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Symptom Clusters in Children and Adolescents Receiving Cisplatin, Doxorubicin, or Ifosfamide

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A review of the literature confirms the presence of significant fatigue, sleep disturbances, and nausea and vomiting in children and adolescents during treatment for cancer. Previous research provides insight into the suffering experienced by such individuals and the potential influence the symptoms have on clinical outcomes. Symptoms experienced by children and adolescents with cancer clearly can cluster, resulting in potential increases in their toxicity when combined. This study explored the relationships among fatigue, sleep disturbance, and nausea and vomiting, as well as how they specifically influenced children's or adolescents' clinical outcomes, measured by behavior, depression, and performance status. The symptom cluster was explored with parallel dimensions of fatigue, sleep disturbance, and nausea and vomiting in children and adolescents with cancer receiving similar chemotherapy during the same time period. The methodology strengthened understanding of the multiplicative effect that two or more symptoms can have on specific clinical outcomes.

The National Institutes of Health (2002) State-of-the-Science on Symptom Management in Cancer: Pain, Depression, and Fatigue found that efforts to manage symptoms of cancer and its treatments have not kept pace with new advances in the causes and cure for cancer. Several studies have addressed distressing cancer symptoms from the perspective of children and their families (Collins et al., 2000; Hedstrom, Haglund, Skolin, & von Essen, 2003; Woodgate & Degner, 2003). Hedstrom et al. 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. described the most common physical symptoms (prevalence higher than 35%) in a group of 160 children with cancer as lack of energy, pain, drowsiness, nausea, cough, and lack of appetite. Docherty (2003) completed a review of the published literature on symptom experiences of children and adolescents with cancer and

Purpose/Objectives: To examine the influence of the proposed symptom cluster of fatigue, nausea and vomiting, and sleep disturbances on clinical outcomes defined as behavior changes, depression, and performance status in children and adolescents before and after receiving cisplatin, doxorubicin, or ifosfamide chemotherapy.

Design: A prospective, descriptive, within-group, before-and-after-chemotherapy design was used.

Setting: Two major childhood cancer treatment hospitals in the United States.

Sample: 67 patients aged 7–18 years who were receiving chemotherapy courses of cisplatin, doxorubicin, or ifosfamide.

Methods: Fatigue, depression, behavior, and performance assessments were completed on the first day of cisplatin, doxorubicin, or ifosfamide therapy and one week later. Patients wore a wrist actigraph on the nondominant hand during the course of therapy and for 48 hours after discharge from the hospital. Nausea and vomiting were measured every 24 hours during the course of therapy and for 48 hours after discharge. A linear mixed model was used to evaluate the influence of the symptom cluster. Regression analysis was used to examine the associations between performance status and the symptom cluster. Principal component analysis with varimax rotation was used to produce the correlation of sleep symptoms.

Main Research Variables: Fatigue, nausea and vomiting, sleep disturbances, behavior, depression, and performance.

Findings: Adolescents with the cluster of increased fatigue and sleep disturbances experienced more depressive symptoms and behavior changes. Children with higher levels of fatigue had increased depressive symptoms. The more fatigue parents perceived in their children or adolescents, the more behavior and emotional difficulties were reported.

Conclusions: Fatigue, sleep disturbance, and nausea and vomiting, when clustered, impacted depressive symptoms and behavior changes in adolescents after chemotherapy. In children, fatigue alone impacted depressive symptoms and behavior changes.

Implications for Nursing: Symptom clusters can have a significant impact on children's and adolescents' quality of life during cancer treatment. Early recognition and intervention for these symptoms are an important nursing role.

found no longitudinal symptom management study designs, limited use of conceptual models or theories, frequent adaptation of instruments designed for adults as symptom measures, and no attention to the impact of symptoms on children's performance status.

Background

Fatigue in Children and Adolescents With Cancer

Fatigue is recognized as the most frequent symptom experienced by children and adolescents with cancer. In a survey of parents of children with cancer and healthcare professionals about cancer-related fatigue, 57% in each group reported fatigue as a frequent symptom (Gibson, Garnett, Richardson, Edwards, & Seppion, 2005). Pediatric patients experience more fatigue in the first few days after the start of a chemotherapy cycle (Gedaly-Duff, Lee, Nail, Nicholson, & Johnson, 2006; Yeh, Chiang, Lin, et al., 2008). Hinds, Hockenberry, Gattuso, et al. (2007) found significant increases in fatigue in response to a five-day pulse of dexamethasone during continuation therapy for acute lymphocytic leukemia. Children and adolescents describe fatigue as a distressing, pervasive symptom with physical, mental, and emotional components characterized by a lack of energy. The experience of fatigue differs by developmental level with school-age children, emphasizing the physical sensation of fatigue, whereas adolescents experience mental tiredness that alternates and at times merges with the physical sensation of fatigue (Hockenberry et al., 2003; Hockenberry-Eaton & Hinds, 2000; Hockenberry-Eaton et al., 1998, 1999).

