

Sickness Behavior Clustering in Children With Cancer

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Abstract

Despite knowing that pediatric cancer patients experience multiple concurrent symptoms, most research focuses on individual symptoms. This study is a secondary data analysis from previous research evaluating symptom clusters and carnitine plasma levels in 67 children and adolescents aged between 7 and 18 years, before and after receiving ifosfamide, doxorubicin, or cisplatin chemotherapy. In preparation for cluster analysis, fatigue, nausea and vomiting, depression, and performance status symptoms were rated in categories of none, mild, moderate, or severe. A conceptual approach was used to evaluate the identification of unique patterns of symptoms that cluster as well as what subgroup members of pediatric oncology patients assemble together. Comparison of symptoms is made with the recent literature on sickness behavior symptoms. The hierarchical agglomerative cluster analysis was used to identify and classify variables into groups based on similarities they possess. This cluster analysis increases awareness of sickness behavior symptoms, patterns, interaction, and synergy. Increasing knowledge of the complex symptom experiences of pediatric oncology patients provides the scientific basis for new directions in symptom intervention.

Keywords

symptom clusters, cancer, children, adolescents, sickness behavior

Symptom cluster research in nursing is an area of recent exploration, with studies searching for symptom relationships, concurrence, and underlying dimensions (Kim, McGuire, Tulman, & Barsevick, 2005). The term *cluster* is defined as an aggregate of symptoms that are related and can be predictable (Dodd, Janson, et al., 2001; Dodd, Miaskowski, & Lee, 2004; Dodd, Miaskowski, & Paul, 2001). The current challenge for exploration of symptom clustering is to clearly demonstrate the meaning of the cluster while addressing patterns of association and interaction. Recent research provides rationale for similarities between symptom experiences by adults with cancer and sickness behavior symptoms, originally discovered as part of a syndrome that occurs during the course of an infection (Cleeland et al., 2003; Dantzer & Kelley, 2007; De La Garza, 2005; Kelley et al., 2003; Myers, 2008). Sickness behavior syndrome is conceptualized as both emotional and physical symptoms and can include lethargy, depression, appetite changes such as anorexia, energy conservation, fever, anhedonia, cognitive impairment, hyperalgesia, and decreased social interaction (Cleeland et al., 2003; Dantzer & Kelley, 2007; De La Garza, 2005; Kelley et al., 2003; Myers, 2008). Chronic

stress or insufficient recovery time from stressful events such as cancer treatment can diminish the body's ability to regulate the inflammatory response, resulting in production of inflammatory cytokines that cause the sickness behavior syndrome.

Despite knowing that most pediatric cancer patients experience multiple concurrent symptoms, most research focused on individual symptoms. Our work in examining fatigue during childhood cancer treatment established the foundation for exploring this symptom and the possible synergistic adverse effects that may occur in the presence of other symptoms (Hockenberry et al., 2010; Hockenberry, Hooke, Gregurich, & McCarthy, 2009). Previous research identifies distressing cancer events and symptoms from the perspective of the children and their

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families (Collins et al., 2000; Hedström, Haglund, Skolin, & von Essen, 2003; Woodgate, & Degner, 2003). Hedström et al. (2003) discovered that the most common causes of distress in a group of 121 children with cancer were treatment-related pain, nausea, and fatigue. Collins et al. (2000) described the most common physical symptoms (prevalence >35%) in a group of 160 children with cancer as lack of energy, pain, drowsiness, nausea, cough, and lack of appetite. Woodgate and Degner (2003) explored expectations and beliefs about childhood cancer symptoms in a group of 39 children and their family members and found that these individuals expected to experience suffering as part of the cancer treatment. Research is emerging on coexisting symptoms measured at the same time interval. For children hospitalized during chemotherapy, the number of nocturnal awakenings significantly correlated with the levels of hospital-related fatigue (Hinds, Hockenberry, Rai, et al., 2007). Children with acute lymphocytic leukemia reported the prevalence of fatigue and night awakenings (Gedaly-Duff, Lee, Nail, Nicholson, & Johnson, 2006). Hinds, Hockenberry, Gattuso, et al. (2007) found significant increases in fatigue and changes in sleep quality in response to a 5-day pulse of dexamethasone during acute lymphocytic leukemia treatment.

