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Symptoms in Children Receiving Treatment for Cancer—Part I: Fatigue, Sleep Disturbance, and Nausea/Vomiting CE

Mary C. Hooke, PhD, APRN, PCNS, CPON, FAAN[1,2], and Lauri A. Linder, PhD, APRN, CPON[3,4]

Abstract

Children and adolescents with cancer often undergo intensive chemotherapy treatment to obtain remission and long-term survival. The pursuit of successful treatment outcomes may lead to high levels of symptom distress related to treatment side effects and toxicities. The Children's Oncology Group Nursing Discipline held a State of the Science Symposium "Symptom Assessment During Childhood Cancer Treatment" in 2018 that included reviews of evidence regarding key symptoms. The purpose of this review is to summarize and synthesize the evidence presented about the prevalence, relationships, trajectories, and associated biomarkers of selected symptoms experienced by children and adolescents during cancer treatment. Five symptoms were selected, with the focus on fatigue, sleep disturbance, and nausea/vomiting and included in Part I of the review. Using Ovid-Medline, studies published between 2008 and 2018 that focused on these specific symptoms during active chemotherapy treatment were selected. Fatigue interferes with normal developmental activities and is associated with sleep disturbances, and its pattern changes within a cycle of chemotherapy as well as across the treatment trajectory. Sleep is disrupted by the hospital environment, treatment medications, and changes in normal childhood and schedules. Disturbances of sleep persist during treatment, preventing recovery from poor quality sleep. Although pharmacologic interventions have advanced for treatment of nausea and vomiting, children and adolescents continue to struggle with this symptom. Its trajectory changes with the intensity of treatment, and over half of the patients report that they experience nausea and/or vomiting. Future research is needed to advance identification of biologic risk factors for symptoms and test effectiveness of symptom-related interventions.

Keywords

symptoms, fatigue, sleep, side effects of treatment

Introduction

Progress in the treatment of childhood cancer has led to a 5-year survival rate of 83% for all types of childhood cancers combined (Siegel, Miller, & Jemal, 2016). This success is attributed to high levels of pediatric clinical trial participation and treatment advances (Siegel et al., 2016). The intensity of treatment needed to improve survival has contributed to distressing symptoms that affect the child or adolescent's quality of life and interfere with ongoing development (Baggott et al., 2011; Kestler & LoBiondo-Wood, 2012). Symptom distress is the result of interacting variables, including biologic, physiological, social, and psychological factors that influence the level of perceived burden, the level of discomfort, and the interference with the child's quality of life (Hinds, Quargnenti, & Wentz, 1992). In their interviews and participant observation, Woodgate and Degner (2003) reported that suffering related to children's cancer symptoms was seen by children and their families as expected and an integral part of overcoming cancer. Furthermore, parents' perceptions of their children's symptom burden have been found to correlate with their own emotional distress (Pöder, Ljungman, & von Essen, 2010).

The organizing framework for the Children's Oncology Group (COG) Nursing Discipline, known as "Resilience in Individuals and Families Affected by Cancer" (Kelly, Hooke, Ruccione, Landier, & Haase, 2014), provides an

[1]University of Minnesota School of Nursing, Minneapolis, MN, USA
[2]Children's Minnesota, Minneapolis, MN, USA
[3]University of Utah College of Nursing, Salt Lake City, UT, USA
[4]Primary Children's Hospital, Salt Lake City, UT, USA

Corresponding Author:
Mary C. Hooke, PhD, APRN, PCNS, CPON, FAAN, University of Minnesota School of Nursing, 5-140 Weaver Densford Hall, 308 Harvard Street SE, Minneapolis, MN 55455, USA.
Email: hook0035@umn.edu

overall context to guide the prioritization of nursing research that focuses on supporting children and families in maintaining or regaining their well-being in the context of serious illness. This framework is grounded in positive health constructs that promote protective factors, such as family cohesion, social support, finding meaning, and courageous coping; it also addresses risk factors that decrease well-being, including illness-related distress and defensive (evasive or avoidant) coping (Kelly et al., 2014). The COG Nursing Discipline has prioritized illness-related distress as a key focus of their work, with the recognition that addressing symptoms is a major focus of pediatric oncology nursing (Landier, Leonard, & Ruccione, 2013).

An important step in moving the COG Nursing Discipline research agenda forward has been to review the current evidence regarding what is currently known about symptoms experienced by children and adolescents with cancer. A group of 10 expert nurse researchers and clinicians within the COG Nursing Discipline collaborated to identify the symptoms to include in this review. The group prioritized five symptoms known to contribute to symptom distress: fatigue, sleep disturbance, nausea and vomiting, pain, and sadness. It was recognized that these symptoms have been investigated in relation to each other in some studies as well as in studies of symptom clusters, in which the interrelationships of multiple symptoms are examined.

Purpose

The purpose of this review is to summarize and synthesize the evidence about the prevalence, relationships, trajectories, and associated biomarkers of selected symptoms experienced by children and adolescents during cancer treatment. The results of this review were presented at the COG Nursing Discipline state of the science symposium "Symptom Assessment During Childhood Cancer Treatment" in Dallas, Texas, in October 2018 (R13CA232442). In Part I of this two-part review, the symptoms of fatigue, sleep disturbance, and nausea/vomiting are presented. In Part II, pain, sadness, and symptom clusters are summarized.

Method

In Part I of this review, the search strategy methodology is explained as it relates to the five symptoms and symptom clusters. In collaboration with the biomedical librarian at the University of Minnesota's School of Nursing (L. Weinfurter, personal communication, May 18, 2018), Ovid-Medline was searched using the following terms: (a) neoplasms OR cancer OR oncology OR leukemia OR lymphoma; (b) child, OR pediatric OR paediatric OR infant OR adolescent OR teen; (c) and then search terms for the specific symptom—that is, fatigue, sleep, pain, and so on. An exclusion term was "survivor," and studies were limited to the English language and dates January 2008 to May 2018. Abstracts were then reviewed individually, and intervention studies and instrument development studies were removed. Studies that focused on symptoms related to radiation therapy and/or surgery without chemotherapy were also removed. If a study included both children in active treatment and survivors, it was included if the sample had greater than 50% of participants in active treatment. The remaining studies were then categorized within the symptom heading by the type of evidence and summarized in tables. The subheadings of the categories included symptom systematic reviews, incidence/prevalence of the symptom, symptom correlations, the symptom trajectory, biologic markers of the symptom, and the symptom experience. Some symptom studies reported outcomes regarding both the prevalence of a symptom and its relationship to other variables, or to its trajectory; however, each study reporting on a single symptom was listed in the table only once. Studies that included measurement of multiple symptoms (i.e., fatigue and sleep disturbance) were repeated in multiple symptom summary tables.