Sleep in Children and Adolescents

Sleep plays an important restorative function for physical and cognitive health in children (Lewin & Dahl, 1999). Lack of sleep or interrupted sleep can result in tiredness, fatigue, and emotional changes (Bonnet, 1994). Current models of sleep recognize two interacting but independent processes that influence sleep. The homeostatic sleep process is a sleep-wake-dependent component of sleep. During the process, the need for sleep increases as a function of previous wakefulness and decreases over the course of a sleep period. The homeostatic sleep process interacts with the second process, the circadian sleep mechanism. The circadian process is entrained to the light-dark cycle, includes a cascade of neurohormonal changes, and has a neuroanatomic locus in the hypothalamus (biologic clock). The sleep homeostatic and circadian mechanisms are independent but interact over a 24-hour period to control wakeful states and sleep timing (Jenni & Carskadon, 2007). Disconnection between the homeostatic and circadian sleep processes can result in sleep disturbance.

Sleep disturbance in children with cancer may be influenced by the direct effects of cancer or the indirect effects of chemotherapy, radiation therapy, pain, brain injury, or fatigue (Rosen, 2007; Rosen, Shor, & Geller, 2008). The circadian and homeostatic systems may be impacted by changes in the neurologic machinery of the brain or by disruptions in the sleep environment (Rosen). In one study, children and adolescents hospitalized to receive chemotherapy experienced as many as 22 staff entries into their rooms during a night shift and had 0–40 nocturnal awakenings per night. The number of awakenings correlated with patients' reports of fatigue (Hinds, Hockenberry, Rai, et al., 2007). In a study that measured sleep at home after outpatient chemotherapy for acute lymphocytic leukemia, children (N = 9) experienced 1–37 awakenings at night (Gedaly-Duff et al., 2006). In a larger study (N = 100), Hinds, Hockenberry, Gattuso, et al. (2007) measured the change in sleep before and during a five-day outpatient course of oral dexamethasone during treatment for acute lymphocytic leukemia. In this study, sleep minutes and sleep duration increased during the steroid pulse. During both measurement periods, sleep efficiency was lower than the level considered acceptable for children.

Nausea and Vomiting in Children and Adolescents

A review of the literature revealed few publications in the previous five years related to nausea and vomiting in children and adolescents with cancer. Medical research articles focus on the use of tropisetron, a 5HT₃ receptor antagonist, to control nausea and vomiting (Aksoylar, Akman, Ozgenc, & Kansoy, 2001; Stiakaki et al., 1999). One nursing research article evaluated parents' observations of children's symptoms in relation to the children's self-reports of nausea and vomiting (Lo & Hayman, 1999). Although major advances have occurred with the development of 5HT₃ antagonists to alleviate chemotherapy-related nausea and vomiting, children and adolescents on aggressive treatment regimens continue to suffer from the symptoms.

Behavior Changes, Depression, and Performance Status in Children and Adolescents

Limited research is available relating to acute and chronic changes in behavior, depression, and performance in children receiving treatment for cancer. Children and adolescents in the authors' initial qualitative work were acutely aware of physical and emotional changes during treatment (Hockenberry-Eaton et al., 1998; Hockenberry-Eaton & Hinds, 2000). Children and adolescents reported frequent mood changes, decreased desire to communicate with others, and a wish to be left alone. In other qualitative studies, children and

adolescents have reported during cancer treatment feeling “cranky” and not like their usual selves (Woodgate, Degner, & Yanofsky, 2003) and having moodiness and sadness (Enskär, Carlsson, Golsäter, Hamrin, & Kreuger, 1997). However, reviews of overall psychosocial functioning among children and adolescents with cancer reveal that most patients do not develop ongoing serious psychological or emotional problems during treatment (Moore, 2004).

Performance status in children and adolescents with cancer is an important functional outcome (Lansky, List, Lansky, Cohen, & Sinks, 1985; Lansky, List, Lansky, Ritter-Sterr, & Miller, 1987). Seriously ill children often are restricted in their activities, resulting in frequent school absences and decreased ability to maintain peer friendships (Suzuki & Kato, 2003). Assessment of changes in performance status can provide insight into the changes in a child’s quality of life caused by cancer therapy and its side effects.

Symptom Clusters

The concept of symptom clustering has been the focus of research in adults with cancer. A symptom cluster is defined as “two or more symptoms that are related to each other and that occur together” (Kim, McGuire, Tulman, & Barsevick, 2005, p. 270). Symptoms in adult patients with cancer that have been examined for covariation include fatigue, insomnia, pain, depression, depression disturbance, and nausea and vomiting (Barsevick, 2007). Research is needed to identify the occurrence of symptom clusters in children and adolescents with cancer (Dodd, Miaskowski, & Lee, 2004). Studies have evaluated the incidence of concurrent symptoms in children during maintenance therapy for acute lymphocytic leukemia. Hinds, Hockenberry, Gattuso, et al. (2007) studied the effect of five-day pulse dexamethasone on children and adolescents and

found that sleep was disrupted and fatigue increased. In a feasibility study of nine children, Gedaly-Duff et al. (2006) reported pain, fatigue, and sleep disturbance for three days after outpatient chemotherapy. In 2008, Yeh, Chiang, Chien, et al. (2008) used the Memorial Symptom Assessment Scale to evaluate the prevalence of symptom clusters in 144 Taiwanese children aged 10–18 who were undergoing cancer treatment. Five symptom clusters were identified; some could be explained through cultural differences. One cluster included the symptoms of fatigue, sleep disturbance, and depression.