Docherty's (2003) review of the published literature on symptom experiences of children and adolescents with cancer revealed no longitudinal symptom management study designs, limited use of conceptual models or theories, frequent adaptation of adult instruments as symptom measures, and no intervention studies to decrease the impact of these symptoms in children with cancer. Only 2 studies were found evaluating symptom clusters in pediatric cancer patients. In a study of 144 older pediatric oncology patients treated in Taiwan, 5 symptom clusters were found—(a) symptoms related to sensory discomfort and body image; (b) symptoms related to circulatory and respiratory problems; (c) fatigue, sleep, and depression; (d) body image and eating difficulties; and (e) gastrointestinal irritation and pain (Yeh et al., 2008). In a previous article published from the database used in this study, the influence of fatigue, nausea and vomiting, and sleep disturbances was examined in relation to clinical outcomes defined as behavior changes, depression, and performance status (Hockenberry et al., 2010). Using a linear mixed model (LMM), we determined that adolescents who experienced increased fatigue and sleep disturbances had more depressive symptoms and behavior changes. Children with higher levels of fatigue had increased depressive symptoms. The more fatigue parents perceived in their children and adolescents, the more behavior and emotional difficulties were reported.

Increasing knowledge of the complex symptom experiences of pediatric oncology patients will provide the

scientific basis for new directions in symptom intervention. This could allow for prioritization of symptoms for assessment and management during treatment (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). The purpose of this exploratory study using cluster analysis on an existing data set was to examine the synergistic symptom effects experienced by pediatric patients during cancer therapy. This study is the first to evaluate unique patterns of symptoms that cluster during childhood cancer treatment as well as explore what subgroup members share similar experiences.

Method

Design

This study is a secondary data analysis from a study evaluating symptom clusters and carnitine plasma levels in children and adolescents before and after receiving cisplatin, ifosfamide, or doxorubicin chemotherapy (Hockenberry et al., 2010). In the first article, an LMM was used to determine how the symptoms of fatigue, sleep disturbance, and nausea and vomiting predicted depression and behavior before and after chemotherapy. Although the LMM provides insight into observations that are interdependent, it gives limited insight into how symptoms related to each other and what subgroups of individuals demonstrate similar symptom profiles. The importance of this secondary analysis is that it allows us to explore subgroups of patients with similar sickness behavior symptom experiences using hierarchical agglomerative cluster analysis to categorize groups of individuals into similar sickness behavior symptom profiles.

Sample

Settings for this study included 2 major childhood cancer treatment centers in the United States. The sample included 67 children and adolescents aged between 7 and 18 years who were receiving intravenous cisplatin, ifosfamide, or doxorubicin chemotherapy. These 3 agents were defined as "study drugs." These 3 agents have similar hospital stays and emetogenic patterns (Robinson & Carr, 2007; Small, Holdsworth, Raisch, & Winter, 2000). Overall, 60 (89.6%) participants received the chemotherapy as inpatients and 7 (10.4%) were in the outpatient clinic. Both Spanish-speaking and English-speaking children and adolescents participated in the study.

Procedure

In the original study, participants and their parents were approached about the study in the hospital setting or outpatient cancer clinic after institutional review board

approval was obtained. The investigator or research nurse at each of the study sites discussed the study and any questions were answered. Consent was obtained from a parent or legal guardian and assent was obtained from children and adolescents. Any child or adolescent who did not want to participate were excluded from the study.

Fatigue instruments were completed on the first day of chemotherapy (all study agents—ifosfamide, cisplatin, or doxorubicin were administered on day 1) and 1 week later. The wrist actigraph was worn on the nondominant hand during the course of chemotherapy and for 48 hours after discharge from the hospital to provide at least 3 nights' measurement for evaluation of sleep–wake patterns and daytime activity performance. Nausea and vomiting were measured every 24 hours during the course of chemotherapy and for 48 hours after discharge. Depression was evaluated using the Child Depression Inventory (CDI) on the first day of chemotherapy and 1 week later. The Lansky Play-Performance Scale (7–12 years) or Karnofsky Performance Status Scale (>12–18 years) was used to measure performance status on the first day of chemotherapy and 1 week later.

Study Measures

Fatigue. The Childhood Fatigue Scale was used in children 7 to 12 years of age. The Childhood Fatigue Scale is a 14-item questionnaire and asks the children about their experience of any fatigue-related symptoms during the past week. The child is asked to rate how much fatigue bothers him or her on a 4-point Likert-type scale ranging from *not at all*, *a little*, *some*, *quite a bit*, to *a lot*. Total score ranges from 0 to 56, higher scores correspond to greater amounts of experienced fatigue. Reliability and construct validity were previously established in a population of 149 children receiving chemotherapy (Hockenberry et al., 2003). In this study, internal consistency reliabilities of the Childhood Fatigue Scale before and after chemotherapy were .761 and .899 (Cronbach's α). The 3 Fatigue subscales, namely energy, function, and mood, were used to further define the symptom in this population. Fatigue severity was classified into 4 categories: no fatigue, mild fatigue (defined as a little or some fatigue), moderate fatigue (defined as quite a bit but occurring less than 50% of the time in the past week), and severe fatigue (defined as happening a lot, or more than 50% of the time in the past week). This same fatigue severity classification was used for each of the 3 subscales.

