hours spent lying down and days of missed work were nonsignificant, except for hours spent lying down during cycle 2 for fatigue class. During cycle 2, the number of hours spent lying down was statistically significantly higher in the high moderate decreasing fatigue class ($\overline{X}=12.36$, SD = 3.77) when compared to the mild decreasing fatigue class ($\overline{X}=10$, SD = 2.54) (F[2, 44] = 2.03, p = 0.02).

Discussion

Results of the current study contribute to a growing body of literature concerned with the trajectories of symptoms experienced by women receiving chemotherapy for breast cancer. Distinct patterns of fatigue and disturbed sleep were identified and antecedents and consequences to those patterns were studied, consistent with the Dynamic Symptoms Model (Brant et al., 2016). Fatigue was reported at a severity greater than 0 by more than 90% of

women, consistent with the high prevalence of fatigue during chemotherapy found in other studies (Bender, Ergÿn, Rosenzweig, Cohen, & Sereika, 2005; Bower et al., 2011; Browall, Persson, Ahlberg, Karlsson, & Danielson, 2009; Downie, Mar Fan, Houédé-Tchen, Yi, & Tannock, 2006; Gaston-Johansson, Fall-Dickson, Bakos, & Kennedy, 1999; Given, Given, Azzouz, & Stommel, 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 occurrence to model change. Three patterns of fatigue were described, including mild decreasing fatigue, low moderate decreasing fatigue, and high moderate decreasing fatigue classes. Across all three classes, fatigue improved during the first 14 days of chemotherapy during both cycles but remained present at day 14, consistent with previous findings that fatigue persists throughout treatment but does not worsen with time (Byar et al., 2006; de Jong et al., 2004; Jacobsen et al., 1999; Payne et al., 2006; Sitzia & Huggins, 1998). In addition, the growth factors during the two cycles of chemotherapy suggest that fatigue in cycle 2 did not differ in pattern during cycle 3, similar to previously reported findings that fatigue does not differ in subsequent chemotherapy cycles (Berger, 1998; Jacobsen et al., 1999).

Disturbed sleep was reported by more than 70% of women, which is slightly higher than previous reports (Beck et al., 2010; Bender et al., 2005; Berger & Higginbotham, 2000; Bower et al., 2011; Fortner et al., 2002; Given et al., 2001; Janz et al., 2007; Kim et al., 2008; Lee, Dibble, Pickett, & Luce, 2005). Two patterns of disturbed sleep were described, including a mild decreasing disturbed sleep class during both cycles, a moderate increasing disturbed sleep class during cycle 2, and a mild increasing disturbed sleep class during cycle 3. Although the severity of disturbed sleep improved slightly with time in the mild decreasing disturbed sleep class during both cycles, the severity of disturbed sleep worsened in the increasing disturbed sleep classes during both cycles, suggesting that some women experienced disturbed sleep progression.

The current findings conflict with a report by Van Onselen et al. (2012), in which three classes of women with sleep disturbance during the six months following surgery for breast cancer were identified: a low and high class, but also a decreasing class that represented 5.3% of their sample (N = 398). The conflicting number of classes may be a result of differing instrumentation and timing of measures and use of model constraints.

None of the demographic or clinical characteristics was found to be associated with class membership, except for chemotherapy regimen. The current findings are consistent with several reports that age and fatigue are not related (Browall et al., 2008; de Jong et al., 2004, 2006; Goldstein et al., 2012; Jacobsen et al., 1999; Von Ah et al., 2008). Findings relating age and disturbed sleep are inconsistently reported, and this relationship was not found in the current sample (Beck et al., 2010; Browall et al., 2008; Colagiuri et al., 2011; Van Onselen et al., 2012). Similarly, the relationship between marital status and fatigue is inconsistently reported, with no relationship being found in the current sample (de Jong et al., 2004; Huang et al., 2014; Jacobsen et al., 1999). The lack of relationship between marital status and disturbed sleep is similar to findings of Colagiuri et al. (2011) and Van Onselen et al. (2012). Although the current finding that employment status does not predict fatigue is supported in the literature, Van Onselen et al. (2012) found an association between

unemployment and disturbed sleep trajectory (de Jong et al., 2004, 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; de Jong et al., 2004; Jacobsen et al., 1999; Van Onselen et al., 2012; Von Ah & Kang, 2008). A lack of sample variation on these demographics and a relatively small sample size in the current study may explain some conflicting findings. Additional research is needed to explore other personal characteristics, including molecular determinants (Cleeland et al., 2003; Miaskowski et al., 2014).