Conceptual Framework

The symptom experiences of children and adolescents with cancer identify person, environmental, and disease factors as antecedents that influence an individual’s symptom experiences during treatment for cancer (Hockenberry-Eaton & Hinds, 2000; Hockenberry-Eaton et al., 1998, 1999). Person factors in the model include gender and age. Environmental factors include hospitalization for chemotherapy (see Figure 1). Prior research reveals that hospitalization plays a major role in causing adverse symptom experiences, including increased fatigue and sleep disturbance. Disease factors influencing symptom experiences in children and adolescents with cancer include the type of cancer and type of chemotherapy administered. In this study, chemotherapy included three known emetogenic agents: ifosfamide, doxorubicin, and cisplatin. Symptoms experienced by children and adolescents with cancer seldom occur in isolation. Fatigue, sleep disturbance, and nausea and vomiting are defined as a symptom cluster after treatment with cisplatin, doxorubicin, or ifosfamide. Dimensions evaluated in this model include the quality, intensity, and timing of the

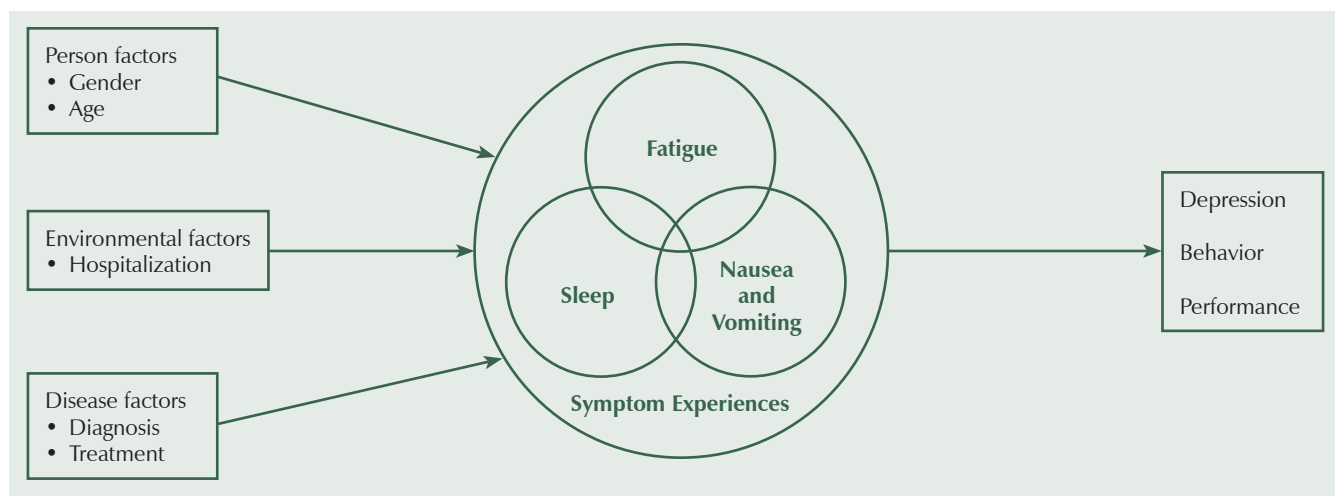


Figure 1. Symptom Experiences in Children and Adolescents With Cancer

symptom cluster following chemotherapy. The influence of the symptom cluster of nausea and vomiting, fatigue, and sleep on specific clinical outcomes is examined. In this model, clinical outcomes are defined by changes in behavior, depression, and performance.

The authors' previous research examining fatigue provides a foundation to continue exploration of that symptom and the possible synergistic adverse effects that may occur when fatigue, sleep disturbance, and nausea and vomiting are experienced. No studies were found in the literature evaluating this symptom cluster specific to a particular chemotherapy regimen for childhood cancer. Even less information is available regarding their synergistic effects and how they may influence behavior, depression, and performance status.

Design

A prospective, descriptive, within-group, before-and-after-chemotherapy research design was used to evaluate the presence of symptom clusters in children and adolescents with cancer. The researchers hypothesized that children and adolescents experiencing increased fatigue, nausea and vomiting, and sleep disturbances would experience behavior changes, depression, and decreased performance after receiving ifosfamide, doxorubicin, or cisplatin chemotherapy. The settings for the study were two major childhood cancer treatment centers in the United States. The sample included 67 children and adolescents aged 7–18 years who were receiving IV cisplatin, ifosfamide, or doxorubicin chemotherapy. The three agents have similar hospital stays and emetogenic patterns (Robinson & Carr, 2007; Small, Holdsworth, Raisch, & Winter, 2000). Sixty (89.6%) of the participants received the chemotherapy as inpatients; seven (10.4%) were in the outpatient clinic. Spanish- and English-speaking children and adolescents participated in the study.

Study Measures

Fatigue

The **Childhood Fatigue Scale (CFS)** was used in children aged 7–12 years. The CFS is a 14-item questionnaire and asks children about their experience of any fatigue-related symptoms during the previous week. Children are asked to rate how much fatigue bothers them on a four-point Likert scale ranging from “not at all” to “a lot.” Total score ranges from 0–56; higher scores correspond to greater amounts of experienced fatigue. Reliability and construct validity were established previously in a population of 149 children receiving chemotherapy (Hockenberry et al., 2003). In this study, internal consistency reliability of the CFS before and after chemotherapy were 0.761 and 0.899 (Cronbach alpha).