The Adolescent Fatigue Scale was used in adolescents aged between 13 and 18 years and is a 14-item self-report scale developed to measure fatigue experienced in the past week. Items describe the intensity of fatigue on a 4-point Likert-type scale. Intensity ratings range from

0 (*no fatigue symptoms*) to 56 (*high fatigue*). Instrument reliability and construct validity as well as the ability to measure change over time were tested in 64 adolescents who completed the scale at 2 to 4 data points as a subject in 1 of 4 studies (Hinds, Hockenberry, Tong, et al., 2007). In this study, internal consistency reliabilities of the Adolescent Fatigue Scale before and after chemotherapy were .766 and .899 (Cronbach's α). Fatigue severity was classified into 4 categories: no fatigue; mild fatigue (defined as a little or some fatigue), moderate fatigue (defined as quite a bit but occurring less than 50% of the time in the past week), and severe fatigue (defined as happening a lot, or more than 50% of the time in the past week). Adolescent Fatigue Scale questions were placed into 3 categories: energy, function, and mood, and the fatigue severity classification was used to evaluate each category.

Sleep Disturbance. The actigraph was used to monitor sleep and daytime activity in children and adolescents in this study because it is a nonintrusive yet sensitive measurement approach. Actigraph has been used to validate parental reports of their child's sleep abnormalities (Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991) while producing more objective and accurate data as compared with parental reports (Sadeh, 1996; Sadeh, Horowitz, Wolach-Benodis, & Wolach, 1998). Analysis of actigraph records revealed sleep–wake patterns that correlated closely with patterns obtained via polysomnographic records and behavioral observations (Sadeh, Acebo, Seifer, Aytur, & Carskadon, 1995; Sadeh et al., 1991; Sadeh, Hauri, Kripke, & Lavie, 1995). Paavonen, Fjallberg, Steenari, and Aronen (2002) found stability in actigraph placement on the wrist and the waist in a group of 20 children aged between 7 and 12 years.

The wrist actigraph. The Mini Motionlogger AAM-32 is a wristwatch style device that weighs 1 ounce and contains a biaxial piezoelectric sensor, microprocessor with programmable epoch length. The epoch length determines data storage capacity; for this study, the epoch length was 1 minute using the zero-crossing mode, providing up to 16 days of storage. A scoring program accompanies this system and computed the following calculations: total sleep minutes, number of nighttime awakenings, and daytime activity. In this study, the actigraph was worn on the nondominant wrist (range 3–9 days, mean = 6 days).

Nausea and Vomiting. The frequency and duration of nausea and vomiting were measured every 24 hours during the course of therapy and for 48 hours after discharge on all children and adolescents. A self-report on the amount of nausea the patient felt was obtained every 24 hours, in the afternoon while the children and adolescents were awake, using a 100-point visual analogue scale. In this study, nausea was categorized using the visual

analogue scale as mild (0-10), moderate (20-40), or severe (>40-100). The number of vomiting episodes was obtained from the daily nursing flowsheet in the medical record. Vomiting severity was categorized as follows: 0-1 episodes = mild, 2-4 episodes = moderate, >4 episodes = severe.

Depression. The Child Depression Inventory (Kovacs, 1992) is a self-rating measure of depression completed by all children and adolescents. It requires one of the lowest reading levels of currently available depression measures, with norms collected from public school children in Grades 2 through 8. The CDI consists of 27 questions, each question consists of 3 possible responses: 0 (*absence of the symptom*), 1 (*mild symptom*), or 2 (*definite symptom*). The total score consists of 5 subscales: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. CDI reliability and construct validity have been previously established in this study. In this study, internal consistency reliabilities of the CDI before and after chemotherapy were .696 and .718 (Cronbach's α). The normal range for the CDI total score is 0 to 16, with scores >16 indicating depression. In this study, children and adolescents "at risk for depression" had CDI scores of 10 to 16. A score of >16 identified the presence of depression in this group of patients.

