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Clinical Subgroups of a Psychoneurologic Symptom Cluster in Women Receiving Treatment for Breast Cancer: A Secondary Analysis

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Purpose/Objectives: To investigate clinical subgroups using an empirically identified psychoneurologic symptom cluster (depressed mood, cognitive disturbance, fatigue, insomnia, and pain) and to examine the differences among subgroups in the selected demographic and clinical variables, as well as in patient outcome (i.e., functional performance).

Design: Secondary analysis.

Setting: A university health science center in Salt Lake City, UT, and a National Cancer Institute–designated comprehensive cancer center in Philadelphia, PA.

Sample: 282 patients with breast cancer undergoing chemotherapy or radiotherapy.

Methods: Cluster analyses were conducted to identify subgroups. Multinomial logistic regression and one-way analyses of variance were used to examine the differences among subgroups.

Main Research Variables: Depressed mood, cognitive disturbance, fatigue, insomnia, pain, and functional performance.

Findings: Patients were classified into four distinct subgroups based on their symptom cluster experience: all low symptom, high fatigue and low pain, high pain, and all high symptom. Such patient classification patterns were consistent across the treatment trajectory, although group memberships were inconsistent. After initiating treatment, two additional subgroups emerged: high depressed mood and cognitive disturbance, and high fatigue and insomnia. Subgroups differed in physical performance status at baseline, symptom burden, and treatment modality in a relatively consistent pattern across time points. Patients in the all-high-symptom subgroup experienced the most serious limitations in activities across all time points.

Conclusions: Patient subgroups exist that share the unique experience of psychoneurologic symptoms.

Implications for Nursing: Findings are useful to determine who needs more intensive symptom management during cancer treatment. Future studies should examine whether specific symptom management strategies are more efficient for certain subgroups.

Symptom clusters are groups of interrelated symptoms that occur together (Kim, McGuire, Tulman, & Barsevick, 2005). Identifying clinical subgroups of patients with cancer with different patterns of symptom severity can help determine who needs more intensive care and assist the development of symptom management strategies tailored to a specific patient subgroup (Gwede, Small, Munster, Andrykowski, & Jacobsen, 2008). The current analyses build on previous research that identified a psychoneurologic symptom cluster (depressed mood, cognitive disturbance, fatigue, insomnia, and pain) (Kim, Barsevick, Tulman, & McDermott, 2008) by evaluating whether subgroups of patients with breast cancer with different patterns of those symptoms could be identified. A psychoneurologic symptom cluster in this study is defined as a set of emotional or behavioral symptoms that could be related to psychological or neurologic dysfunction and that co-occur and are interrelated with each other.

Several studies have provided empirical evidence of the clustering tendency of psychoneurologic symptoms in patients with cancer (Bender, Ergun, Rosenzweig, Cohen, & Sereika, 2005; Chen & Tseng, 2006; Kim et al., 2008). For instance, a previous study by the current authors (Kim et al., 2008) empirically identified two treatment-related symptom clusters by factor analyzing 20 different oncologic symptoms at three different time points across the cancer treatment trajectory in patients with breast cancer. The previously mentioned psychoneurologic cluster was present before and during treatment; an upper gastrointestinal cluster (nausea, vomiting, and decreased appetite) was identified after the commencement of treatment. Of note, in the authors' previous work and in work by others,

symptoms have been grouped or clustered using factor analysis; however, one may approach the question by asking whether patients can be placed in subgroups using cluster analysis to identify groups with similar patterns of symptoms that are distinct from other patterns. Cluster analysis is a classification tool that has been used in diverse disciplines to group units (e.g., patients) into homogeneous subgroups based on their relative similarity on a set of attributes (e.g., symptoms intensity) (Kim & Abraham, 2008).

The authors reported in previous work that symptoms in the empirically derived psychoneurologic cluster did not always occur at the same time or level of severity for all patients (Kim et al., 2008). Other studies also indicated that the experience of psychoneurologic symptoms varies across patients with cancer. In a study of patients with breast cancer (N = 228) by Given, Given, Azzouz, and Stommel (2001), 18% had pain, fatigue, and insomnia simultaneously, whereas 33% experienced any two of those three symptoms. As the number of symptoms reported by the patients increased, the risk for poor functioning increased compared to when they reported no symptoms (Given, Given, Azzouz, & Stommel, 2001).

Several studies (Miaskowski et al., 2006; Pud et al., 2008) identified subgroups of patients with cancer with a priori selected symptoms (fatigue, sleep disturbance, depression, and pain) at one time point in a heterogeneous sample (cancer type, treatment type, and time lapse since treatment). Miaskowski et al. (2006) reported that 15% of their sample (N = 191) experienced a high intensity of all four symptoms (fatigue, depression, sleep disturbance, and pain), whereas 50% experienced a higher intensity of pain or fatigue. The current study expanded those previous analyses by focusing on subgroups of only patients with breast cancer, on the psychoneurologic cluster that was empirically identified in this specific cancer population, on the two major treatments of breast cancer (chemotherapy and radiotherapy), and at the selected time points during cancer treatment trajectory.

The current study was guided by the Symptoms Experience Model (Armstrong, 2003), which describes factors that contribute to the experience of a symptom cluster: demographic characteristics (e.g., age, gender, marital status, race, education, socioeconomic status), disease characteristics (e.g., type and state of disease, type of treatment, comorbid conditions), and individual characteristics (e.g., health knowledge, values, past experience, sense of coherence) (see Figure 1). The model also depicts the consequences of symptoms (e.g., functional status, quality of life, survival, adjustment to illness). The current study used the model only to select and examine the relationships among several variables from the model (e.g., demographic and disease characteristics, consequences of symptoms).