The **Adolescent Fatigue Scale (AFS)** was used in adolescents aged 13–18 years and is a 14-item self-report scale developed to measure fatigue experienced in the previous week. Items describe the intensity of fatigue on a four-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 two to four data points in one of four studies (Hinds, Hockenberry, Tong, et al., 2007). In this study, internal consistency reliability of the AFS before and after chemotherapy were 0.766 and 0.899 (Cronbach alpha).

The **Parent Fatigue Scale (PFS)** was used to obtain responses from parents of the children and adolescents. The PFS consists of 17 items that ask parents their perceptions of the amount of fatigue experienced by their children in the previous week and are rated on a four-point Likert-type scale. Total scores range from 0 (no perceived fatigue) to 68 (high perceived fatigue). Reliability and construct validity of the PFS were established in a population of 147 parents. PFS scores range from 17–68, with higher scores corresponding to greater amounts of perceived fatigue (Hockenberry et al., 2003). In this study, internal consistency reliability of the PFS before and after chemotherapy were 0.884 and 0.908 (Cronbach alpha).

Sleep Disturbance

An actigraph was used to monitor sleep (sleep duration, longest sleep episode, and number of night awakenings) 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 children's sleep abnormalities (Sadeh, Lavie, Scher, Tirosh, & Epstein, 1991) while producing more objective and accurate data as compared to 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 et al., 1991; Sadeh, Acebo, Seifer, Aytur, & Carskadon, 1995; 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 7–12 years.

The wrist actigraph: The Mini Motionlogger AAM-32 is a wristwatch-style device that weighs 1 ounce and contains a biaxial piezoelectric sensor and microprocessor with programmable epoch length. The epoch length determines data storage capacity; for this study, the epoch length was one minute, providing up to 16 days of storage. A scoring program accompanies the system and computes the following calculations: sleep onset, number of awakenings, total sleep minutes, length of awakenings, sleep efficiency, and wake after sleep. In

Table 1. Patient Demographics

Variable	n	%
Gender		
Male	38	57
Female	29	43
Age (years)		
7–12 (children)	35	52
13–18 (adolescents)	32	48
Race		
Caucasian	32	48
Hispanic	24	36
African American	8	12
Asian or Pacific Islander	3	4
Drug treatment		
Cisplatin	19	29
Doxorubicin	27	40
Ifosfamide	21	31
Prior study drug^a	33	49
Diagnosis		
Solid tumor	38	57
Leukemia or lymphoma	29	43

N = 67

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

this study, the actigraph was worn on the nondominant wrist (range = 3–9 days, \bar{X} = 6 days).

Nausea and Vomiting

The amount, frequency, and duration of nausea and vomiting were measured every 24 hours during the course of therapy and for 48 hours after discharge of all children and adolescents. The type, amount, frequency, and method of administration of antiemetics also were measured. A self-report on the amount of nausea a patient felt was obtained every 24 hours, in the afternoon while the children and adolescents were awake, via a 100-point visual analog scale. The number of vomiting episodes was obtained from the daily nursing flowsheet in the medical record. The parent and child were asked to record the presence of nausea, number of times vomiting occurred, oral intake, and whether antiemetics were given for the first 48 hours after discharge.

Behavior Measurements

The **Behavioral Assessment System for Children (BASC)** (Reynolds & Kamphaus, 1992) is a widely used means of self-rating designed to assess emotional and behavioral functioning in children and adolescents. It was empirically developed and has been validated in children with acute and chronic illnesses. The BASC consists of 152 true-or-false items and 186 items for adolescents. It incorporates a multidimensional perspective of clinical scales that measure maladjustment and adaptive scales that measure positive adjustment.

For this study, the Emotional Symptoms Index (ESI) composite score was analyzed. The composite is comprised of the Social Stress, Anxiety, Self-Esteem, Interpersonal Relations, Depression, and Sense of Inadequacy scales. The ESI is the most comprehensive emotional disturbance indicator. It is designed specifically for repeated, frequent administration to track changes and intervention efficacy. Raw scores from the scales are converted to a normative t score. An ESI score of 65 or higher indicates persistent distress, whereas 70 or higher suggests serious emotional disturbance. In this study, internal consistency reliability of the BASC before and after chemotherapy was 0.797 and 0.904 (Cronbach alpha).

The **Behavior Rating Inventory of Executive Function (BRIEF)** (Gioia, Isquith, Guy, & Kenworthy, 2000) is a behavioral rating system that was completed by parents in this study. The BRIEF is designed to objectively assess two factors, behavioral regulation and metacognition, by rating the presence or absence of symptoms involving inhibition, shifting, emotional control, initiation, working memory, planning and organization, organization of materials, and self-monitoring subscales. The questionnaire consists of 86 items that ask a parent whether a behavior has been a problem never, sometimes, or often in the previous six months. For this study, the Behavioral Regulation Index (BRI) was analyzed. The BRI is a composite summary score that includes three scales: inhibition, shifting, and emotional control. The first two, inhibition and shifting, are behavioral expressions, and the third is control over emotional expression. The BRI best reflects the level of behavioral control the child experiences. T scores are used to interpret the raw scale scores; a score higher than 65 denotes problems with the child's ability to self-regulate behavior as reported by his or her parent. Internal consistency reliability for the BRIEF has been established (Gioia et al.). In this study, internal consistency reliability of the BRIEF before and after chemotherapy was 0.934 and 0.946 (Cronbach alpha).