Performance Status. Daytime activity and percent time asleep during the day were measured with the watch actigraph as part of the overall performance evaluation. Performance status data were also collected using 2 other scales.

The Lansky Play-Performance Scale for children was developed to provide a parent-rated measure of performance status for children with cancer. In this study, parents completed the Lansky Play-Performance Scale for children 7 to 12 years of age. It is widely used in pediatric oncology as a measure of child activity and functional status. Level of performance is described in terms of play, degree of limitation, and degree of independence. Ratings are combined into a total score ranging from 0 to 100. The scale has been standardized on 3 groups of children: pediatric cancer patients, patients' siblings, and hospital employees' children. Interrater reliability between parent ratings has been established (L. L. Lansky, List, Lansky, Cohen, & Sinks, 1985; S. B. Lansky, List, Lansky, Ritter-Sterr, & Miller, 1987). For this study performance status was classified into 4 categories: no limitations = 100, mild = 80 to 99, moderate = 50 to 79, and severe = <50.

The Karnofsky Performance Status Scale is a widely used measure of functional status of adult cancer patients. In this study, it was completed by the parent to rate the performance status of 13- to 18-year-olds. Level of performance is described in terms of ability to perform self-care and participate in normal activity. These are

combined into a scale ranging from 0 to 100. In previous studies, interrater reliability has been found to range from .66 (Yates, Chalmer, & McKegney, 1980) to .97 (Mor, Laliberte, Morris, & Wiemann, 1984). For this study performance status was classified into 4 categories: no limitations = 100, mild = 80 to 99, moderate = 50 to 79, and severe = <50.

Statistical Considerations

The primary aim of this study was to examine the synergistic symptoms experienced by pediatric oncology patients during cancer therapy. Symptoms examined were fatigue, performance status, nausea severity, vomiting severity, sleep (sleep minutes, number of wake episodes, and daytime activity), and depression. A conceptual approach was used to evaluate both the identification of symptoms that cluster as well as subgroups of pediatric oncology patients that assemble together. The hierarchical agglomerative cluster analysis was used to identify and classify symptoms into groups or "clusters" based on similarities and characteristics they possess by minimizing the within-group variance and maximizing the between-group variance. This approach was also used to determine the subgroups of patients that might cluster together. Within each cluster, patient demographic characteristics, disease, and treatment were examined to determine the membership of each cluster.

Ward's linkage method with Euclidean distance as the similarity measure was applied to establish the number of clusters. Ward's method is distinct from other methods because it uses an analysis of variance approach to evaluate the distances between clusters. Since the variables included in the analysis were measured on different scales, z-score transformations were applied to selected variables. This avoids the fact that variables with dominating variance will be the primary classification variables.

Results

A total of 67 patients were enrolled in this study (Table 1). There are 38 (56.7%) males and 29 females (43.3%) with a mean age of 12.3 years (range = 7-18 years). There were 32 (47.8%) Caucasians, 24 (35.8%) Hispanics, 8 (11.9%) African Americans, and 3 (4.5%) Asian/Pacific Islanders in the study. There were 27 (40.3%) patients who received doxorubicin, 21 (31.3%) who received ifosfamide, and 19 (28.4%) who received cisplatin. A total of 33 (49.3%) patients in this study had previously received one of the study drugs. In total, 20 (29.1%) patients had no prior chemotherapy treatment of any type. The majority (56.7%) of the patients were diagnosed with solid tumors and 43.3% with leukemia/lymphoma.

Table 1. Patient Demographics

	N	Percentage
Gender		
Male	38	56.7
Female	29	43.3
Age (years)		
7-12 (children)	35	52.2
13-18 (adolescents)	32	47.8
Race		
Caucasian	32	47.8
Hispanic	24	35.8
African American	8	11.9
Asian/Pacific Islander	3	4.5
Drug treatment		
Cisplatin	19	28.4
Doxorubicin	27	40.3
Ifosfamide	21	31.3
Prior study drug ^a	33	49.3
No prior chemotherapy	20	29.1
Diagnosis		
Solid tumor	38	56.7
Leukemia/lymphoma	29	43.3

a. Prior to enrollment patients received cisplatin, ifosfamide, or doxorubicin chemotherapy treatment.

Initially, 3 clusters were found in the analysis. One cluster included only the sleep variables (sleep minutes, number of wake episodes, and daytime activity). A principal component (PC) analysis with varimax rotation was used to produce the representation of the correlation of the sleep symptoms in terms of a PC. This PC accounted for the maximal amount of the variance of the sleep symptoms (70.33% of the variance; Table 2). For the remainder of the discussion on sleep disturbances among patients in this study, the sleep principal component (sleep PC) factor will be used.