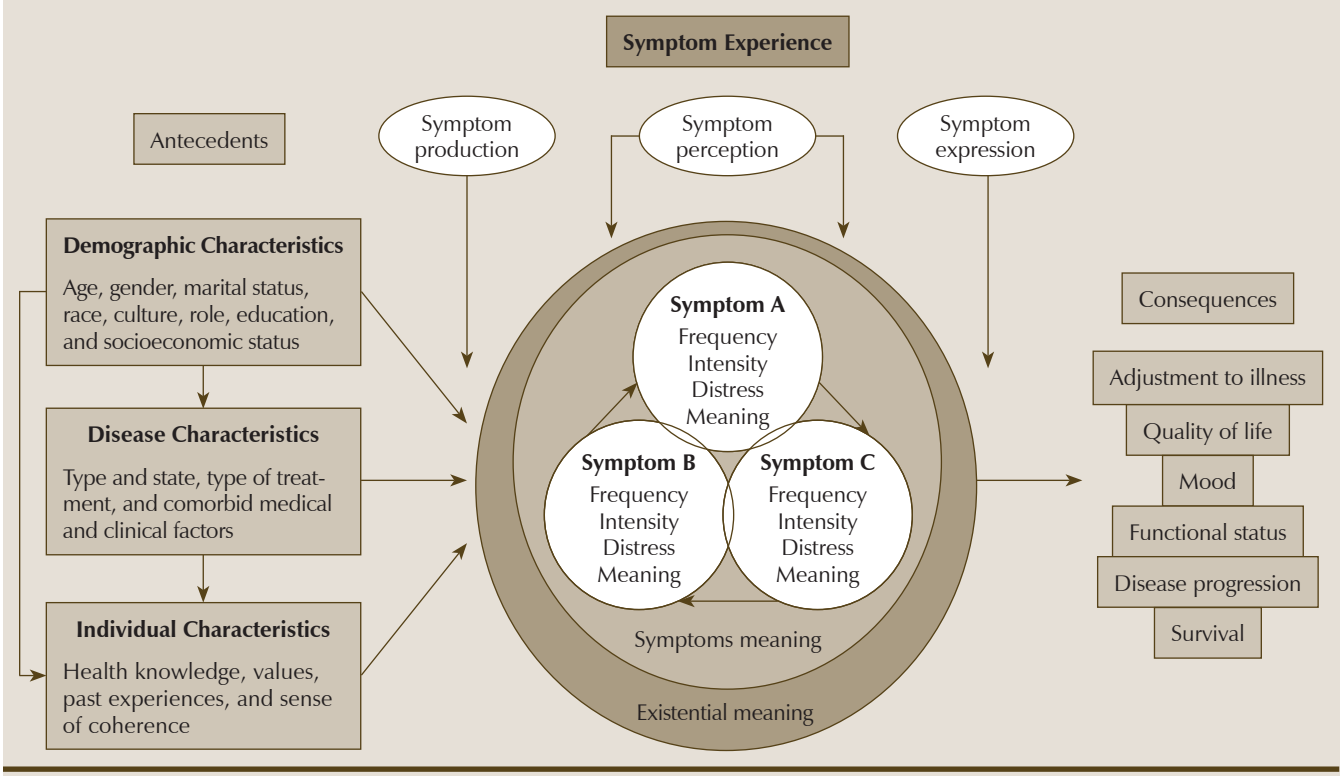


Figure 1. Symptoms Experience Model

Note. From "Symptoms Experience: A Concept Analysis," by T.S. Armstrong, 2003, *Oncology Nursing Forum, 30,* p. 603. Copyright 2003 by the Oncology Nursing Society. Reprinted with permission.

In summary, a growing body of research is investigating the clustering of symptoms. Such research most often has used a symptom factor analytical approach, focusing on the covariance of symptoms. The current study examines the presence of subgroups of individuals who were similar in severity of symptoms within a specific psychoneurologic cluster. This study uses a cluster analysis statistical approach in which subgroups (clusters in a statistical sense) of individuals are identified. The purposes of this study were (a) to identify subgroups of patients with breast cancer with similar patterns of symptoms at three time points during their treatment for cancer and (b) to examine differences among those subgroups in demographic and clinical characteristics, as well as patient outcome.

The following questions were asked in this study.

- What are the subgroups of patients with breast cancer with similar patterns of symptoms at three different time points during cancer treatment?
- How do demographic and clinical variables (age, comorbid conditions, baseline physical performance status, symptom burden from other symptoms at equivalent time points, surgery experience before baseline, current treatment mode, and disease stage) differentiate such clinical subgroups at each time point?
- Do subgroups of patients with breast cancer differ in a concurrently measured functional performance outcome?

Methods

Sample and Setting

The current study was a secondary analysis. The primary study was a randomized, clinical trial of the effectiveness of a cognitive-behavioral intervention (education about fatigue and energy-conservation strategies) for fatigue in patients with cancer (Barsevick et al., 2004). A total of 396 patients with cancer from a university health science center (University of Utah in Salt Lake City) and a National Cancer Institute–designated comprehensive cancer center (Fox Chase Cancer Center in Philadelphia, PA) participated in the primary study from 1999–2002. At the time of enrollment, patients planned to receive at least three cycles of chemotherapy, six weeks of radiotherapy, or concurrent radiotherapy and chemotherapy for various cancer types with a goal of cure or local control; they had not received prior treatment other than surgery for at least one month. Exclusion criteria were patients who planned to receive stem cell transplantation, interleukins, interferon, or tumor necrosis factor; who had a diagnosis of chronic fatigue syndrome or evidence of a psychiatric disorder; who had received treatment for anemia or depression during the prior three weeks; or who were enrolled in another psychoeducational intervention study.

