Original Article

Symptom Trajectories Are Associated With Co-occurring Symptoms During Chemotherapy for Breast Cancer

Meagan Whisenant, PhD, APRN, Bob Wong, PhD, Sandra A. Mitchell, PhD, CRNP, FAAN, Susan L. Beck, PhD, APRN, FAAN, AOCN, and Kathi Mooney, PhD, RN, FAAN

The University of Texas MD Anderson Cancer Center (M.W.), Houston, Texas; College of Nursing (B.W.), University of Utah, Salt Lake City, Utah; Outcomes Research Branch (S.A.M.), National Cancer Institute, Rockville, Maryland; and College of Nursing (S.L.B., K.M.), Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA

Abstract

Context. Symptoms are reported to co-occur during treatment for breast cancer. We previously identified three patterns of fatigue and two patterns of disturbed sleep, depressed mood, and anxiety in women undergoing chemotherapy for breast cancer using a Latent Growth Mixture Model.

Objectives. The purpose of this study was to explore whether membership in symptom classes of fatigue, disturbed sleep, depressed mood, and anxiety is associated with other symptoms at moderate-to-severe levels.

Methods. Using data from three longitudinal studies, Wilcoxon rank-sum tests and Jonckheere-Terpstra tests for trend were used to distinguish between classes of women on co-occurring symptoms. Summative scores were calculated, including the number of days subjects reported moderate-to-severe levels (4 or higher on a 0–10 scale) of seven symptoms during two cycles of chemotherapy and compared to class membership.

Results. Participants ($n = 166$) in the higher fatigue severity class reported more days with moderate-to-severe disturbed sleep, depressed mood, anxiety, nausea, and trouble thinking. Women in the higher severity disturbed sleep class reported more days with moderate-to-severe fatigue, depressed mood, anxiety, and trouble thinking. Women in the higher depressed mood severity class reported more days with moderate-to-severe fatigue, disturbed sleep, anxiety, and nausea. Women in the higher anxiety severity class reported more days with moderate-to-severe fatigue, disturbed sleep, and depressed mood.

Conclusion. Moderate-to-severe symptoms co-occur during cancer treatment for breast cancer. The dynamic process of multiple symptoms may be altered by future identification of a shared etiology. J Pain Symptom Manage 2019;57:183–189.

Key Words

Cancer, fatigue, sleep, depression, anxiety, oncology

Introduction

Cancer symptoms are dynamic and may change over the course of treatment for breast cancer. Not only are symptoms major contributors to decreased quality of life and ability to function, but they may also interrupt treatment and influence treatment effectiveness.[1,2] Prompt evaluation and management of symptoms reduces use of emergency room and hospitalization, cost of treatment, and patient distress,[3,4] The collective consequence of simultaneous multiple symptoms may result in increased impairment when compared to the consequence of a single symptom.[5–8] Multiple symptoms are the norm and risk for mechanisms, and trajectories need to be understood to effectively treat co-occurring symptoms. The study of multiple symptoms simultaneously allows for the identification of shared symptom trajectories, symptom burden, and symptom mechanisms.[9]

There has been considerable work examining relationships between co-occurring symptoms, including

Address correspondence to: Meagan Whisenant, PhD, APRN, Division of Internal Medicine, Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1400 Pressler Drive, Unit 1450, Houston, TX, 77030, USA. E-mail: mswhisenant@mdanderson.org

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relationships found between fatigue and disturbed sleep,[7,10–22] depressed mood,[3,7,10,13,15,19,20,22–26] anxiety,[3,20,27] pain,[7,13,20,25,26] nausea and vomiting,[13,28] and trouble thinking.[7,13,20,29] In addition to the relation to fatigue described earlier, depressed mood,[7,10,18,20,22,30] anxiety,[7,20,22,30] pain,[7,20,31] and trouble thinking[7,20] are reported to co-occur with disturbed sleep. The symptoms of mood disturbance (depressed mood and anxiety) are reported to co-occur.[20,32] 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[7,20,26] and trouble thinking.[7,20,29] In addition, anxiety is reported to co-occur with pain,[20] nausea and vomiting,[28] and trouble thinking.[20,29]