Two Symptom Clusters

The results of the cluster analysis are shown by a dendrogram in Figure 1 and Table 3. The dendrogram lists all the variables and indicates at what level of distance the clusters are joined. Fatigue, performance status, and depression were measures obtained 1 week after chemotherapy. Sleep, vomiting severity, and nausea severity were measured during the week of chemotherapy. Two clusters were identified in the final analysis using Ward's method. Symptom clusters observed in this study are compared with sickness behavior symptoms found in the literature (Table 3).

Patterns unique to cluster 1 included the Fatigue subscales of energy, function, and mood, and depression in this group of patients. Cluster 2 included vomiting

severity, nausea severity, sleep PC, and performance status in children and adolescents in this study. In cluster 1, the prevalence of moderate to severe measures for the Fatigue subscales of energy, function, and mood were 60.3%, 47.6%, and 36.5%, respectively, 1 week after chemotherapy. The prevalence of patients with moderate to severe measures for depression a week after chemotherapy was 18.5%.

Unique patterns in cluster 2 included vomiting severity, nausea severity, sleep PC, and performance status. In cluster 2, the prevalence of moderate to severe nausea, vomiting, and performance status changes were 42.4%, 20.6%, and 13.8%, respectively. Sleep disturbance, identified as sleep PC, is a cluster-2 symptom consisting of sleep minutes, wake episodes, and daytime activity. Children and adolescents in this study slept approximately 8.88 hours per night with an average of 18.5 wake episodes per night. Daytime activity averaged approximately 2.3 hours per day.

Patient Membership Within the Symptom Clusters

Characteristics of children and adolescents with moderate to severe symptoms found in cluster 1 and cluster 2 were evaluated (Tables 4 and 5; Figure 2). Measures included the cancer diagnosis, child or adolescent grouping, prior study drug, and prior chemotherapy of any type.

In cluster 1, adolescents who had a diagnosis of solid tumor and who had received prior chemotherapy were more likely to experience fatigue and depression (Table 4). Chi-square tests for the Fatigue subscales were statistically significant (.01 level) revealing that the majority of patients with moderate to severe fatigue symptoms were adolescents (63.2% to 78.3%).

In cluster 2, patients with moderate to severe nausea had received prior chemotherapy (60.7%) and more than half were diagnosed with solid tumors (57.1%; Table 5). More than half of the children and adolescents in cluster 2 with moderate to severe vomiting had prior experience with chemotherapy and 53.8% were diagnosed with leukemia/lymphoma. A total of 77.8% of the patients diagnosed with leukemia/lymphoma had moderate to severe limitations in performance status a week after chemotherapy. Subgroup evaluation of the characteristics of children and adolescents associated with the sleep PC of cluster 2 revealed that those diagnosed with a solid tumor have significantly more sleep minutes ($p = .011$) as well as more wake episodes ($p = .019$), and significantly less daytime activity ($p = .050$) than patients diagnosed with leukemia/lymphoma (Table 6). In addition, adolescents had significantly more wake episodes ($p = .002$) and less daytime activity ($p = .001$) than children in the study.

Table 2. Total Variance of Sleep Variables

	Initial Eigenvalues			Extraction Sums of Squared Loadings		
	Total	Percentage of Variance	Cumulative Percentage	Total	Percentage of Variance	Cumulative Percentage
Sleep minutes	2.11	70.328	70.328	2.11	70.328	70.328
Wake episodes	0.568	18.941	89.269			
Daytime activity	0.322	10.731	100			

NOTE: Extraction method—principal component analysis.