For the current study, only data from the breast cancer cohort (N = 282) were used: no further inclusion or exclusion criteria were applied. In the primary study, fatigue severity decreased significantly over time in the experimental group in comparison with the control group. However, the experimental and control groups did not have clinically important differences in fatigue level at baseline on a 10-point scale, with higher scores indicating higher fatigue intensity ($\bar{X}$ = 3.3 [SD = 1.8] versus $\bar{X}$ = 3.3 [SD = 1.8]), and at two follow-ups ($\bar{X}$ = 4.6 [SD = 2.2] versus $\bar{X}$ = 4.6 [SD = 2]; $\bar{X}$ = 4.1 [SD = 2.2] versus $\bar{X}$ = 4.7 [SD = 2.1]). For that reason, the groups were combined and analyzed as a unit in this study, but the potential influence of the intervention on the current study was examined.

Because of missing data, the sample size was smaller than 282 in several analyses. The cases used for the analyses were not identical across all time points, although the data were collected longitudinally. A smaller number of participants provided information for key variables across all time points (n = 160), and patients with late-stage cancer tended to drop out of the study or were more likely to have missing information on the key variables at follow-up time points. To establish adequate sample size for analyses and better represent patients with late-stage cancer, all cases available at each time point were used for analysis.

All study participants were women, with a mean age of 55 years (SD = 12.1, range = 30–83). Most were Caucasian (n = 258, 92%) and married (n = 198, 70%), had early-stage cancer (stages 0–II) (n = 245, 87%), and received surgery before the baseline data collection (n = 210, 75%). Information regarding the time lapse after surgery was unavailable. One hundred thirty-eight patients (49%) were employed at the time of recruitment and had at least one comorbid condition (n = 157, 56%). One hundred forty-one patients (50%) received a symptom management intervention for fatigue, the experimental treatment for the primary study. During the study, 125 (44%) received chemotherapy and 157 (56%) received radiotherapy. Approval of the institutional review board at Fox Chase Cancer Center was obtained for this study.

Data Collection Time Points

Data were collected at baseline and two follow-up time points chosen to capture maximum fatigue levels during and after treatment (Barsevick et al., 2004). Studies reported that fatigue is highest at each chemotherapy treatment and then decreases to the next treatment cycle (Berger, 1998; Berger & Higginbotham, 2000); fatigue was highest in the last week of radiotherapy treatment (Irvine, Vincent, Graydon, & Bubela, 1998). Therefore, baseline data were collected prior to the planned chemotherapy or radiotherapy (time 1). The follow-up points were 48 hours after the second

(time 2) and third (time 3) treatments for chemotherapy recipients and the last week of radiotherapy (a total of six weeks of treatment) (time 2) and one month after completion of treatment (time 3) for radiotherapy recipients. The time lapse after treatments was similar across participants within each treatment arm at times 2 and 3.

Instruments

The **General Fatigue Scale** (Meek, Nail, & Jones, 1997) assesses fatigue intensity (1 = no fatigue; 10 = greatest possible fatigue) during various periods (the present day, the past 48 hours, or the past week), the level of distress caused by fatigue, and the effect of fatigue on daily activities. In the current study, only one item from the scale (fatigue intensity in the past week) was used to establish consistency in the time period and symptom dimension across measures.

Two subscales (depression and confusion) of the **Profile of Mood States–Short Form** (McNair, Lorr, & Droppleman, 1981) were used to measure depressed mood and cognitive disturbance. Each subscale includes five items that were scaled from 1 (not at all) to 5 (extremely); each measured the intensity of the two symptoms for the past two to three days, respectively. Cronbach alpha was 0.81 for the depression subscale and 0.75 for the confusion subscale in the current study.

The **Pittsburgh Sleep Quality Index** (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) contains 19 self-rated questions, each with various response options. The tool measured insomnia for the past month. Beck, Schwartz, Towsley, Dudley, and Barsevick (2004) provided evidence of its reliability and validity. Cronbach alpa for the global score was 0.74 in this study.

The **Side Effect Checklist** measured the intensity of 16 treatment-related symptoms for the past week (cough, pain, diarrhea, nausea, vomiting, decreased appetite, constipation, urinary frequency, urinary burning, hot flashes, rectal irritation, swelling of arm or leg, shortness of breath, sore throat or sore mouth, skin damage, and pain or irritation at the IV site). Each was measured using a four-point scale from 1 (not at all severe) to 4 (quite a bit severe). Zero points were given to patients who did not have a symptom. The checklist was modified from the Self-Care Diary (Nail, Jones, Greene, Schipper, & Jensen, 1991), its content validity was tested by oncology clinical experts prior to data collection. Pain was measured with one item from the Side Effect Checklist. In the current study, symptom burden from other symptoms was defined as the mean intensity of the remaining 15 symptoms. The data for all symptom measures were collected at each time point.