Advances in 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.[21,33–37] This methodological approach can capture the unique symptom experience of the individual while describing the synergistic relationship among symptoms within class membership. The Dynamic Symptoms Model incorporates statistical approaches for studying patterns of multiple symptoms over time while acknowledging that symptoms co-occur.[38] Using data across Cycles 2 and 3 for 166 women initiating chemotherapy treatment for newly diagnosed breast cancer, we previously identified three patterns of fatigue and two patterns of disturbed sleep, depressed mood, and anxiety described by a Latent Growth Mixture Model.[39,40] For fatigue, mild decreasing, low moderate decreasing, and high moderate decreasing classes were found during both cycles.[40] For disturbed sleep, a mild decreasing class was found during both cycles and a moderate increasing class was found during Cycle 2 and mild increasing class was found during Cycle 3.[4] For depressed mood, a consistently mild class was found during both cycles and a consistently moderate class was found during Cycle 2 and a moderate improving class was found during Cycle 3.[39] For anxiety, a consistently mild class was found during both cycles and a consistently moderate class was found during Cycle 2 and a low moderate improving class was found during Cycle 3.[39] The purpose of this study was to explore whether membership in these distinct symptom classes is also associated with the presence of moderate or greater severity of other symptoms. This study reports on the co-occurrence of moderate to severe level symptoms within subgroups of women experiencing similar symptom trajectories of fatigue, disturbed sleep, depressed mood, and anxiety using daily symptom reports during chemotherapy for breast cancer.

Methods

Participants

This was a secondary analysis of data collected as part of three longitudinal studies that used an automated telephone system for monitoring symptoms during chemotherapy. Studies 1 and 2 tested the efficacy of an automated telephone symptom monitoring system and Study 3 was an observational study utilizing the same automated system for data collection. The sampling procedures and the automated system are previously described.[41,42] Data collection sites included five ambulatory clinics from three states. Although both Studies 1 and 2 included a control and experimental group, only those in Study 2 were found to have differences in reported symptoms between the control and intervention groups. Eligibility criteria 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 three days during each cycle. From the parent studies, 259 women were identified as eligible. Women from both the control and experimental groups in Study 1 were eligible for inclusion. Ninety-three women were excluded because they either were 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 three days of measures during Cycle 2 and 155 of women who completed three days of measures during Cycle 3.

Measures

Demographic and clinical data were collected at the baseline and included age, gender, race/ethnicity, employment status, education, diagnosis, extent of disease, and chemotherapy protocol. The automated system is further described elsewhere.[42] 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 used 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.[43–45] Symptoms assessed included fatigue, disturbed sleep, depressed mood, anxiety, pain, and nausea/vomiting across the parent studies. In addition, trouble thinking was assessed in Studies 2 and 3, and a subsample was used in analyses that included trouble thinking. For consistency in cycle lengths and to model the symptom trajectories for a time period consistent across participants, only data from the first 14 days of each

cycle were included in the analyses. This secondary analysis was reviewed by the institutional review board at the University of Utah. All participants signed a written, informed consent upon initiation of participation in the original studies.

Analytic Approach

The Software Statistical Package for the Social Sciences (version 23.0) was used for data management and data analysis. *P* values less than 0.05 were considered statistically significant, and there was no adjustment for multiple comparisons as this was a hypothesis-generating study. 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. Summative scores for each symptom were calculated and included the number of days subjects scored 4 or higher on severity of fatigue, disturbed sleep, depressed mood, anxiety, pain, nausea/vomiting, and trouble thinking individually within the first 14 days of each cycle. The summative number of days with each symptom at moderate or greater (a score of 4 or higher) severity was compared to class membership for disturbed sleep, depressed mood, and anxiety using a Wilcoxon rank-sum test and across ordered categories for fatigue using a Jonckheere-Terpstra test for trend.[46]

Results

Women in the sample ($n = 166$) had a mean age of 53 years (SD ± 10.8); 52.4% had early-stage breast cancer. The largest proportion of women were white (91.4%), married (75%), and not working (62.8%).

As shown in Fig. 1, there was a trend toward a greater number of days with moderate-to-severe disturbed sleep (Cycle 2: $P < 0.001$; Cycle 3: $P < 0.001$), depressed mood (Cycle 2: $P < 0.001$; Cycle 3: $P = 0.01$), anxiety (Cycle 2: $P = 0.02$; Cycle 3: $P < 0.01$), nausea/vomiting (Cycle 2: $P < 0.001$; Cycle 3: $P < 0.001$), and trouble thinking (Cycle 2: $P < 0.01$) as fatigue severity class increased. Women in the higher severity class for disturbed sleep reported greater number of days with moderate-to-severe fatigue (Cycle 2: $P = 0.01$), depressed mood (Cycle 2: $P = 0.01$; Cycle 3: $P = 0.01$), anxiety (Cycle 3: $P = 0.01$), and trouble thinking (Cycle 3: $P = 0.02$) (see Fig. 2). Women in the higher severity class for depressed mood reported greater number of days with moderate-to-severe fatigue (Cycle 2: $P = 0.01$; Cycle 3: $P = 0.02$), disturbed sleep (Cycle 3: $P = 0.001$), anxiety (Cycle 2: $P < 0.001$; Cycle 3: $P < 0.001$), and nausea/vomiting (Cycle 3: $P = 0.04$) (see Fig. 3). Women in the higher severity class anxiety reported greater number of days with moderate-to-severe fatigue (Cycle 2: $P < 0.001$; Cycle 3: $P < 0.001$), disturbed sleep (Cycle 3: $P < 0.001$), and depressed mood (Cycle 2: $P < 0.001$; Cycle 3: $P < 0.001$) (see Fig. 4).