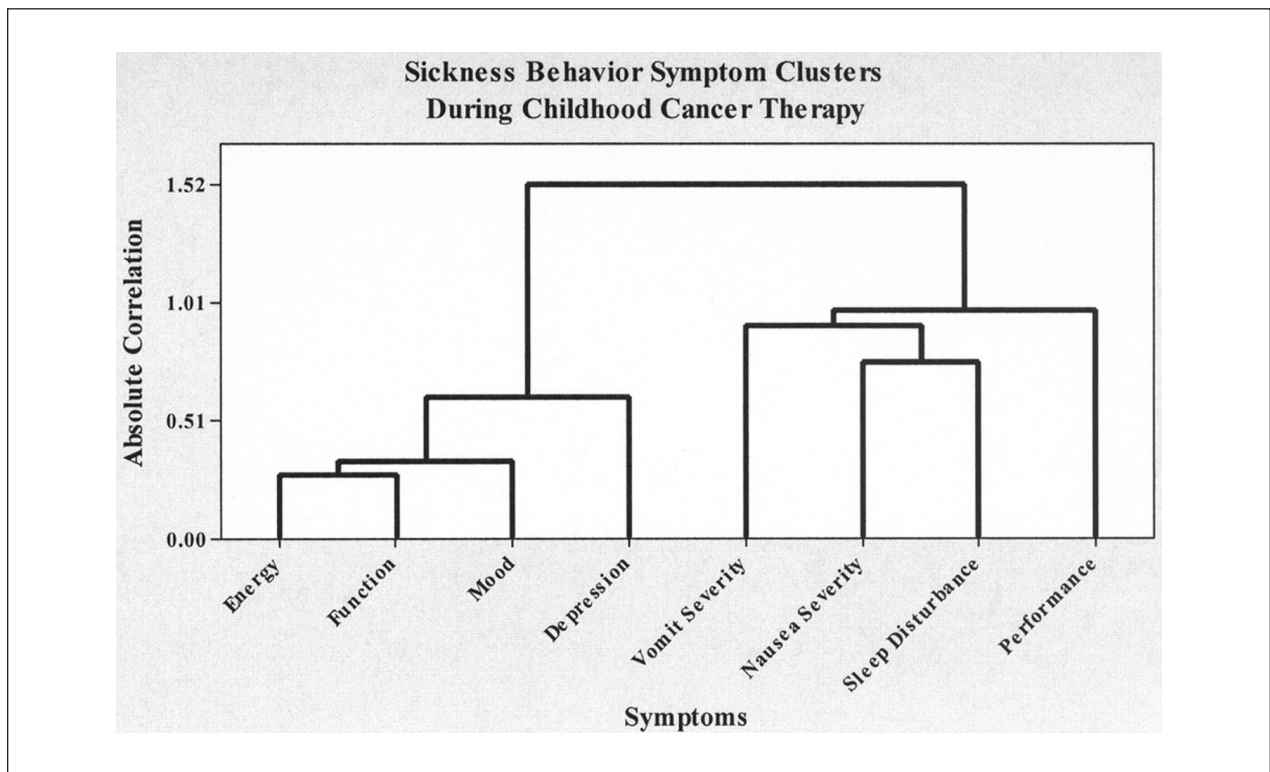


Figure 1. Dendrogram of symptom clusters in children with cancer

Table 3. Sickness Behavior Symptoms in Children With Cancer

Symptoms in Children With Cancer	Sickness Behavior Symptoms
Cluster 1	Emotional
Fatigue—energy	Fatigue or lack of energy.Wake up feeling tired
Fatigue—function	Trouble concentrating or making decisions
Fatigue—mood	Irritability—feeling stressed, nervous, or overwhelmed
Depression	Sadness throughout the day—feelings of emptiness or hopelessness
Cluster 2	Physical
Vomiting severity	Change in appetite
Nausea severity	Change in appetite
Performance status	Aches and pains—loss on interest or enjoyment in activities
Sleep disturbance	Difficulty falling asleep or staying asleep

Table 4. Pediatric Oncology Patients During Cancer Therapy Characteristics of Symptoms in Cluster 1 for Moderate to Severe Measures

Symptoms	Moderate to Severe (%)	Characteristics of Symptoms (%)
Fatigue subscales		
Energy	60.3	Prior chemotherapy (73.7) Adolescents (63.2) ^a Diagnosis: solid tumor (60.5)
Function	47.6	Prior chemotherapy (66.7) Adolescents (70.0) ^a Diagnosis: solid tumor (63.3)
Mood	36.5	Prior chemotherapy (69.6) Adolescents (78.3) ^a Diagnosis: solid tumor (69.6)
Depression (CDI)	18.5	Prior chemotherapy (75.0) Adolescents (58.3) Diagnosis: solid tumor (66.7)

NOTE: CDI, Child Depression Inventory.

a. Chi-square tests between patient age levels (child and adolescent) and symptom levels (none to mild and moderate to severe) were statistically significant at $p < .01$ level.