Factors that could influence subgroup differences were measured at baseline using a **demographic and clinical data sheet** and **Eastern Cooperative Oncology Group performance status** (for baseline physical performance status). Demographic data were obtained from a self-report questionnaire, and clinical data were abstracted from the patient medical record. The Eastern Cooperative Oncology Group performance status is a single-item measure of physical performance status (Oken et al., 1982). The scale ranges from 0 (normal activity without symptoms) to 4 (unable to get out of bed). Inter-rater reliability has been reported as acceptable for this measure (Conill, Verger, & Salamero, 1990).

The **Functional Performance Inventory** (Leidy, 1994) was used to measure the outcome variable (i.e., a functional limitation) at each time point. The inventory includes 65 items and has six subscales: body care, household maintenance, physical exercise, recreation, spiritual activities, and social activities. The mean of the six subscale scores was used in the analyses. A higher score indicated better functioning; the scale for each item was 0 (don't do because of health reason) to 3 (do with no difficulty). Leidy (1999) reported the reliability (alpha = 0.96; intraclass correlation = 0.85) and concurrent validity (significant correlations of the Functional Performance Inventory with existing functional status measures).

Data Analysis

To identify clinical subgroups, cluster analyses of participants were conducted at each time point with the psychoneurologic symptoms (depressed mood, cognitive disturbance, fatigue, insomnia, and pain). Ward's (1963) minimum-variance method was used for cluster extraction because it is used most frequently in research and performs the best at population recovery of clusters (Finch, 2005; Romesburg, 2004). As Ward's (1963) method is sensitive to outliers, the SAS®, version 9.2, command "TRIM" was used to examine the influence of outliers. Outliers were deleted only when the deletion substantially changed a model. Deleted outliers were 16 cases at time 1, 3 at time 2, and 0 at time 3. In cluster analysis, the number of subgroups was selected by examining error variance, simultaneous elevation of pseudo-F statistic over the pseudo-t^2 statistic (Copper & Milligan, 1988), and Mojena's (1977) stopping criterion (within the feasible range). Multinomial logistic regression was used to examine subgroup differences in selected demographic and clinical variables; maximum likelihood estimation was done using the "PROC LOGISTIC" procedure in SAS. One-way analysis of variance (ANOVA) was used to examine differences in functional limitation among the subgroups. Sample size is not a requirement for cluster analysis because it explores the patterns in a given data without an inferential test. For logistic regression, a minimum of 10 cases per variable is recommended (Hosmer & Lemeshow, 1989). To increase the ratio, the minimum number of variables for the final model was

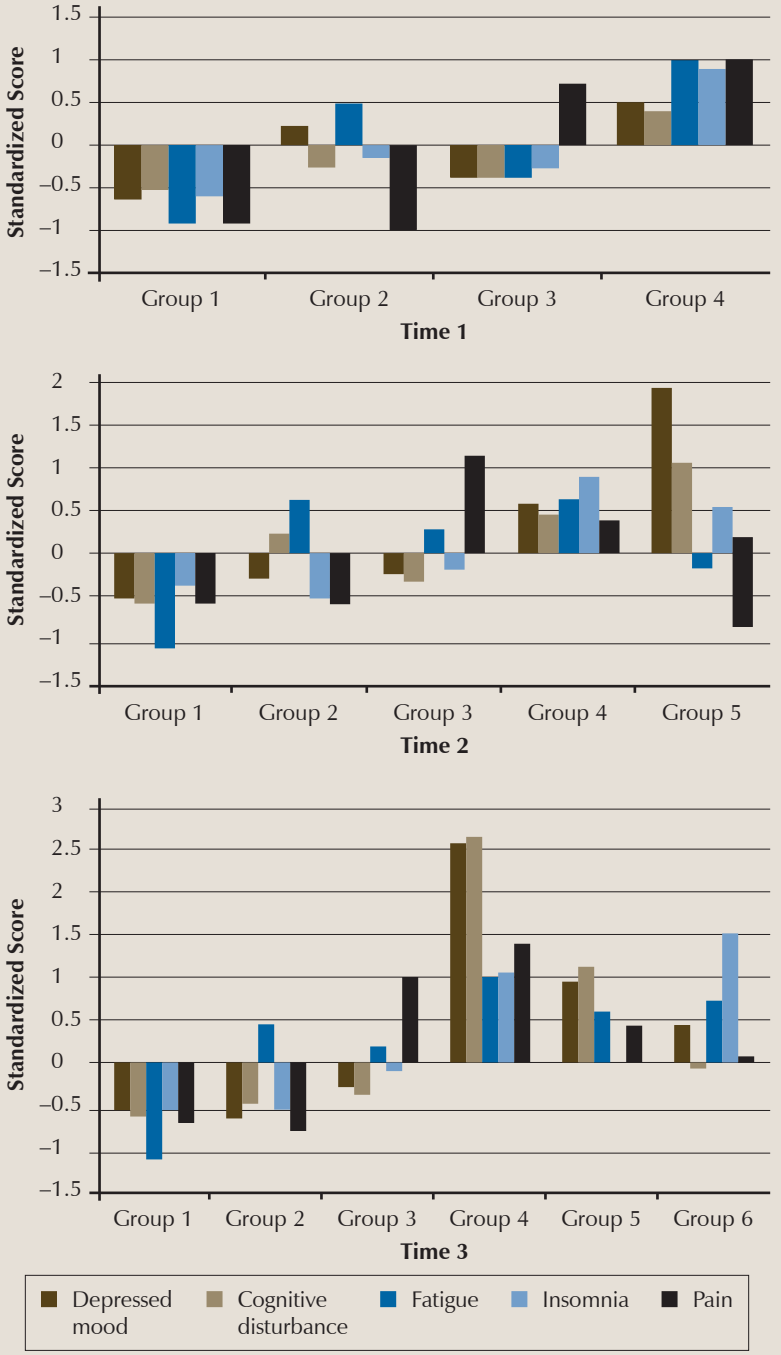
selected via initial analyses. The authors also examined extremely large estimators in the logistic model, which indicate the problems caused by inadequate sample size (Tabachnick & Fidell, 2001).