Depression

The **Child Depression Inventory (CDI)** (Kovacs, 1992) is a self-rating measurement of depression and was completed by all children and adolescents in the study. 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, and each question consists of three possible responses: 0 (absence of the symptom), 1 (mild symptom), or 2 (definite symptom). The total score consists of five subscales: negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem. Normal range for the total score is 0–16; scores higher than 16 are indicative of depression. CDI reliability and construct validity have been previously

Table 2. Summary of Symptom and Outcome Variables

Variable	Adolescents					Children				
	\bar{X}	SD	Minimum	Maximum	p	\bar{X}	SD	Minimum	Maximum	p
Fatigue score										
Time 1	16.5	7.4	5	29		8.5	6.9	0	23	
Time 2	22.6	12.6	1	49	0.016	9.6	9.5	0	35	NS
Depression										
Time 1	6.4	5.3	0	20		5.7	4.5	0	17	
Time 2	7.2	6.7	0	25	NS	4.7	4.1	0	14	NS
Behavior score										
Time 1	47.2	8	37	72		45.2	6.9	38	66	
Time 2	45.4	7.7	37	67	NS	42.7	5.6	37	62	≤ 0.001
Hours slept per night	9.3	2.4	5.8	16	–	8.5	1.5	6.1	12	–
Longest sleep episode (hours)	2.1	0.6	1.2	3.9	–	2.6	1	1.1	5	–
Number of wake episodes per night	21	–	5	34	–	16	–	7	33	–
NS—not significant										
Note. Time 1 was day 1 of chemotherapy, and time 2 was one week after chemotherapy.										

established. In this study, internal consistency reliability of the CDI before and after chemotherapy was 0.696 and 0.718 (Cronbach alpha).

Performance Status

The **Lansky Play-Performance Scale (LPPS) for Children** was developed to provide a parent-rated measurement of performance status for children with cancer. In the current study, parents completed the LPPS for children aged 7–12. The tool is used widely in pediatric oncology as a measurement of child activity and functional status. Level of performance is described in terms of play, degree of limitation, and degree of independence. These are combined into a scale: 100 indicates no limitations, 50–60 means moderate restrictions, and 10 or below indicates completely disabled. For the current study, a score of 70 or less was used to define limitations in performance status. The scale has been standardized on three groups of children: pediatric patients with cancer, patients' siblings, and hospital employees' children. Inter-rater reliability between parent ratings has been established (Lansky et al., 1987; Lansky, List, Lansky, Ritter-Sterr, & Miller, 1985). In the current study, the reliability for the Lansky scores was 0.776.

The **Karnofsky Performance Status scale (KPS)** is a widely used measurement of functional status of adult patients with cancer. In the current study, the KPS was completed by parents 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 100 (normal activity), 50–60 (requires assistance

to care for own needs), to 10 or below (completely disabled). For the current study, a score of 70 or less was used to define limitations in performance status. In previous studies, inter-rater reliability has been found to range from 0.66 (Yates, Chalmer, & McKeegney, 1980) to 0.97 (Mor, Laliberte, Morris, & Wiemann, 1984). In the current study, reliability was 0.121.

Procedure

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 answered questions. 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 was 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 one 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 three nights of measurement for evaluation of sleep-wake patterns. Sleep measures are defined as sleep duration, number of night awakenings, and longest sleep episodes. Nausea and vomiting were measured every 24 hours during the course of chemotherapy and for 48 hours after discharge. The type, amount, frequency, and method of administration of antiemetics

also were measured. Behavior was assessed by the parent's completion of the BRIEF and by the child's or adolescent's completion of the BASC on the first day of ifosfamide, cisplatin, or doxorubicin therapy and one week later. The same parent was used for each assessment. Depression was evaluated with the CDI on the first day of chemotherapy and one week later. Performance status was measured by the LPPS (for patients 7–12 years old) or KPS (patients 12–18 years old) on the first day of chemotherapy and one week later.

Statistical Considerations

A linear mixed model (LMM) was used to determine how the symptoms of fatigue, sleep disturbance, and nausea and vomiting predicted depression and behavior in children and adolescents before and after chemotherapy. LMM provides a powerful and flexible analytic tool for the data and allows subjects to have missing time points, inclusion of time-varying covariates, and a structured covariance matrix. Log transformation values of BASC composite scores and the square-root transformation values for CDI scores were used to satisfy the assumptions of normally distributed outcomes. Multinomial logistic regression and binary logistic regression analyses were used to examine associations among performance status and the five subscales of the CDI scores, respectively, with fatigue, sleep disturbance, and nausea and vomiting. Principal component analysis with varimax rotation was used to demonstrate that sleep disturbance accounted for 60.9% of the variables in the model (Joliffe & Morgan, 1992). Statistical significance for all tests was set at the 0.05 level. SPSS® 15.0 for Windows® was used for all statistical analyses.