Table 5. Pediatric Oncology Patients During Cancer Therapy Characteristics of Symptoms in Cluster 2 for Moderate to Severe Measures

Symptoms	Moderate to Severe (%)	Characteristics of Symptoms (%)
Nausea severity	42.4	Prior chemotherapy (60.7) Diagnosis: solid tumor (57.1)
Vomiting severity	20.6	Prior chemotherapy (53.8) Diagnosis: leukemia/lymphoma (53.8)
Performance status	13.8	Prior chemotherapy (55.6) Diagnosis: leukemia/lymphoma (77.8)

Discussion

Symptom cluster research allows for exploration of the complexities associated with childhood cancer treatment. It is striking to note how similar the symptoms in this study are when compared with the complexities of symptoms described in the sickness behavior syndrome literature (Cleeland et al., 2003; Dantzer & Kelley, 2007; De La Garza, 2005; Kelley et al., 2003; Myers, 2008). Sickness behavior syndrome is conceptualized as both emotional and physical responses to illness; children and adolescents in this study suffered from both changes in emotions and behaviors and experienced numerous physical symptoms. These findings support the argument that cancer treatment greatly diminishes the body's ability to defend itself against chemotherapy induced by-products of cellular metabolism resulting in symptoms modeling those found in the sickness behavior syndrome.

In this secondary data analysis, a hierarchical agglomerative cluster analysis approach revealed 2 symptom

clusters. The first cluster in this study included the Fatigue subscales of energy, function, and mood and the symptom of depression, similar to the cluster reported in the only other published study on symptom clustering in pediatric cancer patients reported by Yeh et al. (2008). Yeh et al. identified a symptom cluster that included fatigue and depression, as well as the patient's self-report of sleep disturbance. In our study, however, sleep was measured by actigraphy, a more objective sleep measure, and this symptom did not cluster with fatigue and depression. Barsevick (2007) has noted that symptom clusters may vary depending on the use of subjective compared with objective measurements. In this study, the cluster of fatigue and depression is logical and supports overlaps in the characteristics of these 2 symptom experiences. For example, children with depression report a lack of energy and ability to function as well as mood impairment (Hockenberry et al., 2010). When we used an LMM in our earlier analysis of this data set, we found that fatigue and depressive symptoms clustered in both adolescents