Discussion

Severity class membership for fatigue, disturbed sleep, depressed mood, and anxiety 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 increased as fatigue severity class increased. In addition, the number of days with moderate-to-severe fatigue was increased in the more severe disturbed sleep class. Several studies have reported a similar relationship.[11–13,21,22,47] Liu et al. (2012) found that fatigue was significantly related to sleep problems and also that women with poor sleep during chemotherapy were already experiencing disturbed sleep at the baseline and that sleep disturbance did not increase during chemotherapy while fatigue did. This is consistent with findings in our sample. The relationship between fatigue and sleep disturbance suggests a synergistic effect that warrants further study.

There was a trend for increasing number of days with moderate-to-severe depressed mood as fatigue severity class increased in both cycle. The mean days of moderate-to-severe depressed mood was particularly

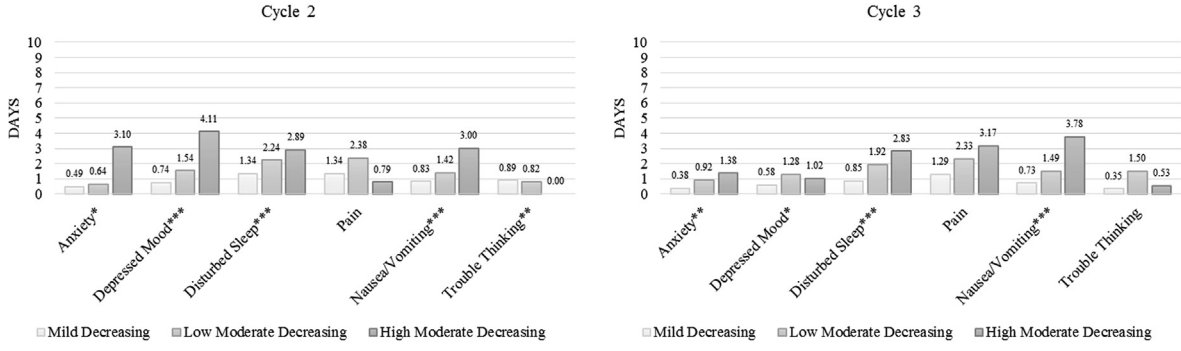

Fig. 1. Associations between fatigue class and co-occurring symptoms. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, Jonckheere-Terpstra test for trend.

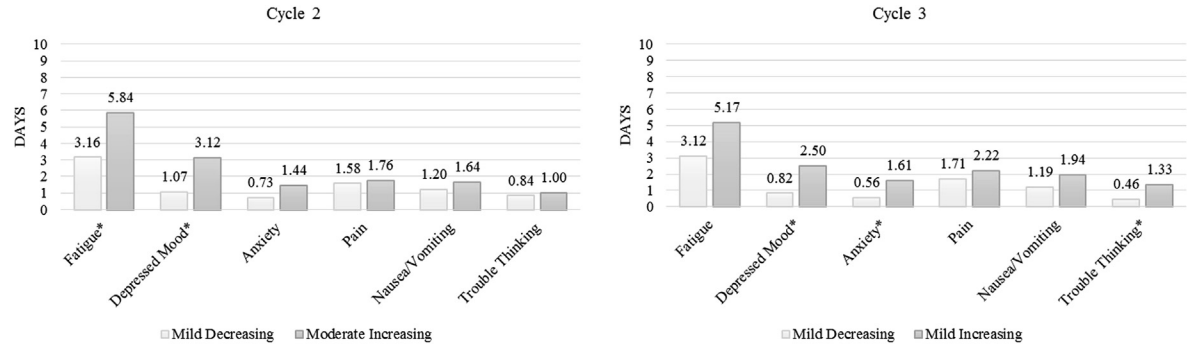

Fig. 2. Associations between disturbed sleep class and co-occurring symptoms. *$P < 0.05$, Wilcoxon rank-sum test.