Results

Fatigue

Conceptual Definition. Fatigue was defined as a distressing, pervasive symptom with physical, mental, and emotional components characterized by a lack of energy. The symptom is experienced differently by developmental level with school-age children emphasizing the physical sensation while adolescents emphasizing mental and emotional tiredness along with the physical sensation of fatigue (Hockenberry-Eaton & Hinds, 2000).

Summary of Studies. Using the search methods previously described combined with the symptom "fatigue", 148 publications were identified. A review of abstracts and full text publications eliminated instrument development studies, fatigue intervention studies, or studies that focused on pediatric cancer survivors. The resulting 30 studies are summarized in Table 1. Studies were predominantly conducted in the United States and Canada but also included sites in China, Greece, Sweden, and Taiwan. Self-report instruments of fatigue were completed by children and adolescents or by parent proxy. Biologic markers focused on the relationship of fatigue to carnitine (a micronutrient), measures of oxidative stress, or genetic polymorphisms.

Systematic Reviews of Fatigue. The four systematic reviews of fatigue reported that fatigue is a prevalent, distressing symptom that negatively affects quality of life and is a

Table 1. Studies Reporting Fatigue.

Title and citation	Sample	Fatigue measures	Findings
Systematic reviews ($n = 4$)			
Review of symptom experiences in children and adolescents with cancer (Kestler & LoBiondo-Wood, 2012)	50 studies and 2 dissertations	CFS, FS-A, PFS, PedsQL-Fatigue	Fatigue is a prevalent, complex symptom that significantly affects the child's QOL throughout treatment into survivorship
Cancer-related fatigue in adolescents and young adults: A systematic review of the literature (Nowe et al., 2017)	12 studies of patients with cancer, ages 15 to 39 years	MF1-20, PedsQL-Fatigue, EORTC-QLQ C30, & others	Cancer-related fatigue was higher in AYA than in healthy peers and in older cancer patients
Teenage and young adult cancer-related fatigue is prevalent, distressing, and neglected: It is time to intervene. A systematic literature review and narrative synthesis (Spathis et al., 2015)	60 articles of AYA aged 13 to 24 years at time of cancer diagnosis or treatment	Most common instruments FS-A, MFS, and MSAS	Fatigue is one of the most prevalent, severe, and distressing symptoms. It is a significant barrier to physical and social activities It compounds dependence and social isolation in AYA with cancer
The lived experience of fatigue in children and adolescents with cancer: A systematic review (Tomlinson et al., 2016)	11 qualitative studies of children with cancer, ages 6 to 19 years	Most semistructured interviews	Fatigue feels like tiredness, weariness, loss of strength, dizziness, feeling drained and emotional. Negative impact of fatigue includes not being able to participate in regular activities
Studies of incidence/prevalence of symptom ($n = 2$)			
An evaluation of the factors that affect the health-related quality of life of children following myelosuppressive chemotherapy (Baggott et al., 2011)	61 children ages 10 to 18 years measured 1 week after myleosuppressive chemotherapy	MSAS 10-18	Fatigue was reported by 70.5% of children.
Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer (Miller, Jacob, & Hockenberry, 2011)	39 children ages 10 to 17 years receiving inpatient chemotherapy	MSAS 10-18	Fatigue was prevalent with a presence in 49.6% of children.

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Table 1. (continued)

Title and citation	Sample	Fatigue measures	Findings
Studies of correlations of symptom ($n = 8$)			
Health-related quality of life and its association with self-esteem and fatigue among children diagnosed with cancer (Al-Gamal & Long, 2016)	70 children with cancer ages 5 to 16 years living in Jordan	PedsQL-Fatigue	Children with higher fatigue had lower QOL scores.
Fatigue in adolescents with cancer compared with healthy adolescents (Daniel, Brumley, & Schwartz, 2013)	102 U.S. adolescents ages 13 to 19 years in active cancer treatment and caregivers; healthy controls	PedsQL-Fatigue	Adolescents with cancer had significantly more fatigue than healthy controls in all domains except cognitive fatigue. Higher fatigue was related to self-report of depressive symptoms, poorer QOL, higher negative affect, and behavioral disengagement coping style.
Fatigue, sleep-wake disturbances, and quality of life in adolescents receiving chemotherapy (Erickson et al., 2011)	20 adolescents ages 12 to 19 years measured over a 28-day chemotherapy cycle	PedsQL-Fatigue	Fatigue was highest during Week 2 after chemotherapy. At baseline, higher fatigue was associated with poorer psychosocial QOL. General fatigue and cognitive fatigue were significantly correlated with poorer sleep quality; cognitive fatigue was also associated with daytime functioning.
Fatigue and physical performance in children & adolescents receiving chemotherapy (Hooke, Garwick, & Gross, 2011)	30 children ages 6 to 17 years receiving first 3 cycles of chemotherapy	CFS, FS-A	Children ages 6 to 12 years who had an increase in physical performance on 6-minute walk test had decreased fatigue
Fatigue and sleep experiences at home in children and adolescents with cancer (Nunes, Jacob, Adlard, Secola, & Nascimento, 2015)	35 U.S. children ages 8 to 17 years in active cancer treatment for mixed diagnoses	PedsQL-Fatigue	More than half of the children struggled with fatigue had home; sleep/rest fatigue was associated with sleep duration. Adolescents had greater fatigue than children.
Physical activity (PA) and sleep among children and adolescents with cancer (Orsey, Wakefield, & Cloutier, 2013)	36 children ages 8 to 18 years in active treatment	CFS, FS-A, PFS	Fatigue was associated with sleep quality noted in a sleep diary but not with disturbances in sleep by actigraphy.
Chemotherapy-related fatigue in childhood cancer: Correlates, consequences, and coping strategies (Whitsett, Gudmundsdottir, Davies, McCarthy, & Friedman, 2008)	12 children ages 7 to 17 years currently receiving chemotherapy	CFS, FS-A	A significant relationship was found between fatigue and depression. Analysis of qualitative interviews showed that each symptom was unique and distinguishable.
Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents (Zupanec, Jones, & Stremler, 2010)	64 children ages 4 to 18 years receiving maintenance therapy for ALL	FS-A, PFS for children <13 years	Fatigue in children with ALL was significantly correlated with sleep problems and sleep habits.