Results

Demographic Characteristics

A total of 67 patients were enrolled in the study. See Table 1 for a breakdown of demographics. Twenty (30%) of the participants were receiving chemotherapy for the first time, 14 (21%) had received prior chemotherapy but not one of the study drugs, and 33 (49%) had received one or two prior chemotherapy courses with at least one of the three study drugs. Sixty (90%) of the participants received the chemotherapy as inpatients. The study drugs were administered by IV infusion with standardized mg/m² pediatric doses. Total doses received were ifosfamide 4,000–17,500, \bar{X} = 9,000 mg/m², cisplatin 75–200, \bar{X} = 100 mg/m², and doxorubicin 25–120, \bar{X} = 60 mg/m². Twenty-nine (43%) patients were diagnosed with leukemia or lymphoma, and 38 (57%) of the patients had solid tumors. Mean time since diagnosis until study enrollment for adolescents was 5.6 weeks (range = 0.3–24.7 weeks), and the mean time for children was 7.8 weeks (range = 0.1–27.3 weeks).

Descriptive Data and Changes in Variables

Adolescents: Fatigue scores measured by the AFS increased in adolescents from 16.5 on day 1 of chemotherapy to 22.6 one week later [$t(25) = -2.58, p = 0.016$]. During the course of chemotherapy, 81.3% of adolescents experienced nausea measured by self-report; almost half (48%) of adolescents experienced vomiting episodes. Adolescents averaged 9.3 hours of sleep with 21 night awakenings per night, with the longest sleep episode averaging 2.1 hours. Behavior scores decreased in adolescents from 47.2 on day 1 of chemotherapy to 45.4 one week later, with 7.4% of adolescents becoming

Table 3. Pearson Correlations Among the Variables in the Linear Mixed Model for Depression on Day 1 of Chemotherapy (Time 1) and One Week After Chemotherapy (Time 2)

Variable	Depression Time 1	Vomiting	Nausea	Sleep Disturbance	Fatigue
Adolescents					
Depression time 2	0.51*	-0.21	-0.06	-0.32	0.59*
Depression time 1	–	-0.82	-0.13	-0.422*	-0.2
Vomiting	–	–	0.37*	0.19	-0.16
Nausea	–	–	–	0.31	0.03
Sleep disturbance	–	–	–	–	0.15
Children					
Depression time 2	0.44*	-0.11	0.11	-0.09	0.42*
Depression time 1	–	-0.37*	-0.16	-0.1	-0.01
Vomiting	–	–	0.14	-0.13	0.2
Nausea	–	–	–	0.14	0.15
Sleep disturbance	–	–	–	–	0.09

* $p < 0.05$

Note. Depression was measured by the Child Depression Inventory, behavior by the Behavioral Assessment System for Children, vomiting by the frequency of vomiting during course of chemotherapy, nausea by patient self-report on a 100-point visual analog scale, sleep disturbance by a wrist actigraph that determined sleep-wake data and sleep episodes in one-minute intervals, and fatigue by the Childhood Fatigue Scale and Adolescent Fatigue Scale.

Table 4. Pearson Correlations Among the Variables in the Linear Mixed Model for Behavior on Day 1 of Chemotherapy (Time 1) and One Week After Chemotherapy (Time 2)

Variable	Behavior Time 1	Vomiting	Nausea	Sleep Disturbance	Fatigue
Adolescents					
Behavior time 2	0.79*	-0.33	-0.22	-0.39*	0.28
Behavior time 1	-	-0.26	-0.25	-0.45*	0.07
Vomiting	-	-	0.21	0.41*	-0.44*
Nausea	-	-	-	0.31	0.03
Sleep disturbance	-	-	-	-	0.15
Children					
Behavior time 2	0.88*	-0.17	-0.04	-0.06	0.15
Behavior time 1	-	-0.25*	-0.18	-0.04	-0.09
Vomiting	-	-	0.33	0.02	0.04
Nausea	-	-	-	0.14	0.15
Sleep disturbance	-	-	-	-	0.09

* $p < 0.05$

Note. Depression was measured by the Child Depression Inventory, behavior by the Behavioral Assessment System for Children, vomiting by the frequency of vomiting during course of chemotherapy, nausea by patient self-report on a 100-point visual analog scale, sleep disturbance by a wrist actigraph that determined sleep-wake data and sleep episodes in one-minute intervals, and fatigue by the Childhood Fatigue Scale and Adolescent Fatigue Scale.

at risk for behavioral problems (defined by the BASC score). Adolescent depression scores increased from 6.4 on day 1 of chemotherapy to 7.2 one week later, with 10% of the adolescents demonstrating depression one week after chemotherapy. None of the adolescents had a performance status of 70 or lower on day 1 of chemotherapy, but one week later, 16.1% had a performance status of 70 or lower ($p = 0.003$).

Children: Children 12 years of age and younger had increased fatigue scores measured by the CFS, from 8.5 on day 1 of chemotherapy to 9.6 one week later, but the change was not statistically significant. During the course of chemotherapy, 82.9% of children experienced nausea measured by self-report; 40.6% of the children experienced vomiting episodes. Children slept an average of 8.5 hours with 16 awakenings per night, with the longest sleep episode averaging 2.6 hours. Children 12 years of age and younger had decreased behavior scores from 45.2 on day 1 of chemotherapy to 42.7 one week later, with 2.9% of children becoming at risk for behavioral problems. Depression scores of children decreased from 5.7 on day 1 of chemotherapy to 4.7 one week later. Children's CDI scores were within the normal range. On day 1 of chemotherapy, 11.4% of children 12 years of age and younger had a performance status of 70 or lower; one week later, 11.8% had a performance status of 70 or lower. See Table 2 for a summary of symptom and outcome variables for children and adolescents.