Women in the current sample who received doxorubicin were more likely to be in the high moderate decreasing fatigue class when compared to the mild decreasing fatigue class. The effects of chemotherapy type on fatigue severity have been reported with inconsistent findings (Berger, 1998; Berger & Farr, 1999; de Jong et al., 2006). Although doxorubicin use had a significant effect on fatigue class membership in the current sample, whether that effect is dose-dependent or related to other agents received in combination with doxorubicin is unknown, and additional studies are needed.

Although days of missed work were 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. However, only 37% of the sample was employed. A larger cohort of employed participants may have revealed a significant relationship between these variables.

Increased hours spent lying down was associated with membership in the high moderate decreasing fatigue class when compared to the mild decreasing fatigue class during cycle 2 only, consistent with other studies (Berger & Farr, 1999; Berger & Higginbotham, 2000; de Jong 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, and further examination with larger samples may better highlight this association.

Limitations

Particular care should be given to the nature of the data in the current study and the usefulness of LGMM in modeling symptom trajectories with daily reporting. In the identified models, and given the use of daily symptom severity reporting, more variability is likely within the classes than the presented growth factors adequately represent. In addition, many days for which women reported 0 severity on symptoms may have decreased the aggregate means for the growth factors. The current study was limited by a lack of data for several relevant variables of interest, including comorbidities, menopausal status, symptom management, and previous sleep patterns, and the inability to separate varying chemotherapy regimens because of sample size. The use of a single-item measure for symptom severity has limitations, including the risk of increased measurement error when compared to measures using multiple items. However, single-item measures are reliable and valid for collecting symptom data and minimize participant burden when monitoring multiple symptoms over time. In addition, the sample size was modest and the sample was fairly homogenous in demographic variables, including marital status and ethnicity. Although 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.

Implications for Nursing

The findings of the current study suggest that clinical practice must incorporate assessment and management of fatigue and disturbed sleep early during the course of chemotherapy. Recognizing the existence of a percentage of women who experience fatigue and disturbed sleep at moderate to severe levels across multiple cycles of chemotherapy is important, because not all women will need the same level of symptom management. The identified trajectory classes suggest that women who report an initial value of moderate or greater severity of fatigue or disturbed sleep may continue with the symptom. Many of the classes showed an improvement in trajectory, but not always to a mild level. In addition, the existence of increasing disturbed sleep class trajectories suggests that some women experienced a worsening in disturbed sleep. Clinicians should be aware that women who report an initial symptom severity at moderate to severe levels may benefit from increased symptom surveillance and management. This is particularly important because these women may be at increased risk for poorer outcomes, including decreased activity and missed work as in the current sample, as well as decreased quality of life and increased healthcare resource use (Beck et al., 2010; Bradley et al., 2007; Byar et al., 2006; Cleeland, 2000). Potential interventions for at-risk women may include patient and caregiver education regarding self-care, careful monitoring and assessment, and referral or pharmacologic intervention. Additional research should focus on determining whether these classes are replicable and stable across multiple cycles and continue to study potential antecedents of class membership, including sleep-related variables, comorbidities, and genetic and molecular factors (Miaskowski et al., 2014).

Conclusion

The current results suggest that women receiving chemotherapy for breast cancer experience distinct trajectories of severity of fatigue and disturbed sleep. Regardless of class membership, and except for a small percentage of women in the worsening disturbed sleep classes, severity of symptoms remained fairly stable or improved during the chemotherapy cycle. Additional research should focus on replication of the current study and identifying potential correlates of class membership to clarify which individuals are likely to experience severe fatigue and disturbed sleep during chemotherapy.

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Knowledge Translation

- Fatigue and disturbed sleep occur at moderate to severe levels for a percentage of women throughout chemotherapy.
- Women receiving chemotherapy for breast cancer experience distinct trajectories of severity of fatigue and disturbed sleep.
- Clinicians should be aware that women who report an initial symptom severity on the first day of chemotherapy at moderate to severe levels may benefit from increased symptom surveillance and management.