Results

Clinical Subgroups at Three Time Points

Cluster analysis revealed different numbers of subgroups at each time point: four subgroups at time 1, five at time 2, and six at time 3 (see Figure 2). For the cluster analysis, scores for all symptoms were standardized at each time point ($\bar{X}$ = 0, SD = 1). Those scores have relative meaning and allow comparisons among symptoms in terms of intensity at each time point. A 0.5 standard deviation (i.e., half of a standard deviation) higher or lower than the mean (i.e., 0 in the current study) was considered to be high or low symptom intensity (Norman, Sloan, & Wyrwich, 2003). Across time points, group 1 experienced low intensity of all five symptoms (lower than the mean) and was designated as the all-low-symptom subgroup, whereas group 4 reported higher intensity and was designated as the all-high-symptom subgroup. Group 2 was characterized by high fatigue and low pain, whereas group 3 was the high-pain subgroup. At times 2 and 3, additional subgroups were found. Although the symptom profile of group 5 was not identical across time points, this group had a relatively more intense depressed mood and cognitive disturbance compared to other symptoms at both times 2 and 3 and was designated as the high depressed mood and cognitive disturbance subgroup. Group 6 was found only at time 3; it uniquely had high fatigue and insomnia.

Table 1 presents the mean symptom intensity scores (original scale scores) in each subgroup. Overall, patients experienced mild to moderate levels of symptom intensity with more intense psychoneurologic symptoms after chemotherapy or radiotherapy (times 2 and 3) than before treatment (time 1). One-way ANOVA demonstrated that all five symptoms contributed to distinguishing one subgroup from another at each time point. However, F-statistic values suggest that pain was the most important contributor in subgroup separation at times 1 and 2, whereas cognitive disturbance was the most important at time 3. The number of patients in group 1 (all-low-symptom subgroup) was similar across time points. However, substantial decreases in the number of patients occurred in other subgroups, such as group 4 (n = 59 at time 1, 41 at time 2, and 10 at time 3). This



Group 1—all low symptom; Group 2—high fatigue and low pain; Group 3—high pain; Group 4—all high symptom; Group 5—high depressed mood and cognitive disturbance; Group 6—high fatigue and insomnia

Note. Because these were built on the standardized scores, which allow for comparisons across groups and across different symptoms, the direction and size of the bar in the graph may not be consistent with the original scale scores presented in Table 1. In addition, insomnia in group 5 at time 3 was almost zero and was not captured.

Figure 2. Standardized Symptom Intensity Scores in Each Group

Table 1. Mean Symptom Intensity Scores by Group

	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Time 1 (N = 242[a])	64	26	46	19	73	30	59	24					
Time 2 (N = 200[a])	67	34	34	17	44	22	41	21	14	7			
Time 3 (N = 194[a])	65	34	27	14	38	20	10	5	28	14	26	13	
Symptom	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**ANOVA**
Time 1													**F(3, 238)[b]**
Depressed mood	1.2	0.2	1.7	0.6	1.4	0.4	1.9	0.5					30.87*
Cognitive disturbance	1.5	0.3	1.6	0.4	1.5	0.3	2	0.5					23.18*
Fatigue	2.3	0.9	6	2.2	3.7	1.7	7.1	2					94.99*
Insomnia	4.8	2.9	6.8	3.1	6.2	3.1	10.6	3.1					40*
Pain	0	0.1	0	0	2.2	0.7	2.7	0.8					379.79*
Time 2													**F(4, 195)[b]**
Depressed mood	1.2	0.3	1.4	0.4	1.4	0.4	2	0.6	2.9	0.4			67.57*
Cognitive disturbance	1.4	0.3	2	0.5	1.6	0.3	2.1	0.4	2.4	0.4			43.49*
Fatigue	3	1.4	7.4	1.5	6.5	2	7.7	1.7	5.1	2			70.28*
Insomnia	5.9	3.1	5.1	1.8	6.7	2.9	10.6	3.3	9.4	3.3			23.64*
Pain	0.1	0.4	0.2	0.5	2.6	0.7	1.6	1.2	0.1	0.3			106.91*
Time 3													**F(5, 188)[b]**
Depressed mood	1.2	0.3	1.1	0.2	1.3	0.4	3.5	0.6	2.3	0.6	1.9	0.6	67.3*
Cognitive disturbance	1.4	0.3	1.6	0.3	1.6	0.3	3.5	0.4	2.6	0.3	1.8	0.3	120.21*
Fatigue	2.7	1.1	6.6	1.7	6.1	2.4	8.3	1.8	7.1	1.8	7.8	1.5	59.99*
Insomnia	5.1	3	5.1	1.9	6.7	3	11.7	3.9	7.1	3.2	13.4	2.6	38.68*
Pain	0	0	0	0	2.1	0.7	2.6	0.7	1.4	1.5	1	1.1	57.46*

* $p < 0.0001$

[a] The sample size is smaller than 282 and varies across time points because of missing information in symptom variables.

[b] F values have the same degrees of freedom across symptom variables at each time point.