Variable Correlations

Adolescents: Pearson correlations among the four independent symptom variables were small; however, for the CDI depression score, there was significant cor-

relation between nausea and vomiting ($r = 0.374$) in adolescents. Pearson correlations among the independent variables of fatigue, nausea and vomiting, and sleep disturbance identified in the LMM for depression and behavior are shown in Tables 3 and 4. In adolescents, depressive symptoms on day 1 of chemotherapy and fatigue were significantly correlated with depression one week after chemotherapy. Significant correlations between nausea and vomiting and depression on day 1 of chemotherapy and sleep disturbances were identified. Behavior on day 1 of chemotherapy and sleep disturbance significantly correlated with behavior a week later. Vomiting was significantly correlated with sleep disturbance and fatigue. Sleep disturbance and behavior on day 1 also were significantly correlated.

Children: For children, depressive symptoms on day 1 of chemotherapy and fatigue were significantly correlated with depression one week later. Depressive symptoms in children on day 1 of chemotherapy were significantly correlated with vomiting. Behavior on day 1 of chemotherapy was significantly correlated with behavior a week later in children.

Relationship of the Symptom Cluster to Depression

Results of the LMM demonstrated evidence of increased sleep disturbance and fatigue existing as a symptom cluster in adolescents but not in children.

Adolescents: Depressive symptoms increased from day 1 of chemotherapy to one week later in adolescents but did not reach statistical significance. The average depression score increased from 6.42 at the start of chemotherapy to 7.23 one week later. The LMM demonstrated that adolescents who experienced the symptom

cluster of sleep disturbance and fatigue had increased depressive symptoms. Sleep disturbance ($F[1,31] = 13.895, p = 0.001$) and fatigue ($F[1,38] = 73.762, p < 0.001$) as a cluster were significant predictors of depression in adolescents. Nausea and vomiting did not significantly contribute to the model.

Children: In children, no significant increase occurred in depressive symptoms from day 1 of chemotherapy to one week later. However, fatigue was a significant predictor ($F[1,67] = 18.427, p < 0.001$) of depressive symptoms in children. Sleep disturbance and nausea and vomiting did not reach significance in the model. All first-order interaction terms were examined and were not significant in the model (see Table 5).

Relationship of the Symptom Cluster to Behavior

Adolescents: LMM analysis revealed that behavior in adolescents was influenced by the symptom cluster of sleep disturbance and fatigue. Although most of the adolescents had behavior scores within the normal range, LMM analysis revealed that scores moved toward “at risk” for behavior changes in the presence of sleep disturbance and fatigue. The symptom cluster of sleep disturbance and fatigue influenced changes in interpersonal relations, stress, and anxiety among adolescents.

Children: In children, fatigue ($F[1,42] = 19.007, p < 0.001$) was the only significant predictor of behavior change; as fatigue intensified, behavior scores increased. In children, fatigue was the only symptom that significantly predicted changes in behavior. Five of the subscales measuring behavior followed a similar trend in children; fatigue influenced behavior changes in interpersonal relations, stress, anxiety, depression, and sense of inadequacy (see Table 6).

Relationship of the Symptom Cluster to Performance Status

To evaluate the effect of fatigue, sleep disturbance, and nausea and vomiting on performance status, multinomial logistic regression analysis was performed with the backward stepwise method. The researchers made no significant findings of the symptom cluster of fatigue, sleep disturbance, and nausea and vomiting with regard to the performance status measures for children and adolescents.

Parents’ perception of their children’s and adolescents’ fatigue was a significant indicator ($F[1,89] = 12.535, p = 0.001$) of behavioral control and emotional expression in children and adolescents. The more fatigue the par-

ents perceived in their children or adolescents, the more behavioral and emotional difficulties were observed.

Discussion

This study examined the proposed symptom cluster of fatigue, sleep disturbance, and nausea and vomiting experienced by children and adolescents receiving cisplatin, doxorubicin, or ifosfamide chemotherapy. Results of this study demonstrated that although correlations among the symptoms (fatigue, sleep disturbance, nausea and vomiting) were small, when clustered, fatigue and sleep disturbance created a significant impact on depressive symptoms and behavior changes in adolescents one week after chemotherapy. Fatigue increased over time for adolescents and clustered with sleep disturbance as a significant predictor of behavior changes and depressive symptoms. This symptom cluster in adolescents is similar to findings reported in adults with cancer. Pain, fatigue, and insomnia were significant and independent predictors of change in patient function following initial cancer treatment in a group of older adult patients (Given, Given, Azzouz, & Stommel, 2001). Pain and fatigue predicted changes in functional status in 93 adult patients receiving chemotherapy (Dodd, Miaskowski, & Paul, 2001). Although children 12 years of age and younger experienced shortened sleep intervals, similar to adolescents, sleep disturbance did not form a cluster with fatigue to impact behavior changes or depressive symptoms. However, children with higher levels of fatigue had increased depressive symptoms and behavior changes over time. The developmental differences between adolescents and children may have influenced symptom cluster development, which warrants further investigation.