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Table 1. (continued)

Title and citation	Sample	Fatigue measures	Findings
Studies of the trajectory of symptom ($n = 9$)			
A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy (Ameringer, Elswick, Shockey, & Dillon, 2013)	9 adolescents ages 13 to 18 years with cancer, measured on Day 1 and Day 2 of a chemotherapy cycle, 1 week later, and Day 1 of next cycle	FS-A	Fatigue changed significantly and was highest on Day 2 of chemotherapy and lowest a week later when blood counts were dropping. On Day 1 of the next cycle, fatigue and sleep were significantly correlated.
Changes in sleep and fatigue in newly treated pediatric oncology patients (Crabtree et al., 2015)	153 children ages 2 to 18 years measured 30 days and 8 weeks after newly diagnosed with cancer	PFS, CFS	Children with leukemia and lymphoma had significant improvement in fatigue by parent report compared with children with solid tumors and CNS tumors; fatigue by child report remained unchanged.
Patterns of fatigue in adolescents receiving chemotherapy (Erickson et al., 2010)	20 adolescents ages 12 to 19 years receiving chemotherapy measured over 4 weeks	Daily fatigue report form VAS	In adolescents receiving chemo every 3 to 4 weeks, fatigue peaked 2 to 4 days after chemo and then declined in a roller coaster pattern. Those receiving chemo in 1- to 2-week cycles, fatigue peaked 1 to 4 days after chemo, followed a yo-yo pattern but did not decline over the 4 weeks.
Parents' perceptions of their child's symptom burden during and after cancer treatment (Hedén, Pöder, Essen, & Ljungman, 2013)	160 parents of 89 Swedish children ages infant to 17 years undergoing chemotherapy for cancer measured 6 times over treatment course	Parent proxy of MSAS 10-18	The prevalence and distress of fatigue decreased over the trajectory of treatment
Symptom trajectories in children receiving treatment for leukemia: A latent class growth analysis with multitrajectory modeling (Hockenberry et al., 2017)	236 children ages 3 to 18 years with ALL measured during the first 18 months of treatment	PFS, CFS, FS-A	Fatigue decreased over the 4 measurements.
The influence of oxidative stress on symptom occurrence, severity, and distress during childhood leukemia treatment (Hockenberry et al., 2014)	36 children ages 3 to 15 years undergoing the first 16 months of ALL treatment	MSAS 10-18, parent proxy	Fatigue (lack of energy) decreased over the course of treatment but continue to be a prevalent symptom.
Evaluating cancer related fatigue during treatment according to children's, adolescents' and parents' perspectives in a sample of Greek young patients (Perdikaris et al., 2009)	69 children ages 7 to 15 years receiving chemotherapy and/or radiation treatment for cancer measured in the first month of treatment, 2 to 4 months later, and then at 6 to 10 months	PFS, CFS, FS-A	Fatigue increased significantly for all age-groups and was associated with hospitalization.
Fatigue and oxidative stress in children undergoing leukemia treatment (Rodgers et al., 2016)	38 children ages 3 to 12 years measured 3 times during the first year of ALL therapy	PFS, CFS	Fatigue in young children had a steady decline while school-age children's fatigue remained unchanged.
Clinical factors associated with fatigue over time in paediatric oncology patients receiving chemotherapy (Yeh et al., 2008)	48 Taiwanese children ages 7 to 17 years measured over the 11 days after starting a cycle of chemotherapy	PedsQL-Fatigue	Fatigue increased during the first 3 days after chemotherapy; children receiving corticosteroids had the highest level of fatigue on Day 5

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Table 1. (continued)

Title and citation	Sample	Fatigue measures	Findings
Studies of biologic marker of symptom ($n = 5$)			
Carnitine plasma levels and fatigue in children/adolescents receiving cisplatin, ifosfamide, or doxorubicin (Hockenberry, Hooke, Gregurich, & McCarthy, 2009)	67 children ages 7 to 18 years receiving their first or second course of cisplatin, doxorubicin, or ifosfamide chemotherapy	CFS, FS-A	Increased fatigue and decreased carnitine were significantly correlated a week after chemotherapy in children who had received prior chemotherapy.
The influence of oxidative stress on symptom occurrence, severity, and distress during childhood leukemia treatment (Hockenberry et al., 2014)	36 children ages 3 to 15 years undergoing the first 16 months of ALL treatment	MSAS 10-18, parent proxy	Symptoms, including fatigue, measured on the MSAS were associated with increased oxidative stress.
A cross-sectional study of carnitine deficiency and fatigue in pediatric cancer patients (Lai, Haertling, Weinstein, Rademaker, & Goldman, 2016)	142 children ages 8 to 17 years, 56% were receiving chemotherapy	Peds FACIT-F and PedsQL-Fatigue	No significant association between fatigue and carnitine level was found.
Fatigue and oxidative stress in children undergoing leukemia treatment (Rodgers et al., 2016)	38 children ages 3 to 12 years measured 3 times during the first year of ALL therapy	PFS, CFS	Measures of increased oxidative stress during the more intensive phases of therapy correlated with fatigue in school-age children.
Mechanisms of dexamethasone-induced disturbed sleep and fatigue in paediatric patients receiving treatment for ALL (Vallance et al., 2010)	100 children ages 5 to 18 years in maintenance therapy for ALL	PFS, CFS, FS-A	Polymorphisms in three genes (*AHSG, IL6, POLDIP3*) were significantly associated with sleep measures but not with fatigue.
Studies of experience of symptom ($n = 2$)			
The experience of cancer-related fatigue in Taiwanese children (Chiang, Yeh, Wang, & Yang, 2009)	17 children ages 7 to 18 years in different stages of cancer, in Taiwan	Interviews	Children under age 9 years focused on physical sensation of fatigue while older children included psychosocial dimensions also. Children described fatigue as a "tiredness" or "weariness" that doesn't go away with rest.
The experiences of cancer-related fatigue among Chinese children with leukaemia: A phenomenological study (Wu et al., 2010)	14 children in China ages 7 to 18 years with leukemia	Focus group	Fatigue was multifactorial with open interpretations; fatigue interfered with most aspects of life.

Note. ALL = acute lymphoblastic leukemia; AYA = adolescents and young adults; CFS = Child Fatigue Scale; CNS = central nervous system; EORTC-QLQ 30 = European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30; FS-A = Fatigue Scale for Adolescents; MFI-20 = Multidimensional Fatigue Inventory; MFS = Multidimensional Fatigue Scale; MSAS 10-18 = Memorial Symptom Assessment Scale for 10- to 18-year-olds; Peds FACIT-F = Pediatric Functional Assessment of Chronic Illness Therapy-Fatigue; PedsQL-Fatigue = Pediatric Quality of Life Inventory Multidimensional Fatigue Scale; PFS = Parent Fatigue Scale; QOL = quality of life; VAS = visual analogue scale.

barrier to the normal activities that are an important part of childhood and adolescence (Kestler & LoBiondo-Wood, 2012; Nowe et al., 2017; Spathis et al., 2015; Tomlinson et al., 2016).