ANOVA—analysis of variance; Group 1—all low symptom; Group 2—high fatigue and low pain; Group 3—high pain; Group 4—all high symptom; Group 5—high depressed mood and cognitive disturbance; Group 6—high fatigue and insomnia

Note. Mean of symptom intensity in each subgroup is presented in the original scale. The ranges of score were as follows: depressed mood (1–5), cognitive disturbance (1–5), fatigue (1–10), insomnia (0–21), pain (0–4). For all symptoms, higher scores indicated higher intensity.

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

finding may have been because of attrition of patients with severe symptoms during the study, regression to the mean, change in the symptom set point, or effective symptom management. Newly emerged subgroups at times 2 and 3 also may have been responsible for this finding. More patients in the all-low-symptom subgroup (group 1) remained in the same subgroup across time points; in other subgroups, only a few patients remained in the same subgroup (see Table 2).

Differences in Demographic and Clinical Characteristics

Initially, the group differences in four demographic variables (age, marital status, employment status, and race) and seven clinical variables (disease stage, comorbid condition, baseline physical performance status, symptom burden from other symptoms at equivalent time points, surgery before baseline, current treatment mode, and symptom management intervention for fatigue) were of interest. However, the final model included only six variables. The initial analyses were conducted with the inclusion of all variables of interest and examined variables that did not contribute to subgroup differentiation. Race had no variance in a few subgroups. Marital status, employment status, and the symptom management intervention did not contribute to subgroup differentiation at all time points (all $p \geq 0.05$ in type 3 analyses). The likelihood ratio tests indicated no difference between the models with and without those variables (all $p > 0.05$). Therefore, those variables were completely excluded in the final logistic model to create a parsimonious model.

Group 4 was chosen as a reference for contrasting groups with regard to the six selected variables at each time point. As the all-high-symptom subgroup, it was believed to be the target for symptom assessment and management (see Table 3). At time 1, age, baseline physical performance status, symptom burden, and previous surgery significantly differentiated group 4 from two or more of the other groups. Group 4 tended to have poorer baseline performance status and was more likely to have had surgery than other subgroups.

This group also tended to be younger and had a higher overall symptom burden than groups 1 and 3. Group 4 did not differ from the other groups by disease stage and comorbid conditions. The effects of comorbid conditions were examined in a separate model according to (a) the total number of comorbid conditions and (b) the presence or absence of comorbid conditions. Neither method indicated the contribution of comorbid conditions in differentiating subgroups, controlling for other variables.

At time 2, group 4 tended to have more comorbid conditions than group 2, worse baseline performance status than groups 1 and 2, and a higher symptom burden than groups 1, 2, and 5. At time 3, group 4 tended to have poorer baseline physical performance status than group 1 and was more likely to have high symptom burden than groups 1 and 2. In both time 2 and 3, group 4 was less likely than group 5 to have received chemotherapy.

In sum, the all-high-symptom subgroup (group 4) differed from other subgroups in baseline physical performance status, symptom burden from other symptoms, and treatment modality in a relatively consistent pattern across time points.

Differences in Patient Outcomes

Subgroups differed in the patient outcome with respect to limitations in daily activities at each time point (see Table 4). ANOVA post-hoc comparisons showed that across all time points, group 4 (all-high-symptom subgroup) had more serious limitations than most other groups.

Discussion

Four patient subgroups with distinct patterns of psychoneurologic symptom experience (depressed mood, cognitive disturbance, fatigue, insomnia, and pain) were consistently identified across the treatment trajectory in the current study: all low symptom, high fatigue and low pain, high pain, and all high symptom. Miaskowski et al. (2006) performed a cluster analysis of patients with cancer with an a priori chosen symptom cluster (fatigue, sleep disturbance, depressive symptoms, and pain) and found four almost identical subgroups. Miaskowski et al.'s (2006) sample included patients with breast cancer (27%). The current study and Miaskowski et al.'s (2006) confirm the existence of patient subgroups with unique psychoneurologic symptom experiences. Replication of findings also may have been caused by the similarity in the construct of symptoms measured in both studies. The current study's replication of those four subgroups across the three time points further supports their external validity in patients with breast cancer.

Table 2. Patients Who Remained in the Same Symptom Cluster Across Time Points

Group	Time 1 to Time 2	Time 2 to Time 3	All Time Points
All low symptom	31	37	22
High fatigue and low pain	8	3	1
High pain	11	14	4
All high symptom	15	–	–

Note. The sample size varied for each group across the three time points because of missing data.

Psychoneurologic symptoms in patients with cancer are prevalent, distressing, and challenging to manage (National Institutes of Health, 2002). However, about 25% of patients do not develop clinically significant psychoneurologic symptoms (National Institutes of Health, 2002). The current study indicates that a group of patients with a simultaneous risk for five psychoneurologic symptoms during cancer treatment exists. In addition, patients with all-high psychoneurologic symptoms experienced the most serious limitations in their functional performance across all types of daily activities. Similarly, Miaskowski et al. (2006) reported that patients in the all-high subgroup had the lowest quality of life and that the all-low subgroup had the best patient outcomes in quality of life and functional status. In another study with patient subgroups by Gwede et al. (2008), patients with breast cancer in the high-symptom-prevalence subgroup had poorer quality of life than those in the low-symptom-prevalence subgroup. Quality of life in Gwede et al.'s (2008) study included diverse areas such as pain, mental health, and physical or social functioning. Several other studies have shown that the number of symptoms reported was inversely associated with patient outcomes, such as functional status or quality of life (Gift, Jablonski, Stommel, & Given 2004; Portenoy et al., 1994). Taken together, the deleterious effect of the high-intensity psychoneurologic symptoms on patient outcomes is evident, and managing those symptoms effectively can improve quality of life in patients with cancer. Clinicians must pay particular attention to patients who experience all of those symptoms at a higher level of intensity.