Fatigue scores were higher and increased over time in adolescents, and although scores increased for children, changes were not statistically significant one week after

Table 5. Depression Linear Mixed Model Analyses for Adolescents and Children

Variable	Parameter Estimate	Standard Error	F	p
Adolescents				
Intercept	0.842	0.242	3.215	0.083
Time	0.233	0.13	13.895	0.001
Sleep disturbance	-0.477	0.128	73.762	-
Fatigue	0.069	0.008	-	-
Children				
Intercept	1.283	0.217	3.025	0.091
Time	0.312	0.179	18.423	< 0.001
Fatigue	0.061	0.0142	-	-

Note. Depression was measured by a Child Depression Inventory total score. Sleep disturbance was measured by a wrist actigraph to determine the sleep-wake data and sleep episodes in one-minute intervals. Fatigue-related symptoms were measured by the Childhood Fatigue Scale or Adolescent Fatigue Scale.

Table 6. Behavior Linear Mixed Model Analyses for Adolescents and Children

Variable	Parameter Estimate	Standard Error	F	p
Adolescents' Emotional Symptom Index (Composite)				
Intercept	1.628	0.016	–	–
Time	0.023	0.009	7.493	0.011
Sleep disturbance	–0.025	0.009	8.303	0.007
Fatigue	0.0012	0.0005	4.948	0.033
Children's Emotional Symptom Index (Composite)				
Intercept	1.608	0.009	–	–
Time	0.025	0.005	29.179	< 0.001
Fatigue	0.002	0.0005	19.007	< 0.001

Note. Sleep disturbance was measured by a wrist actigraph to determine the sleep-wake data and sleep episodes in one-minute intervals. Fatigue-related symptoms were measured by Childhood Fatigue Scale or Adolescent Fatigue Scale.

chemotherapy. Children responded with much lower fatigue scores in comparison to adolescent scores. This finding may be attributed to the unique developmental differences in how children versus adolescents experience fatigue. Previous research supports that children focus more on the physical sensation of fatigue, whereas adolescents recognize mental tiredness as an important part of the symptom (Hockenberry-Eaton & Hinds, 2000; Hockenberry-Eaton et al., 1999). Lack of change in children's physical fatigue one week after chemotherapy would cause fatigue scores to remain stable. In adolescents, physical fatigue may have remained stable but mental fatigue may have increased, reflected in higher fatigue scores one week after chemotherapy.

Sleep disturbance, defined by sleep duration, number of night awakenings, and longest sleep episode measured by actigraphy, occurred in children and adolescents. Although children and adolescents experienced total sleep hours comparable to those found in healthy children, night awakenings were frequent, resulting in shortened sleep intervals that were no greater than 2.5 hours for either group. Average total sleep hours for adolescents in this study exceeded that of pediatric outpatients with well-controlled asthma (8.2 hours) and that of age-matched, healthy children (8.3 hours) (Sadeh et al., 1998). Sleep duration in children, 7–12 years of age in this study, was comparable to normal sleep duration ranges for that age group (Iglowstein, Jenni, Molinari, & Largo, 2003). Frequent environmental disruptions experienced by children and adolescents in this study were most likely caused by the necessity of close nursing observation following cisplatin, doxorubicin, or ifosfamide chemotherapy and may have contributed to shortened sleep intervals. Lack of baseline sleep measurement data before the cycle of chemotherapy limits the authors' ability to determine whether children's sleep intervals

changed significantly during the study period.

Findings from this study confirm that nausea and vomiting continue to be common symptoms experienced during chemotherapy. During the course of chemotherapy, 82% of the adolescents and children experienced nausea; almost half (48%) of the adolescents and 41% of the children experienced vomiting episodes. Because nausea and vomiting did not cluster with other independent variables in this study, symptoms of nausea and vomiting may be independent of sleep disturbance and fatigue. Further research is needed in regard to the two symptoms.

Parent proxy measures of perceived fatigue and behavior changes were used as an additional indicator of the effect fatigue may have on behavior, depressive symptoms, and physical performance. The proxy indicators confirmed that fatigue parents perceived in their children or adolescents led to behavior changes. This finding revealed that others closest to children or adolescents are able to determine the presence and intensity of symptoms that may ultimately influence clinical outcomes. Parents can contribute to the understanding of the influence that symptoms may have on their children's or adolescents' well-being.

Implications for Nursing

A major strength of the study is the evaluation of a symptom cluster with parallel dimensions of fatigue, sleep disturbance, and nausea and vomiting observed in children and adolescents with cancer receiving similar chemotherapy during the same time period. This methodology strengthened understanding of the multiplicative effect of two or more symptoms on each other. The role symptom clusters may play on children's and adolescents' health status during specific treatment courses provides new insight related to the synergistic relationships these symptoms have on each other. Investigating comparable dimensions of a symptom cluster within the same time frame using analogous instrument scaling methods must continue to be an important research focus for future investigation of symptom clusters experienced during treatment for childhood cancer.

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Children's Research Hospital in Memphis, TN. This research was funded by a Symptom Cluster Research Grant from the ONS Foundation Center for Leadership, Information and Research through an unrestricted grant from Schering Oncology Biotech. Hockenberry can be reached at mjhocken@txccc.org, with copy to editor at ONFEditor@ons.org. (Submitted October 2008. Accepted for publication April 21, 2009.)

Digital Object Identifier: 10.1188/10.ONF.E16-E27

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