Prevalence of Fatigue. Multiple studies of fatigue in children with cancer not only measured the prevalence of the symptom but also explored its relationship to other symptoms. These studies are summarized in the correlational reports and are thus combined under the Correlations/Associations section of Table 1. Fatigue is a prevalent, distressing symptom during cancer treatment, which was reported in more than half of children in the home setting (Nunes et al., 2015), in 49.6% of children hospitalized for chemotherapy (Miller et al., 2011), and in 70.5% of children a week after myleosuppressive chemotherapy (Baggott et al., 2011). In adolescents, fatigue reached a peak during the second week after chemotherapy (Erickson et al., 2011), was at higher levels than in children with cancer (Nunes et al., 2015), and was higher in those receiving cancer treatment compared with their adolescent healthy peers (Daniel et al., 2013).

Correlates of Fatigue. Fatigue in adolescents was associated with poorer overall quality of life (Daniel et al., 2013) and poorer psychosocial quality of life (Erickson et al., 2011). This was also a consistent finding in a combined cohort of children and teens (Al-Gamal & Long, 2016). Fatigue is related to sleep disturbance in both children and teens. Adolescents with general and cognitive fatigue had poorer sleep quality and daytime functioning (Erickson et al, 2011). In children and adolescents, sleep/rest fatigue was correlated with sleeping longer (Nunes et al., 2015). Those with acute lymphoblastic leukemia (ALL) and higher fatigue had poorer scores related to sleep habits and problems (Zupanec et al., 2010), while children with mixed diagnoses and higher fatigue had poorer sleep quality as measured by sleep diaries (Orsey et al., 2013).

In examining relationships between fatigue and depression, fatigue was related to depressive symptoms in adolescents and also led to a disengagement coping style (Daniel et al., 2013). Whitsett and colleagues (2008) initially reported a significant relationship between fatigue and depression; however, follow-up qualitative interviews led the researchers to conclude that each symptom was separate and uniquely distinguishable. In exploring new areas of fatigue correlations, school-age children who increased their physical performance on a 6-minute walk test from a baseline measure demonstrated a decrease in fatigue levels (Hooke et al., 2011.

Fatigue Trajectory. Multiple studies have evaluated fatigue in children over the trajectory of treatment for ALL, which is the most frequently occurring cancer in children. Most studies in children with ALL have reported that fatigue decreased during treatment (Hockenberry et al., 2014; Hockenberry et al., 2017; Rodgers et al., 2016), although it continued as a prevalent symptom (Hockenberry et al., 2014) and was persistent in school-age children compared with young children (Rodgers et al., 2016). A cohort of children with mixed cancer diagnoses also experienced a decrease in fatigue as treatment progressed (Hedén et al., 2013). Other researchers found that children with leukemia or lymphoma had a decrease in fatigue, while fatigue in children with solid tumors or brain tumors remained unchanged during treatment (Crabtree et al., 2015). These patterns were not found in a study of children measured over a 10-month period in which fatigue increased for all age-groups and was associated with hospitalization (Perdikaris et al., 2009). Within a cycle of chemotherapy, fatigue peaked in the first 2 to 4 days after starting the cycle (Ameringer et al., 2013; Erickson et al., 2010; Yeh et al., 2008); the pattern of fatigue in the remainder of the cycle differed during the following week, depending on whether the chemotherapy was repeated at Week 2, 3, or 4 (Erickson et al., 2010).

Fatigue Biologic Markers. Carnitine, a micronutrient needed for energy production, has been studied in relation to fatigue levels with conflicting results. One study found no relationship between carnitine levels and fatigue (Lai et al., 2016), while another study found that when carnitine levels decreased, fatigue increased in children who had received previous chemotherapy (Hockenberry et al., 2009). Measures of oxidative stress have been correlated with increased fatigue in children with ALL as well (Hockenberry et al., 2014; Rodgers et al., 2016). Researchers investigated specific genetic polymorphisms in relation to fatigue in children with ALL but did not find a significant relationship (Vallance et al., 2010).

Experience of Fatigue. Qualitative studies were conducted in Taiwan and China that are consistent with earlier studies in the United States, published in the early 2000s (Davies, Whitsett, Bruce, & McCarthy, 2002; Hockenberry-Eaton, & Hinds, 2000) that found that fatigue is a physical sensation that includes a psychosocial dimension in older children (Chiang et al., 2009) and that fatigue was multifactorial and interfered with daily life (Wu et al., 2010).

Sleep Disturbance

Conceptual Definition. Sleep disturbance encompasses problems with initiating and maintaining sleep, excessive somnolence, a disrupted sleep–wake schedule, or any dysfunction associated with sleep, sleep stages, or partial arousals. Sleep disturbance is affected by changes

in the child's psychosocial, environmental, and biological processes (Daniel, Schwartz, Mindell, Tucker, & Barakat, 2016).

Summary of Studies. Search strategies previously described were combined with the keywords "sleep" or "sleep wake disorders." Abstracts of 75 publications were reviewed, and studies not meeting inclusion criteria were removed. The remaining 20 studies are summarized in Table 2. Studies were conducted in the United States, Canada, Japan, and the Netherlands. Measurements of sleep disturbance included actigraphy (an objective measure of movement), polysomography, sleep diaries, interviews, and self-report measurements by patients and/or parents.

Systematic Reviews of Sleep Disturbance. Sleep was disturbed during hospitalization for cancer treatment due to noise, light, and staff interruptions, which contribute to less sleep and night awakenings (Lee et al., 2017). In adolescents with cancer, sleep disturbances were characterized by difficulty falling asleep, parasomnias, daytime napping and sleepiness; poor sleep contributed to difficulties in emotional regulation, social skills, cognition, and physical coordination (Olson, 2014).