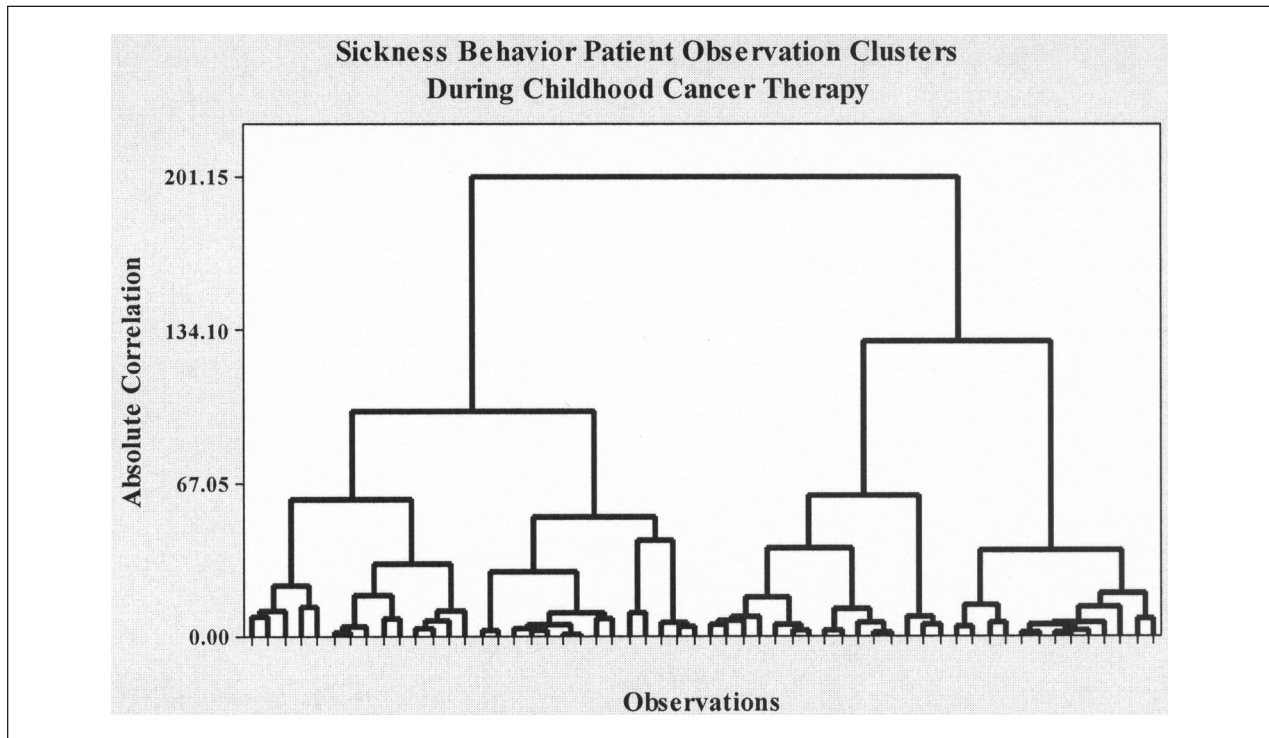


Figure 2. Dendrogram of observation clusters of children with cancer

Table 6. Pediatric Oncology Patients During Cancer Therapy Tests for Sleep Disturbance Symptoms in Cluster 2

Symptoms	Mean (SD)	t Test	p
Sleep minutes			
Solid tumor	564.97 (134.9)		
Leukemia/lymphoma	493.20 (83.9)	2.624 (60)	.011
Wake episodes			
Child	15.99 (6.3)		
Adolescent	21.15 (6.4)	-3.266 (63)	.002
Solid tumor	20.21 (6.9)		
Leukemia/lymphoma	16.27 (6.2)	2.400 (63)	.019
Daytime activity			
Child	154.81 (40.8)		
Adolescent	118.63 (37.1)	3.638 (60)	.001
Prior chemotherapy	145.32 (40.7)		
No prior chemotherapy	121.07 (43.8)	-2.113 (60)	.039
Solid tumor	128.25 (45.4)		
Leukemia/lymphoma	149.59 (36.9)	-2.001 (60)	.050

and children with adolescents also experiencing sleep disturbance as part of the cluster (Hockenberry et al., 2010). With this current examination using a hierarchical agglomerative cluster analysis approach, the sleep component was no longer included in the cluster.

The second cluster in our study included vomiting intensity, nausea intensity, sleep PC, and performance status. This cluster was not evident when we used the

LMM analysis of this data set (Hockenberry et al., 2010). In Yeh et al.'s (2008) study, one of the clusters included nausea and vomiting, lack of appetite, pain, and change in taste. The cluster found in our work includes nausea and vomiting, and the interrelationship of these 2 symptoms is logical. It is conceivable that the nausea and vomiting experienced by these patients caused increased awakening during the night and contributed to the sleep disruption. Additionally, adjuvant antiemetic medications such as dexamethasone may have caused sleep disturbance and warrants further exploration. Inclusion of performance status in this cluster is of interest and demonstrates how symptom distress interferes with the child's or adolescent's activities of daily living. Relationships between the characteristics of the patients within this cluster and individual symptoms in this cluster varied widely. There was no specific subgroup that shared similar symptom patterns within the cluster.

Conceptualizing the importance of not only the symptoms that cluster but also subgroups of patients with similar symptom experiences is essential. In the exploration of symptom clusters, Barsevick et al. (2006) stress the need to explore subgroups within a specific cluster. In our cluster of fatigue and depression, adolescents with the diagnosis of a solid tumor and who had received previous chemotherapy were more likely to experience this symptom cluster. Patients with solid tumors have repeated cycles of chemotherapy that are both intensive and consistent. Treatment for solid tumors greatly differs from

acute lymphocytic leukemia therapy that has specific phases of treatment and varies in intensity over time. Perhaps symptoms in this cluster become cumulative with repeated courses of intense chemotherapy for patients with solid tumors. In addition, adolescents may be more sensitive to the symptoms of fatigue and depression because of an increased understanding of their disease and awareness of treatment side effects.

It is recognized that a best practice for the analysis of symptom clusters has not been identified (Barsevick et al., 2006). In our secondary analysis, changing our analysis approach revealed new findings. Additionally, the variability of diagnoses, chemotherapy treatments, and place in the trajectory of treatment confound the analysis of symptom clusters (Barsevick et al., 2006). Larger multisite studies are needed to control for these variables. The study was also limited by the number of symptoms that were assessed. For example, pain was not assessed although it is frequently reported in children with cancer. Larger studies with a consistent cancer diagnosis and chemotherapy interventions will allow researchers to focus on the measurement of symptoms most likely experienced by that group. There is growing recognition that at least some of the symptoms experienced during childhood cancer treatment may share common biologic mechanisms. The sickness behavior syndrome model provides a foundation for exploration of symptoms and the body's adaptive and motivational reactions to childhood cancer therapy. Future exploration using symptom clusters research that includes methods to increase our biobehavioral understanding of side effects associated with childhood cancer treatment is needed.

Declaration of Conflicting Interests

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