high during Cycle 2 in the highest severity fatigue class (mean = 4.11 days, SD = 3.77) when compared to both the mild fatigue class (mean = 0.74 days, SD = 1.66) and the low moderate fatigue class (mean = 1.54 days, SD = 2.38). The mean days for depressed mood at moderate to severe levels in the highest fatigue class (mean = 1.02 days, SD = 3.11) was significantly decreased when compared to the low moderate fatigue class (mean = 1.28 days, SD = 2.87) in Cycle 3, although with a smaller mean difference. It is unknown whether individuals were provided treatment that may have alleviated depressed mood during Cycle 3 and thus reduced the number of days with moderate-to-severe depressed mood. In addition, membership in the moderate latent class for depressed mood was related to a greater number of days with moderate-to-severe fatigue during both cycles. This is not surprising, as fatigue has been associated with symptoms of mood disturbance in both cross-sectional correlation and symptom cluster studies.[3,7,10,13,19,20,22–27,29,48,49]

There was also a positive relationship between the number of days with moderate-to-severe depressed mood and moderate disturbed sleep class membership during both cycles, suggesting women experienced both depressive symptom and sleep symptoms concurrently. Not surprisingly, sleep disturbance was also increased for women in the moderate depressed mood class during Cycle 3. Others have found depressive symptoms predict or are positively related to difficulty with sleeping.[7,10,18,20,22,30] Colagiuri et al. (2011) suggest that there may be a reciprocal relationship between sleep difficulty and depressive symptoms, where sleep difficulty may result from increased depressive symptoms and/or sleep difficulty may lead to increasing depressive symptoms. Disturbed sleep and depression have been identified in a symptom cluster, along with fatigue and pain, in women undergoing treatment for breast cancer.[22,33]

The number of days with moderate to severe levels of anxiety increased as fatigue severity class increased during both cycles, and membership in the moderate anxiety latent class was associated with a greater number of days with moderate-to-severe fatigue. This is consistent with others' findings that fatigue and anxiety are reported to co-occur in women with breast cancer.[3,20,27] A similar relationship was seen between disturbed sleep class and anxiety during Cycle 3 and disturbed sleep and anxiety class during Cycle 3, which is a relationship that has been reported in other samples.[20,30]

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.[30,32,50,51] Gold

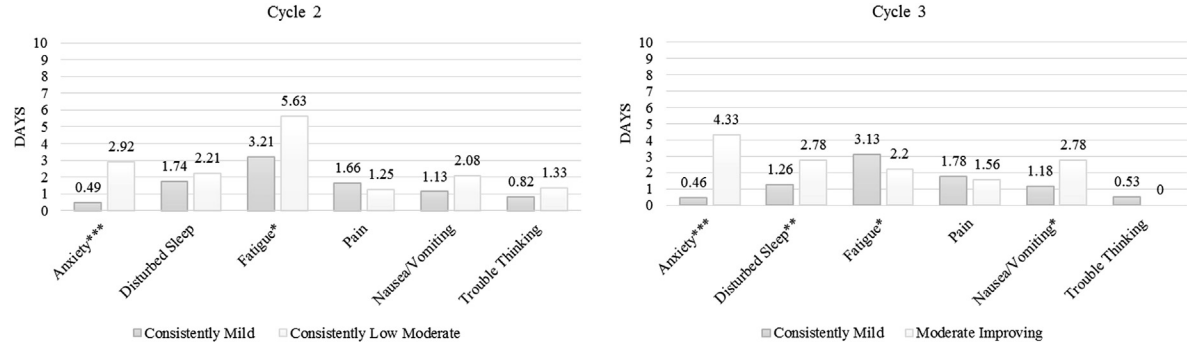

Fig. 3. Associations between depressed mood class and co-occurring symptoms. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, Wilcoxon rank-sum test.