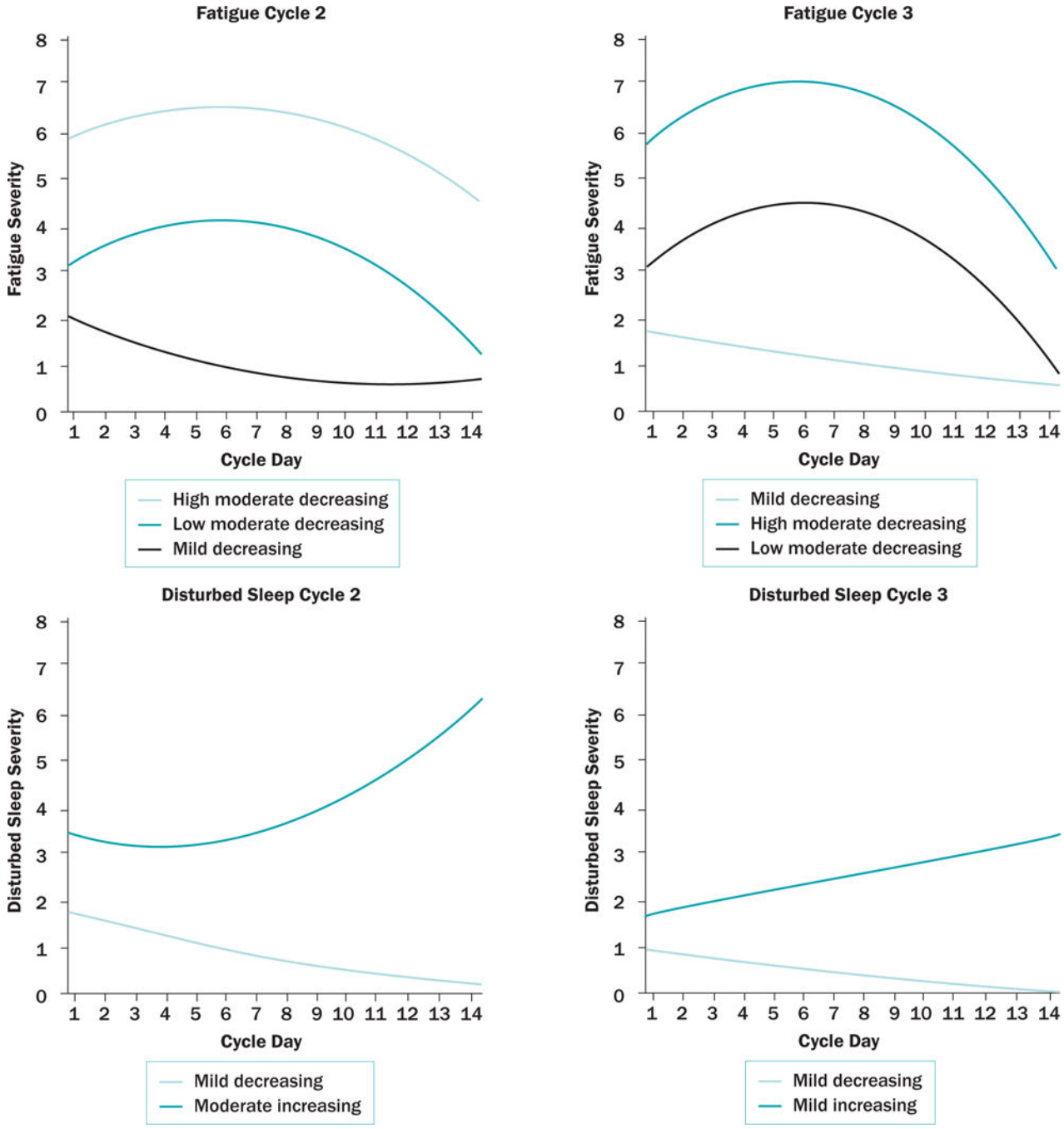

FIGURE 1.
Individual Symptom Trajectory Models

TABLE 1

Sample Characteristics (N = 166) Characteristic n %

Characteristic	n	%
Ethnicity		
Non-Hispanic	162	98
Hispanic	2	1
Unknown	2	1
Marital status		
Partnered	123	74
Non-partnered	41	25
Unknown	2	1
Employment status		
Not employed	103	62
Full-time	48	29
Part-time	13	8
Unknown	2	1
Education		
Some high school	6	4
High school graduate	31	19
Some college	52	31
Associate degree	15	9
Bachelor’s degree	36	22
Postgraduate	22	13
Unknown	4	3
Income ($)		
Less than 9,999	8	5
10,000–29,999	16	10
30,000–49,999	37	22
50,000–69,999	20	12
70,000 or more	57	34
Unknown	10	6
Declined to state	18	11
Stage of disease		
I	20	12
II	67	40
III	38	23
IV	36	22
Unknown	5	3
Chemotherapy regimen		
Cyclophosphamide with doxorubicin	68	41
Docetaxel	23	14
Cyclophosphamide with methotrexate and 5-fluorouracil	16	10

Characteristic	n	%
Docetaxel and carboplatin	13	8
Cyclophosphamide with docetaxel	12	7
Cyclophosphamide with doxorubicin and docetaxel	9	5
Cyclophosphamide with doxorubicin and 5-fluorouracil	6	4
Cyclophosphamide with 5-fluorouracil	4	2
Other	15	9

Note. Because of rounding, percentages may not total 100.