Early identification of patients with a simultaneous risk for psychoneurologic symptoms can enhance the effectiveness and efficiency of symptom management. At all time points, poorer baseline physical performance status predicted a high intensity of all psychoneurologic symptoms. In addition, greater intensity of other symptoms (symptom burden) predicted a high intensity of all psychoneurologic symptoms. Similarly, Given, Given, Azzouz, Kozachik, and Stommel (2001) found that older patients with cancer who had pain and fatigue had a greater number of other symptoms compared to patients with only fatigue or pain or no fatigue or pain. However, the mechanism by which symptom burden

was related to increased psychoneurologic symptoms cannot be concluded from the current study.

In the current study, race, marital status, and employment status did not differentiate subgroups. The effects of age, previous surgery experience, and comorbid conditions were inconsistent across time points. Findings from previous studies also were inconsistent. For example, Miaskowski et al. (2006) found that subgroups differed in age and marital status, but not in other study variables. In their study, younger patients were more likely to be in the all-high subgroup than the all-low subgroup (similar to the current findings) and married women were less likely to be in the all-high subgroup (contrary to the current findings). Gwede et al. (2008) examined differences between two subgroups (high-symptom-prevalence group versus low-symptom-prevalence group) in often-studied demographic and clinical variables. Only disease stage differed between subgroups in an unexpected direction: the high-symptom-prevalence group was more likely to have stage I disease. The effect of most demographic- and disease-related variables on symptom experience remains inconclusive because of different sample characteristics and different analytical approaches in the small number of studies that examined symptom clusters.

Table 3. Logistic Regression Distinguishing Subgroups Versus Group 4 With Demographic and Clinical Variables by Time Point

Variable	Group 1	Group 2	Group 3	Group 5	Group 6
Time 1 (N = 195[a])					
Intercept	1.09	1.74	–0.02		
Age	0.08***	0.03	0.05*		
	(1.09)		(1.05)		
Comorbidity	–0.24	–0.01	–0.01		
Baseline physical performance	–2.12****	–1.69****	–0.69*		
	(0.12)	(0.18)	(0.5)		
Symptom burden[b]	–3.15**	0.17	–1.38*		
	(0.04)		(0.25)		
Previous surgery[c]	–3.31****	–2.59***	–1.27		
	(0.04)	(0.08)			
Disease stage and current treatment mode[d]	–0.3	–0.24	0.08		
Time 2 (N = 160[a])					
Intercept	3.81	1.9	2.03	0.83	
Age	0.01	0.01	–0.01	0.01	
Comorbidity	–0.36	–1.2**	0.17	–0.73	
		(0.3)			
Baseline physical performance	–1.23**	–0.82*	–0.52	–0.27	
	(0.29)	(0.44)			
Symptom burden[b]	–4.39****	–2.75**	–1.23	–3.12**	
	(0.01)	(0.06)		(0.04)	
Previous surgery[c]	–0.6	0.5	–0.15	–0.67	
Disease stage and current treatment mode[d]	0.75	0.25	–0.82	2.04*	
				(7.68)	
Time 3 (N = 155[a])					
Intercept	4.27	2.32	0.35	–1.84	–0.19
Age	0.05	0.04	0.05	0.08	0.05
Comorbidity	–0.45	0.19	0.11	–1.03	–0.14
Baseline physical performance	–1.29*	–0.64	–0.59	–0.29	0.06
	(0.27)				
Symptom burden[b]	–5.76****	–3.99***	–1.7	–1.32	–1.81
	(0.003)	(0.02)			
Previous surgery[c]	–0.99	–0.91	0.14	–0.24	–0.18
Disease stage and current treatment mode[d]	1.17	1.45	0.53	1.99*	0.35
				(7.36)	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$

[a] The sample size varies across time points because of missing information in study variables.

[b] Symptom burden was the mean intensity of 15 other symptoms at equivalent time points.

[c] Effect of surgery was examined as whether patients received surgery immediately before baseline.

[d] Disease stage and type of treatment were highly correlated. At time 1, disease stage was tested; at times 2 and 3, type of treatment was evaluated.

Group 1—all low symptom; Group 2—high fatigue and low pain; Group 3—high pain; Group 4—all high symptom; Group 5—high depressed mood and cognitive disturbance; Group 6—high fatigue and insomnia

Note. The negative or positive sign given to each estimate (number outside parentheses) indicates the direction of the relationship. Odds ratios are reported within parenthesis only for significant group differences.

Treatment modality differentiated the high depressed mood and cognitive disturbance subgroup from the all-high subgroup. However, in previous studies, treatment type was unrelated to symptom experience (Miaskowski et al., 2006; Pud et al., 2008). This may have occurred because the high depressed mood and cognitive disturbance subgroup was not identified in previous studies. In addition, previous studies were limited in examining the effect of treatment because the time lapse since treatment varied across patients. However, the time-lapse was similar within the same treatment mode group in the current study.