Prevalence of Sleep Disturbance. Research regarding the incidence of sleep disturbance in children with cancer has identified some of the risk factors contributing to sleep problems. Seventy-six percent of children treated for craniopharyngioma experienced daytime sleepiness due to hypothalamic involvement of their tumor (Jacola et al., 2016). The hospital experience contributed to sleep problems, including difficulty going to sleep, earlier bedtime, and poorer sleep quality (Setoyama et al., 2016); and shorter sleep than what was needed for healthy children, as well as sleep interrupted with frequent awakenings (Linder & Christian, 2013). At home, children with cancer continued to experience disrupted sleep with less efficient sleep and shorter sleep time than healthy controls (Orsey et al., 2013; Setoyama et al., 2016). Sleep problems persisted during outpatient treatment for ALL, with children in maintenance therapy still having sleep latency and more variable sleep patterns 2 weeks after a corticosteroid pulse (Matthews et al., 2014), and more sleep problems in general than healthy controls (van Litsenburg et al., 2011).

Correlates of Sleep Disturbance. During hospitalization, sound, light, medication doses, pain, and nausea all contributed to sleep disruption in children with cancer (Linder & Christian, 2013). In children with ALL in maintenance therapy, parent–child co-sleeping was correlated with sleep problems (McCarthy et al., 2016), and parent's rating of their own sleep correlated with their rating of their child's sleep (Daniel et al., 2018). Additionally, in children in maintenance therapy for ALL, pain and worry were associated with impaired sleep. In children undergoing active cancer treatment, socioeconomic status did not relate to sleep quality, while children who were more physically active during the day had better sleep at night (Orsey et al., 2013; Orsey & Wakefield, 2016).

Sleep Disturbance Trajectory. In adolescents undergoing repeated measures of sleep over a cycle of chemotherapy, sleep difficulty increased the night before an admission for chemotherapy and peaked on Day 2 of chemotherapy (Ameringer et al., 2013); a similar pattern was seen in a different adolescent cohort with sleep–wake problems, daytime sleepiness, and poor sleep quality increasing during the week after chemotherapy while alertness decreased (Erickson et al., 2011). In children and adolescents, sleep times measured during the first 8 weeks of cancer treatment, times for going to bed and waking up became significantly later, while the length of sleep duration remained the same.

Sleep Disturbance Biomarkers. Research on biomarkers related to sleep in children with cancer has focused on children with ALL receiving corticosteroids during maintenance therapy. Children with a hypersensitive response to dexamethasone, as measured by salivary cortisol, demonstrated more sleep issues (Warris et al., 2016), and during the dexamethasone pulse, children had more sleep time and daytime napping (Rosen et al., 2015). Those with the pro-inflammatory cytokine polymorphisms, TNF (-308G>A) or IL-6 (-174G>C), had significantly more disturbed sleep during their corticosteroid pulse (Vallance et al., 2011). Additionally, children receiving dexamethasone had poorer sleep than those receiving prednisone during maintenance ALL treatment (Daniel, Li, et al., 2016).

Experience of Sleep Disturbance. As part of their work in creating a model of sleep disturbance, Daniel, Schwartz, and colleagues (2016) interviewed parents about their children's sleep during cancer treatment; parent responses confirmed that psychosocial, environmental, and biological processes affected their child's sleep. In another study, parents also recognized that multiple factors, and especially medications, affected their children's sleep during ALL maintenance treatment (Zupanec et al., 2010).

Nausea and Vomiting

Conceptual Definition. Nausea is defined as an unpleasant, subjective feeling of wanting to vomit. Vomiting is an objective event in which there is an expulsion of stomach contents. Retching is defined as attempting to vomit but not being able to produce any stomach contents.

Table 2. Studies Reporting Sleep Disturbance.

Title and citation	Sample	Sleep measures	Findings
Systematic reviews ($n = 2$)			
Systematic review of sleep in hospitalized pediatric cancer patients (Lee, Narendran, Tomfohr-Madsen, & Schulte, 2017)	7 studies with children ages 1 to 18 years	Actigraphy, sleep diary, VAS	Sleep was disturbed during hospitalization. Noise, light levels, and staff room interruptions are associated with decreased total sleep minutes and increase nighttime awakenings.
Sleep–related disturbances in adolescents with cancer: A systematic review (Olson, 2014)	41 studies of adolescents ages 10 to 19 with leukemia and/or brain tumors	Actigraphy, NPSG, self-report questionnaires, interviews	Sleep disturbances included difficulty falling asleep, disordered breathing, parasomnias, napping, and excessive daytime sleepiness. Insufficient sleep was associated with deficits in social skills, emotional regulation, physical coordination, and cognition.
Studies of incidence/prevalence of symptom ($n = 3$)			
Investigating the role of hypothalamic tumor involvement in sleep and cognitive outcomes among children treated for craniopharyngioma (Jacola et al., 2016)	62 children ages infant to 21 years, newly diagnosed with craniopharyngioma	NPSG, ESS-parent, clinical evaluation	Excessive daytime sleepiness was present in 76% of the participants, which was related to hypothalamic tumor involvement.
Sleep in mother and child dyads during treatment for pediatric acute lymphoblastic leukemia (Matthews, Neu, Cook, & King, 2014)	26 mother–child dyads; children ages 3 to 12 years in maintenance ALL treatment 2 weeks after steroid pulse	Actigraphy and sleep diary, CSHQ-A	Compared with healthy control group, children had greater sleep latency and more variable sleep patterns.
Objective assessment of sleep status and its correlates in hospitalized children with cancer: Exploratory study (Setoyama, Ikeda, & Kamibeppu, 2016)	11 Japanese children ages 2 to 12 years hospitalized for chemotherapy	Actigraphy and sleep diary	During their hospitalization, children had longer sleep onset latency, earlier bedtime, and poorer sleep quality by self-report.

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Table 2. (continued)