TABLE 2

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

	Reported Severlty Greater Than 0 at Least Once		Days of Severlty Greater Than 0			Reported Severlty Greater Than 3 at Least Once		Days of Severlty Greater Than 3			Days Symptom Reported Level 0		Days Symptom Reported Level 1-10		Days Symptom Reported Level 4-10	
Symptom	**n**	**%**	$\overline{X}$	**SD**	**Range**	**n**	**%**	$\overline{X}$	**SD**	**Range**	**n**	**%**	**n**	**%**	**n**	**%**
Cycle 2																
Fatigue[a]	153	93	7.53	3.69	1–14	115	70	5.09	3.47	1–14	659	36	1,152	64	585	32
Disturbed sleep[b]	126	76	3.63	2.56	1–13	103	62	2.87	2.07	1–13	1,354	75	457	25	296	16
Cycle 3																
Fatigue[a]	148	95	7.09	3.93	1–14	105	67	4.95	3.7	1–14	654	38	1,050	62	520	31
Disturbed sleep[b]	110	71	3.4	2.64	1–13	85	55	2.46	1.76	1–11	1,330	78	374	22	209	12

[a] N = 165 for cycle 2 and 156 for cycle 3; 1,811 (78%) days reported cycle 2; 1,704 (78%) days reported cycle 3; 499 (22%) days missing cycle 2; 480 (22%) days missing cycle 3

[b] N = 84 for cycle 2 and 75 for cycle 3; 948 (81%) days reported cycle 2; 825 (80%) days reported cycle 3; 228 (19%) days missing cycle 2; 211 (20%) days missing cycle 3

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TABLE 3

Model Fit for Latent Growth Mixture Models

Model[a]	Log Likelihood	BIC	Entropy	Posterior Probability	Class Proportions
Fatigue					
Cycle 2					
1 class	−4,309.41	8,651.7	NA	NA	NA
2 class	−3,954.18	7,958.98	0.944	0.988, 0.989	69%, 31%
3 class	−3,847.23	7,742.81	0.944	0.977, 0.95, 0.982	59%, 30%, 11%
4 class	−3,800.81	7,657.7	0.943	0.95, 0.96, 0.984, 0.935	57%, 12%, 22%, 10%
Cycle 3					
1 class	−4,062.06	8,156.06	NA	NA	NA
2 class	−3,652.62	7,344.68	0.963	0.998, 0.968	72%, 28%
3 class	−3,570.33	7.187.62	0.941	0.986, 0.95, 0.96	64%, 25%, 11%
4 class	−3,538.36	7,131.18	0.881	0.935, 0.869, 1, 0.956	53%, 22%, 22%, 3%
Disturbed sleep					
Cycle 2					
1 class	−4,067.91	8,168.7	NA	NA	NA
2 class	−3,906.86	7,854.34	0.984	0.997, 0.995	89%, 11%
3 class	−3,855.66	7,759.66	0.958	0.945, 0.989, 0.968	84%, 10%, 5%
Cycle 3					
1 class	−3,582.73	7,197.38	NA	NA	NA
2 class	−3,441.79	6,923.02	0.925	0.981, 0.98	81%, 19%
3 class	−3,385.73	6,818.42	0.962	0.987, 0.995, 0.969	82%, 14%, 5%

[a]Classes were added stepwise to the model to determine the solution that best fit the data, evaluated on the BIC and entropy, and examined for the number of participants in each class and graphed visually.

BIC—Bayesian information criterion; NA—not applicable

Note. Shading indicates the selected model solution.