When sorting patients through any method, the creation of all-low or all-high-symptom subgroups is possible. The identification of the two subgroups with pain and fatigue intensity in almost opposite directions is intriguing. However, what led to such a unique symptom pattern is unclear, as no clinical or demographic variables successfully characterized the two groups. Further studies are warranted with regard to distinguishing characteristics of those subgroups. Findings from such studies

can guide the development of symptom management strategies. For example, pain in the surgery site may occur without fatigue, and the management for this type of pain may be different from the management for general body aches occurring with fatigue during chemotherapy. The current study mainly examined demographic and disease characteristics from the Symptoms Experience Model, and the contribution of those variables was limited. The role of other characteristics (e.g., anxiety), which were not fully explored in the current study, warrants examination.

In the current study, additional subgroups emerged after initiating treatment (chemotherapy or radiotherapy): a subgroup with a high depressed mood and cognitive disturbance, and another with high fatigue and insomnia. The two groups were similar to the all-high symptom subgroup in terms of symptom profile. Therefore, they may be part of the all-high-symptom subgroup. Chemotherapy recipients were more likely than radiotherapy recipients to be in the high depressed mood and cognitive disturbance subgroup after initiating cancer treatment. In consideration of the close connection between disease stage and treatment regimen, future studies should examine whether patients with more advanced-stage disease undergoing a higher dose of chemotherapy or a certain chemotherapy regimen experience a more intense depressed mood and cognitive disturbance. Although four subgroups existed across time points, patients did not belong to the same subgroup at all time points. Changing group membership may indicate that patients' symptom experience is influenced by situational factors at each time point, rather than by innate patient characteristics (e.g., age, race, education). In fact, symptom burden at each time point was the strongest distinguishing characteristic of the subgroups after treatments were given. Situational factors may include changes in treatment regimen, the use of invasive techniques, or drugs used for symptom management. Those possible predictors of the symptom experience warrant further examination. Other potential predictors of symptom experience could include biologic processes (e.g., inflammation and genetic variation) or individual psychological factors (e.g., health knowledge or belief, coping, positive affect, sense of coherence) (Armstrong, 2003; Lee et al., 2004; Miaskowski et al., 2006). Unstable group membership suggests that active interventions to modify those situational factors can improve symptom experience during treatment.

Table 4. Differences in Functional Performance Inventory by Group at Each Time Point

Variable	Score n	Score $\bar{X}$	Score SD	Statistics
Time 1 (N = 242)				F(3, 238) = 17.3*
Group 1	64	2.95	0.08	4 < 1, 2, 3; p < 0.0001
Group 2	46	2.84	0.23	3 < 1; p < 0.05
Group 3	73	2.83	0.21	
Group 4	59	2.62	0.41	
Time 2 (N = 200)				F(4, 194) = 13.65*
Group 1	67	2.86	0.19	4 < 1, 2, 3, 5; p < 0.01
Group 2	34	2.75	0.3	
Group 3	44	2.74	0.23	
Group 4	41	2.46	0.42	
Group 5	14	2.76	0.2	
Time 3 (N = 194)				F(5, 188) = 14.82*
Group 1	65	2.9	0.2	4 < 1, 2, 3; p < 0.0001
Group 2	27	2.8	0.3	5 < 1, 2, 3; p < 0.01
Group 3	38	2.74	0.25	6 < 1, 2; p < 0.05
Group 4	10	2.25	0.56	4 < 6; p = 0.058
Group 5	28	2.5	0.4	
Group 6	26	2.56	0.29	

* $p < 0.0001$

Group 1—all low symptom; Group 2—high fatigue and low pain; Group 3—high pain; Group 4—all high symptom; Group 5—high depressed mood and cognitive disturbance; Group 6—high fatigue and insomnia

Limitations

The current study had several limitations. The comparisons of findings across the time points are tentative because this study used different sample sizes across time points, and the analyses were done at each time point. For example, the four cluster profiles remained similar but not identical; therefore, the authors concluded that some patients most likely moved to another subgroup because of changes in their symptom experience. However, the possibility that the cluster profile itself changed over time cannot be excluded, considering that the four cluster profiles were not identical across times and additional cluster profiles emerged after chemotherapy or radiotherapy. Of note, the current study was done in an exploratory manner and was not aimed at examining intraindividual change in symptom experience over time. Future studies should use larger data sets, which could allow for more complex statistical modeling that would include different patterns of symptom experience and the predictors of change in symptom experience over time. Such studies can be better guided by the more integrated theoretical framework, which incorporates temporal aspects of symptom experience, more extensive influencing factors (e.g., symptom management interventions), and inter-relationships between antecedents and consequences (Brant, Beck, & Miaskowski, 2009). Symptom intensity and functional problems may be underestimated in this study because of the nature of the primary study (randomized, clinical trial; longitudinal data collection). Although the authors attempted to salvage cases with severe symptoms by using all available cases at each time point, those cases tended to drop out of the study at the follow-up time points. Future studies should include more patients with advanced-stage cancer.

Conclusion

The current study showed patient subgroups that shared a unique experience of psychoneurologic symptoms. Those subgroups were distinguishable by clinical characteristics and patient outcome. Patients with all five psychoneurologic symptoms at a higher intensity had the worst patient outcome. Although more confirmatory evidence of the clinical utility of subgroups is required, findings from this study suggest that poor performance status prior to treatment and high symptom burden at the equivalent time point place patients at risk for high psychoneurologic symptoms during treatment. Future studies should examine whether specific symptom management strategies are more efficient and effective for a certain clinical subgroup.

Implications for Nursing Practice

Findings from the current study are useful to determine who needs more intensive symptom management during cancer treatment. Clinicians must pay special attention to patients who experience all psychoneurologic symptoms at a higher level of intensity because those patients have a poor outcome.

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