Title and citation	Sample	Sleep measures	Findings
Studies of correlations of symptom ($n = 6$)			
The relationship between child and caregiver sleep in acute lymphoblastic leukemia maintenance (Daniel, Walsh, Meltzer, Barakat, & Kloss, 2018)	68 children ages 3 to 12 years in ALL maintenance therapy	CSHQ-A	Caregiver self-report of sleep was correlated with caregiver rating of child's sleep
Nighttime sleep characteristics of hospitalized school-age children with cancer (Linder & Christian, 2013)	15 Children ages 5 to 12 years hospitalized for chemotherapy	Actigraphy and sleep diaries	Children had nighttime sleep that was shorter than what was needed by healthy school-age children and was marked by frequent, sustained awakenings. Sound, light, medication doses, pain, and nausea accounted for 57% of variance of sleep minutes.
Are parenting behaviors associated with child sleep problems during treatment for acute lymphoblastic leukemia? (McCarthy, Bastiani, & Williams, 2016)	73 children ages 2 to 6 years in ALL maintenance therapy	TCSQ	More children with ALL had clinical levels of sleep disturbance compared with healthy norms. Parent–child co-sleeping was correlated with child sleep disturbance
Does socioeconomic status impact physical activity and sleep among children with cancer? (Orsey & Wakefield, 2016)	50 children ages 8 to 18 years in active treatment	Actigraphy	Socioeconomic status was not associated with sleep quality. Sleep efficiency and physical activity were strongly correlated.
Physical activity (PA) and sleep among children and adolescents with cancer (Orsey et al., 2013)	36 children ages 8 to 18 years in active treatment	Actigraphy and sleep diaries	Children had decreased total sleep time, increase wake after sleep onset, increased awakenings, and decreased sleep efficiency compared with health norms Higher physical activity was associated with improved sleep quality and efficiency.
Impaired sleep affects quality of life in children during maintenance treatment for acute lymphoblastic leukemia: An exploratory study (van Litsenburg et al., 2011)	17 children ages 2 to 18 years midway through maintenance ALL treatment on and off dexamethasone	CSHQ	Children had more sleep problems than healthy norms. Sleep did not differ on and off dexamethasone. Pain and worry were moderately correlated with impaired sleep.
Studies of the trajectory of symptom ($n = 3$)			
A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy (Ameringer et al., 2013)	9 adolescents ages 13 to 18 years with cancer, measured on Day 1 and Day2 of a chemotherapy cycle, 1 week later, and day 1 of next cycle	VAS for sleep difficulty	There was a significant increase in sleep difficulty with a peak on Day 2 and an increase on night before chemo admission.
Changes in sleep and fatigue in newly treated pediatric oncology patients (Crabtree et al., 2015)	153 children ages 2 to 18 years measured 30 days and 8 weeks after newly diagnosed with cancer	Kosair Sleep Questionnaire (parent); CSHS (parent); CRSP (ages $\geq$ 8 years)	Times for going to bed and waking up became significantly later while sleep duration did not change.
Fatigue, sleep–wake disturbances, and quality of life in adolescents receiving chemotherapy (Erickson et al., 2011)	20 adolescents ages 12 to 19 receiving chemotherapy measured weekly over 1 month	GSDS	In the week after chemotherapy, sleep–wake problems, daytime sleepiness, and poor sleep quality increased while alertness decreased; sleep symptoms improved after Week 2.

(continued)

Table 2. (continued)

Title and citation	Sample	Sleep measures	Findings
Studies of biologic marker of symptom (n = 4)			
Predicting the neurobehavioral side effects of dexamethasone in pediatric acute lymphoblastic leukemia (Warris et al., 2016)	50 children in the Netherlands ages 3 to 16 years in maintenance ALL treatment with dexamethasone	SDSC	Children with a hypersensitive response (salivary cortisol) to dexamethasone had more sleep problems and somnolence.
The impact of dexamethasone and prednisone on sleep in children with acute lymphoblastic leukemia (Daniel, Li, Kloss, Reilly, & Barakat, 2016)	81 children ages 3 to 12 years in ALL maintenance	CSHQ-A	Dexamethasone led to poorer sleep quality than prednisone during ALL maintenance.
The effects of dexamethasone on sleep in young children with acute lymphoblastic leukemia (Rosen et al., 2015)	25 children ages 2 to 9 years receiving ALL maintenance treated with dexamethasone	Actigraphy, CSHQ	During the dexamethasone pulse, sleep time and daytime napping increased.
Disturbed sleep in pediatric patients with leukemia: The potential role of interleukin-6 (-174GC) and tumor necrosis factor (-308GA) polymorphism (Vallance et al., 2011)	88 children receiving maintenance therapy for ALL measured pre and during corticosteroid pulse	Actigraphy	Two proinflammatory cytokines, TNF (-308G>A) or IL-6 (-174G>C) polymorphisms had significantly more disturbed sleep
Studies of experience of symptom (n = 2)			
Initial validation of the sleep disturbances in pediatric cancer model (Daniel, Schwartz, et al., 2016)	Parents of 20 children ages 3 to 12 years with ALL	Semistructured interviews	Parents responses confirmed that changes in their child's psychosocial, environmental, and biological processes affected sleep.
Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents (Zupanec et al., 2010)	Children ages 4 to 18 years receiving maintenance ALL treatment	Qualitative open-ended questions	Parents reported that sleep was disturbed, while others stated it was improved. Medications interfered with sleep. Interventions that helped included comforting behaviors, sleeping with someone, and food and drink.

Note. ALL = acute lymphoblastic leukemia; CRSP = Children's Report of Sleep Patterns; CSHQ = Children's Sleep Habits Questionnaire; CSHQ-A = Children's Sleep Habits Questionnaire–Abbreviated; CSHS = Children's Sleep Hygiene Scale; ESS = Epworth Sleepiness Scale; GSDS = General Sleep Disturbance Scale; NPSG = nocturnal polysomography; SDSC = Sleep Disturbance Scale for Children; TCSQ = Tayside children's sleep questionnaire; VAS = visual analogue scale.

Summary of Studies. The keywords "nausea or vomiting" were combined with the search strategy previously described, which resulted in 64 publications. These abstracts were reviewed; intervention studies, many of which employed antiemetics, were removed. Articles describing guidelines for use of antiemetics in children with cancer were also removed, as were studies on the development of nausea self-report measurements. Thirteen studies met the inclusion criteria and are summarized in Table 3. Study sites included one each from Sweden and Italy, with the others coming from the United States and Canada. Measurement included self-report instruments of nausea and through observation, documentation, and/or self-report of episodes of vomiting and/or retching.

Systematic Reviews of Nausea and Vomiting. In their systematic review of chemotherapy-induced nausea and vomiting (CINV), Ruggiero and colleagues (2018) concluded that CINV continues to only be partially controlled. There is a need for improved assessment of CINV risk that includes emetogenic risk, as well as the child's clinical characteristics and developmental level.