TABLE 4

Growth Factor Means and Predicted Frequencies for Each Class

Class	Intercept	Slope	Quadratic Term	Class Count
Fatigue				
Cycle 2				
Mild decreasing	2.25*	−0.26*	0.01*	97.94
Low moderate decreasing	3.21*	0.32	−0.03*	51.46
High moderate decreasing	5.66*	0.34	0.01	18.26
Cycle 3				
Mild decreasing	1.76*	−0.12	0.00	106.24
Low moderate decreasing	2.52*	0.65*	−0.06*	41.5
High moderate decreasing	5.43*	0.6*	−0.06*	18.26
Disturbed sleep				
Cycle 2				
Mild decreasing	1.74*	−0.2*	0.01	145.85
Moderate increasing	3.76*	−0.28	0.03	18.15
Cycle 3				
Mild decreasing	0.87*	−0.07	0.00	133.65
Mild increasing	1.66*	0.14	0.00	31.35

* $p < 0.05$

TABLE 5

Tests of Difference in Means and Associations Among Categories for Antecedents and Outcomes of Fatigue Class Membership

	Mild Decreasing (N = 95)		Low Moderate Decreasing (N = 50)		High Moderate Decreasing (N = 19)		
Characteristic	$\overline{X}$	**SD**	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**Omnibus Test**
Cycle 2							
Age (years)	51.79	10.7	53.56	10.2	57.51	11.76	F(2, 159) = 2.35, p = 0.1
Hours spent lying down	10	2.54	10.79	2.64	12.36	3.77	F(2, 44) = 2.03, p = 0.02 *
Days missed work (n = 20)	1.9	1.52	3.13	2.03	2.5	2.12	F(2, 17) = 1.05, p = 0.37
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**Omnibus Test**
Education							$\chi^2 = 2.16$, p = 0.99
Less than high school	4	4	1	2	1	5	
High school	20	21	8	16	3	16	
Undergraduate	57	60	33	66	13	68	
Postgraduate	12	13	7	14	2	11	
Unknown	2	2	1	2	–	–	
Marital status							$\chi^2 = 1.54$, p = 0.85
Married	72	76	37	74	13	68	
Not married	23	24	12	24	6	32	
Unknown	–	–	1	2	–	–	
Employment							$\chi^2 = 2.91$, p = 0.58
Employed	32	34	22	44	6	32	
Not employed	63	66	27	54	13	68	
Unknown	–	–	1	2	–	–	
Stage							$\chi^2 = 4.6$, p = 0.8
I	13	14	5	10	2	11	
II	34	36	25	50	8	42	
III	24	25	10	20	4	21	
IV	21	22	10	20	5	26	
Unknown	3	3	–	–	–	–	

Characteristic	Mild Decreasing (N = 95) $\overline{X}$	SD	Low Moderate Decreasing (N = 50) $\overline{X}$	SD	High Moderate Decreasing (N = 19) $\overline{X}$	SD	Omnibus Test
Doxorubicin							$\chi^2 = 7.75$, p = 0.02 *
Yes	41	43	27	54	14	74	
No	47	50	20	40	3	16	
Unknown	7	7	3	6	2	11	
Taxane							$\chi^2 = 3.01$, p = 0.22
Yes	34	36	14	28	3	15	
No	54	57	33	66	14	74	
Unknown	7	7	3	6	2	11	

Characteristic	Mild Decreasing (N = 97) $\overline{X}$	SD	Low Moderate Decreasing (N = 39) $\overline{X}$	SD	High Moderate Decreasing (N = 18) $\overline{X}$	SD	Omnibus Test
Cycle 3							
Age (years)	52.9	10.31	52.53	12	54.13	12	F(2, 150) = 0.13, p = 0.88
Hours spent lying down	10.44	2.94	10.71	2.51	10.05	2.51	F(2, 150) = 0.35, p = 0.7
Days missed work (n = 27)	1.33	1.5	1.43	1.72	2.2	1.65	F(2, 24) = 0.51, p = 0.61
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**Omnibus Test**
Education							$\chi^2 = 3.47$, p = 0.75
Less than high school	3	3	1	3	1	5	
High school	20	21	5	13	5	28	
Undergraduate	58	60	26	66	10	56	
Postgraduate	12	12	7	18	2	11	
Unknown	4	4	–	–	–	–	
Marital status							$\chi^2 = 0.78$, p = 0.74
Married	69	71	29	74	15	83	
Not married	26	27	10	26	3	17	
Unknown	2	2	–	–	–	–	
Employment							$\chi^2 = 0.06$, p = 1.00