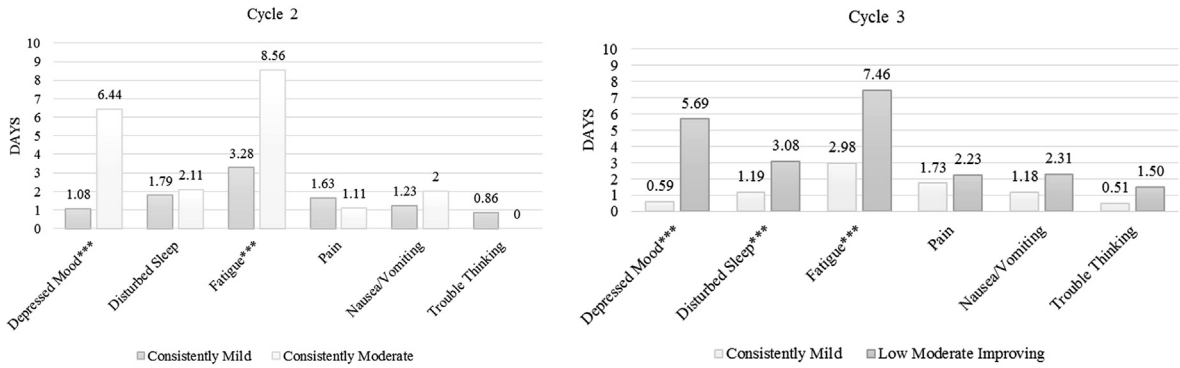

Fig. 4. Associations between anxiety class and co-occurring symptoms. ***$P < 0.001$, Wilcoxon rank-sum test.

et al. (2016) report on a collective of combined anxiety and depression syndrome, 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.

In both cycles, the number of days with moderate-to-severe nausea/vomiting was increased in the highest severity fatigue class when compared to the mild fatigue class. While those in the mild fatigue class experienced less than one day, those in the high fatigue class experienced three to four days of nausea/vomiting at moderate to severe levels. There are reports of an association between fatigue and nausea/vomiting during treatment for cancer,[13,52,53] suggesting a synergistic relationship where unrelieved nausea/vomiting may contribute to prolonged or persistent fatigue.

While nausea and vomiting have been associated with anxiety, that relationship was not found in our sample.[53] One explanation may be that the relationship between anxiety and nausea reported by Poon et al. (2013) was specific to anticipatory anxiety measured before receiving chemotherapy, not a trajectory of anxiety over the course of chemotherapy. Interestingly, nausea/vomiting was increased for those in the moderate depressed mood class during Cycle 3. 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/vomiting.

Trouble thinking was significantly related to fatigue during Cycle 2 and disturbed sleep class during Cycle 3. This is consistent with others' findings that cognitive function is related to fatigue and disturbed sleep during treatment with chemotherapy.[7,13,20,29] The lack of association among these symptoms during both cycles 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.

There were some limitations to this study, including a fairly homogenous sample. Caution should be used in interpreting our results with regards to the extracted predicted class memberships. Predicted class memberships are based on probabilities and, while treated as observed variables, are unobserved variables. While considered reliable and valid, single-item measure for symptom severity has limitations, including the risk for increased measurement error.[43–45] In addition, the present study was a secondary analysis, where the analysis was limited to the variables measured in the parent studies. Only data from the first 14 days of each cycle were used in this analysis. The results may not be generalizable to the entire cycle for 21- or 28-day cycles, and research is needed to describe the trajectory classes for the full cycle of chemotherapy and co-occurring symptoms within those classes.

Class membership for fatigue, disturbed sleep, depressed mood, and anxiety was associated with co-occurring symptoms at moderate or greater levels in our sample. Those in the higher severity fatigue classes experienced a greater severity of disturbed sleep, depressed mood, anxiety, nausea/vomiting, and trouble thinking. Only trouble thinking was not related to class membership during both cycles, suggesting some consistency of co-occurring symptoms with fatigue across cycles. Those in the higher severity disturbed sleep class experienced a greater severity of fatigue, depressed mood, anxiety, and trouble thinking. Women in the higher severity depressed mood class experienced greater fatigue, sleep disturbance, anxiety, and nausea/vomiting. Women in the higher severity class for anxiety experienced greater fatigue, sleep disturbance, and depressed mood. A unique contribution of the present study is the description of co-occurring moderate-to-severe symptoms within unique symptom subgroups of women receiving multiple cycles of chemotherapy for breast cancer. Identification of a symptom trajectory of fatigue, disturbed sleep, depressed mood, or anxiety

similar to those of our described symptom classes and knowledge of the potential for co-occurring moderate-to-severe symptoms within those classes may allow clinicians to target those at risk for co-occurring symptoms. Clinicians may then target those individuals for intervention, potentially avoiding poor outcomes that may be associated with moderate-to-severe symptoms, including decreased functional status, decreased vocational functioning, problems with adherence, and increased health care utilization. Given the co-occurrence of symptoms described in the literature and the co-occurrence of moderate-to-severe symptoms within subgroups of women experiencing higher severity of fatigue, disturbed sleep, depressed mood, and anxiety in our sample, the potential for a shared etiology exists. Future work may focus on identifying classes of women with similar symptom trajectories and co-occurring symptoms in larger samples across varying cycle lengths and locating a gateway symptom or shared etiology for moderate-to-severe co-occurring symptoms to inform risk evaluation for symptom severity. Further study is needed to examine associations between interindividual variability in co-occurring symptoms and molecular or genomic factors.

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