Prevalence of Nausea and Vomiting. Age is an important risk factor for experiencing CINV. In their study utilizing symptom heuristics with adolescents and young adults measured within 96 hours of receiving chemotherapy, 65.3% of adolescents and young adults reported nausea, which was the most frequently reported symptom (Ameringer et al., 2015). In pediatric patients, age 18 and younger with acute myeloid leukemia, older age increased the risk of needing a change in antiemetics and rescue antiemetics due to breakthrough nausea and vomiting (Freedman et al., 2014). In children aged 2 to 9 years receiving chemotherapy for standard risk ALL, older age and more intensive treatment were associated with a higher risk of nausea (Dupuis et al., 2016). In children and adolescents receiving intrathecal methotrexate during maintenance ALL therapy, most had complete vomiting control; however, 49% lacked complete nausea control, with 17% experiencing severe nausea (Flank et al., 2017). In children with ALL or osteosarcoma receiving methotrexate, uncontrolled nausea and vomiting was present in 60% of those receiving intermediate dose methotrexate and in 30% of those receiving high-dose methotrexate, indicating poorer emetic control in those receiving lower doses (Vol et al., 2016). In children receiving inpatient chemotherapy, nausea was reported by more than 50% of children and was the most severe and bothersome symptom (Miller et al., 2011). When children received moderate to highly emetogenic chemotherapy, 25% to 42% experienced acute nausea and vomiting; delayed nausea and vomiting was underestimated by nurses (Rodgers, Kollar, et al., 2012).

Correlates of Nausea and Vomiting. During the week after myelosuppressive chemotherapy, higher levels of nausea were correlated with longer hospitalization, and with the number and severity other symptoms, demonstrating the impact of nausea on other patient outcomes (Baggott et al., 2011). Anticipatory anxiety prechemotherapy in adolescents was predictive of higher levels of nausea (Ameringer et al., 2013).

Nausea and Vomiting Trajectory. Within the context of chemotherapy cycles, nausea was highest in adolescents on the second day of chemotherapy, and it decreased significantly by the start of the next cycle (Ameringer et al., 2013). This pattern differed in a cohort of children and adolescents receiving moderate to highly emetogenic chemotherapy, with delayed nausea peaking 2 to 7 days into the cycle (Rodgers, Kollar, et al., 2012). During ALL treatment, children with moderate levels of nausea at the end of induction therapy had an increase in nausea during the delayed intensification phase of therapy (Hockenberry et al., 2017). This pattern was also seen in children with standard risk ALL who experienced an increase in nausea from consolidation to the beginning of maintenance therapy (Dupuis et al., 2016). In a group of children with mixed cancer diagnoses, parents reported decreasing levels of nausea over the first 4 months of treatment with 44% reporting nausea at 4 months and 30% reporting vomiting in their child at 4 months.

Discussion

Symptom distress is prevalent in children and adolescents receiving cancer treatment. Pediatric cancers are treated over a period of months to years. This can be a significant amount of time in a developing child's life during which symptom experiences affect the child's quality of life and interfere with the "work" of childhood.

Fatigue is pervasive and distressing to both children and their parents. It disrupts the energy needed for healthy experiences across the developmental continuum. Over the continuum of treatment, fatigue decreases in children with ALL as treatment intensity decreases (Hedén et al., 2013; Hockenberry et al., 2014); however, it may become more prevalent in others (Perdikaris et al., 2009; Rodgers et al., 2016), especially children with brain tumors and solid tumors as the cycles of intensive chemotherapy are repeated (Crabtree et al., 2015). In studies that measured fatigue over a cycle of chemotherapy, fatigue appeared to vacillate in relation to its impact and resolution within the course of chemotherapy (Ameringer et al., 2013; Erickson et al., 2010; Yeh et al., 2008). Fatigue is associated with sleep disturbances (Ameringer et al., 2013; Erickson et al., 2011; Nunes et al., 2015; Orsey et al., 2013; Zupanec et al., 2010); it

Table 3. Studies Reporting Nausea and Vomiting.

Title and citation	Sample	Nausea and vomiting measures	Findings
Systematic reviews ($n = 1$)			
Acute chemotherapy-induced nausea and vomiting in children with cancer: Still waiting for a common consensus on treatment (Ruggiero et al., 2018)	Not specified		A system is needed that includes both emetogenic level of chemotherapy regimen and child's clinical characteristics. CINV continues to be distressing and is only partially controlled.
Studies of incidence/prevalence of symptom ($n = 6$)			
Symptoms and symptom clusters identified by adolescents and young adults with cancer using a symptom heuristics app (Ameringer, Erickson, Macpherson, Stegenga, & Linder, 2015)	72 AYAs ages 13 to 29 years, measured within 96 hours of receiving chemotherapy	C-SCAT with 30 symptoms from MSAS	Nausea was most frequent symptom with 65.3% of AYAs reporting it.
Nausea and vomiting in children and adolescents receiving intrathecal methotrexate: A prospective, observational study (Flank et al., 2017)	70 children ages 4 to 18 with ALL receiving IT MTX during second or later cycle of ALL maintenance	PeNAT, Number of vomiting, retching episodes	Among the participants, 51% had complete CINV control, 17% severe nausea, 51% complete nausea control, and 96% complete vomiting control.
Predictors of antiemetic alteration in pediatric acute myeloid leukemia (Freedman et al., 2014)	1,686 patients with AML $<$ 18 years of age in the Pediatric Health Information System	Antiemetic alteration in medical record	An increasing age was associated with an increased risk of needing an antiemetic switch and antiemetic rescue.
Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer (Miller et al., 2011)	39 children ages 10 to 17 years receiving inpatient chemotherapy	MSAS 10-18	Nausea was the most prevalent symptom in more than 50% of children. It was also rated the highest in severity and how bothersome it was.
Nausea and vomiting perspectives among children receiving moderate to highly emetogenic chemotherapy treatment (Rodgers, Kollar, et al., 2012)	40 children ages 7 to 12 years receiving MEC or HEC	Adapted Rhodes Index of N & V for Pediatrics	Among children, 25% to 42% reported acute nausea and vomiting. Nurses underestimated delayed N & V.
Poor chemotherapy-induced nausea and vomiting control in children receiving intermediate or high-dose methotrexate (Vol et al., 2016)	30 children ages 7 to15 years receiving intermediate or high dose MTX for ALL or osteosarcoma	PeNAT, Number of vomiting, retching episodes	Uncontrolled nausea and vomiting was present in 60% of children receiving intermediate dose MTX and 30% of those receiving high-dose MTX.