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	Mild Decreasing (N = 95)		Low Moderate Decreasing (N = 50)		High Moderate Decreasing (N = 19)		
Characteristic	$\overline{X}$	**SD**	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**Omnibus Test**
Employed	36	37	15	38	7	39	
Not employed	59	61	24	62	11	61	
Unknown	2	2	–	–	–	–	
Stage							$\chi^2 = 7.69$, p = 0.25
I	11	11	6	15	–	–	
II	37	38	20	51	9	50	
III	27	28	5	13	6	33	
IV	22	23	7	18	3	17	
Unknown	–	–	1	3	–	–	
Doxorubicin	–	–					$\chi^2 = 8.59$, p = 0.01 *
Yes	45	46	22	56	15	83	
No	51	53	16	41	3	17	
Unknown	1	1	1	3	–	–	
Taxane							$\chi^2 = 6.06$, p = 0.05
Yes	38	39	11	28	2	11	
No	58	60	27	69	16	89	
Unknown	1	1	1	3	–	–	

* $p < 0.05$

TABLE 6

Tests of Difference in Means and Associations Among Categories for Antecedents and Outcomes of Disturbed Sleep Class Membership

	Mild Decreasing (N = 139)		Moderate Increasing (N = 25)		
Characteristic	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**Omnibus Test**
Cycle 2					
Age (years)	53.06	10.63	52.03	11.54	t(159) = 0.19, p = 0.66
Hours spent lying down	10.66	2.59	9.87	3.88	t(28.1) = 0.98, p = 0.33
Days missed work (n = 20)	2.44	1.93	2.5	1.29	t(18) = 0.00, p = 0.95
Characteristic	**n**	**%**	**n**	**%**	**Omnibus Test**
Education					$\chi^2 = 1.08$, p = 0.94
Less than high school	6	4	–	–	
High school	26	19	4	16	
Undergraduate	85	61	18	72	
Postgraduate	18	13	3	12	
Unknown	4	3	–	–	
Marital status					$\chi^2 = 1.01$, p = 0.61
Married	104	75	17	68	
Not married	33	24	8	32	
Unknown	2	1	–	–	
Employment					$\chi^2 = 0.87$, p = 0.64
Employed	48	35	11	44	
Not employed	88	63	14	56	
Unknown	3	2	–	–	
Stage					$\chi^2 = 3.8$, p = 0.4
I	14	10	6	24	
II	57	41	10	40	
III	33	24	4	16	
IV	31	22	5	20	
Unknown	4	3	–	–	

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	Mild Decreasing (N = 139)		Moderate Increasing (N = 25)		
Characteristic	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**Omnibus Test**
Doxorubicin					$\chi^2 = 0.22$, p = 0.66
Yes	68	49	14	56	
No	60	43	10	40	
Unknown	11	8	1	4	
Taxane					$\chi^2 = 0.25$, p = 0.65
Yes	44	32	7	28	
No	84	60	17	68	
nknown	11	8	1	4	

	Mild Decreasing (N = 137)		Mild Increasing (N = 18)		
Characteristic	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**Omnibus Test**
Cycle 3					
Age (years)	52.79	10.95	52.7	9.18	t(150) = 0.00, p = 0.97
Hours spent lying down	10.69	2.74	9.65	3.23	t(150) = 1.48, p = 0.14
Days missed work (n = 27)	1.5	1.71	1.6	1.52	t(25) = 0.01, p = 0.91

Characteristic	**n**	**%**	**n**	**%**	**Omnibus Test**
Education					$\chi^2 = 2.31$, p = 0.62
Less than high school	5	4	1	6	
High school	26	19	2	11	
Undergraduate	86	63	12	66	
Postgraduate	17	12	2	11	
Unknown	3	2	1	6	
Marital status					$\chi^2 = 2.25$, p = 0.41
Married	103	75	11	61	
Not married	32	24	7	39	
Unknown	2	1	–	–	
Employment					$\chi^2 = 0.29$, p = 1.00

	Mild Decreasing (N = 139)		Moderate Increasing (N = 25)		
Characteristic	$\overline{X}$	**SD**	$\overline{X}$	**SD**	**Omnibus Test**
Employed	53	39	7	39	
Not employed	82	60	11	61	
Unknown	2	1	–	–	
Stage					$\chi^2 = 1.83$, p = 0.77
I	17	13	2	11	
II	58	42	7	39	
III	32	23	3	17	
IV	27	20	6	33	
Unknown	3	2	–	–	
Doxorubicin					$\chi^2 = 0.18$, p = 0.67
Yes	72	53	10	56	
No	63	46	7	39	
Unknown	2	1	1	5	
Taxane					$\chi^2 = 0.5$, p = 0.59
Yes	44	33	7	39	
No	91	66	10	56	
Unknown	2	1	1	5	