(continued)

Table 3. (continued)

Title and citation	Sample	Nausea and vomiting measures	Findings
Study of correlations of symptom (n = 1)			
An evaluation of the factors that affect the health-related quality of life of children following myelosuppressive chemotherapy (Baggott et al., 2011)	61 children ages 10 to 18 years receiving myelosuppresive chemotherapy	MSAS 10-18; PedsQL Cancer	In the week after chemotherapy, higher levels of nausea were associated with longer hospitalization, and number and severity of other symptoms.
Studies of the trajectory of symptom (n = 5)			
A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy (Ameringer et al., 2013)	9 adolescents 13 to 18 years with cancer, measured on Day 1 and Day 2 of a chemotherapy cycle, 1 week later, and Day 1 of next cycle	100 mm VAS for nausea	Anticipatory anxiety was associated with higher ratings of nausea. Nausea changed significantly with the highest score on Day 2 and the lowest on Day 1 of the next cycle.
Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group (Dupuis et al., 2016)	160 children ages 2 to 9 years in treatment for standard risk ALL	PedsQL Cancer	In standard risk ALL treatment, an older age and more intensive treatment was associated with a higher risk of nausea. Nausea increased from consolidation to beginning of maintenance.
Parents' perceptions of their child's symptom burden during and after cancer treatment (Hedén et al., 2013)	160 parents of 89 children ages infant to 17 years undergoing chemotherapy for cancer measured 6 times over treatment course	Parent proxy of MSAS 10-18	Prevalence of parent report of nausea and vomiting decreased over treatment with occurrence of nausea 1 week from diagnosis at 68%, 2 months at 52%, and 4 months at 44%. Vomiting decreased from an occurrence at 1 week from diagnosis: 60%, 2 months at 34%, and 4 months at 30%.
Symptom trajectories in children receiving treatment for leukemia: A latent class growth analysis with multi-trajectory modeling (Hockenberry et al., 2017)	236 children ages 3 to 18 years with ALL measured during the first 18 months of treatment	VAS	Children with moderate levels of nausea had an increase from end of induction to delayed intensification
Children's coping strategies for chemotherapy-induced nausea and vomiting (Rodgers, Norville, et al., 2012)	40 children ages 7 to 12 years receiving moderately or highly emetic chemotherapy measured before, within 24 hours of starting, and 1 to 7 days after chemotherapy	Adapted Rhodes Index of N & V for Pediatrics	Nausea and vomiting significantly changed during the chemotherapy cycle and was the highest in delayed time period. Coping strategies remained consistent with the more frequent strategies including wishful thinking, distraction, emotional regulation, and problem solving.

Note. ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; AYA = adolescents and young adults; C-SCAT = Computerized Symptom Capture Tool; CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy; IT = intrathecal; MEC = moderate emetogenic chemotherapy; MSAS 10-18 = Memorial Symptom Assessment Scale 10- to 18-year-olds; MTX = methotrexate; N = nausea; PeNAT = Pediatric Nausea Assessment tool; PedsQL-Cancer = Pediatric Quality of Life Cancer Module; V = vomiting; VAS = Visual Analog Scale.

is difficult to discern the temporal relationship between the two or if it is a continuous cycle of fatigue that leads to poor sleep that leads to worsening fatigue. The symptom interferes with the child or adolescent's quality of life (Al-Gamal & Long, 2016; Daniel et al, 2013; Erickson et al., 2011; Kestler & LoBiondo-Wood, 2012) as well as engagement in the normal activities of childhood and adolescence because normal activities required too much energy (Spathis et al., 2015; Tomlinson et al., 2016). When compared with their healthy peers, adolescents with cancer consistently have a greater burden of fatigue (Daniel et al., 2013; Nowe et al., 2017). Measures of oxidative stress are increased with higher levels of fatigue (Hockenberry et al., 2014; Rodgers et al., 2016), but other studies of biomarkers have not demonstrated strong associations.

Sleep is essential for healthy development and is needed for physical and mental health (Chaput et al., 2016), but many children with cancer have poor sleep (Jacola et al., 2016; Olson, 2014, Setoyama et al., 2016). Sleep in children with cancer was negatively affected by the hospital environment (Lee et al., 2017; Linder & Christian, 2013; Setoyama et al., 2016), corticosteroid medications that are part of treatment (Daniel, Li, et al., 2016; Rosen et al., 2015; Warris et al., 2016), loss of normal structural routines (i.e., getting up for and attending school) (Crabtree et al., 2015), and other symptoms including fatigue, pain, and worry (van Litsenburg et al., 2011). Sleep disturbance continues throughout treatment, which then prevents a "sustained recovery period" and return to quality sleep (Ameringer et al., 2013; Crabtree et al., 2015; Erickson et al., 2011). Little is known about sleep's relationship to healthy behaviors in children with cancer, although preliminary studies showed improvement in sleep quality with physical activity (Orsey et al., 2013). Early research has identified genetic polymorphisms related to disturbed sleep during corticosteroid medications (Vallance et al., 2011).

Although pharmacologic interventions for nausea and vomiting have advanced over the past 10 years (Ruggiero et al., 2018), nausea and vomiting continue to be persistent and distressing during pediatric cancer treatment (Ameringer et al., 2015; Flank et al., 2017; Miller et al., 2011; Rogers, Norville, et al., 2012; Ruggiero et al., 2018; Vol et al., 2016). The trajectory of nausea and vomiting changes with intensity of treatment (Dupuis et al., 2016; Hedén et al., 2013; Hockenberry et al., 2017; Rogers, Kollar, et al., 2012). Nausea creates further anxiety in children and adolescents with cancer and makes life unpleasant (Ameringer et al., 2013; Rogers, Norville, et al., 2012). Interventions are needed that are tailored to the emetogenic risk of the treatment, child's development, and past success or failure with management of this symptom.

Acknowledgment of the prevalence, severity, and distress of symptoms that occur during cancer treatment brings recognition of the suffering experienced by children and adolescents. Further research is needed to gain insight into biomarkers that inform symptom risks. Interventions are needed that are tailored to the child's physiologic symptom risk, developmental level, as well as psychosocial and psychological functioning. Nurses are well positioned to partner with families to test interventions that decrease symptom distress to improve resilience and quality of life during and after pediatric cancer treatment. In Part II of this review, insight into the symptoms of pain, sadness, and symptom clusters are provided, as well as discussion of the implications of these reviews.

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ORCID iDs

Mary C. Hooke https://orcid.org/0000-0002-6137-9224
Lauri A. Linder https://orcid.org/0000-0003-2638-4164

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Author Biographies

Mary C. Hooke, PhD, APRN, PCNS, CPON, FAAN, is an associate professor at the University of Minnesota's School of Nursing. She has a clinical appointment as an advanced practice nurse at Children's Minnesota. Her research interests include supportive care and symptom management for children and adolescents with cancer with a focus on the relationship of physical activity to distressing symptoms.

Lauri A. Linder, PhD, APRN, CPON, holds a joint appointment as an associate professor at the University of Utah College of Nursing and as a Pediatric Oncology Clinical Nurse Specialist at Primary Children's Hospital. Her research interests include supportive care and symptom management for children, adolescents, and young adults with cancer with attention to novel uses of technology to support patients in communicating their experiences.