Pain, Sleep Disturbance, and Fatigue in Children With Leukemia and Their Parents: A Pilot Study

Vivian Gedaly-Duff, DNSc, RN, Kathryn A. Lee, PhD, RN, FAAN, Lillian M. Nail, PhD, RN, FAAN, H. Stacy Nicholson, MD, MPH, and Kyle P. Johnson, MD

Purpose/Objectives: To determine the feasibility of collecting symptom data at home from school-age children with acute lymphoblastic leukemia (ALL) and from their fathers and mothers and to obtain initial descriptions of pain, sleep disturbance, and fatigue experienced by the family members at home.

Design: Prospective and descriptive.

Setting: Children's homes in Oregon and southwestern Washington.

Sample: 9 children with ALL (aged 8–16 years), 6 fathers, and 7 mothers. The children received vincristine during the maintenance phase of their outpatient chemotherapy treatments.

Methods: With age-appropriate, paper-and-pencil diaries and wrist actigraphy, data were collected for three days in the families' homes. Families were reminded by telephone to complete their sleep and activity diaries.

Main Research Variables: Pain, sleep disturbance, and fatigue in school-age children and their fathers and mothers.

Findings: Most of the families who were approached indicated willingness to participate in the study. After receiving outpatient chemotherapy, the children reported pain, sleep disturbance, and fatigue data over three days. Fathers and mothers also reported symptoms. Actigraphy showed children waking more often during the night than mothers or fathers.

Conclusions: Children's pain, sleep disturbance, and fatigue suggest that the symptoms are influencing families' quality of life. Larger studies are needed to examine the symptom patterns and health outcomes of children, fathers, and mothers over the course of chemotherapy.

Implications for Nursing: Improving sleep and managing pain and fatigue after chemotherapy treatment for children with ALL may improve health outcomes for children and parents.

Key Points . . .

- Children being treated for leukemia and their fathers and mothers are willing to participate in research that uses diaries and actigraphy.
- The number of nighttime awakenings was higher than normal in children over three days after outpatient chemotherapy. The fathers and mothers also had higher than normal awakenings.
- Symptom reports over the same three days suggest that pain, sleep disturbance, and fatigue cluster together after children's chemotherapy treatments.
- Parents' symptoms, although different from the children's, also occurred during the three days of caregiving and other family functions, such as work and parenting other children.

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, accounting for one-third of cancer diagnoses in children younger than 15 and 28% of cancer diagnoses in those younger than 20 (Ries et al., 2005). Children with ALL are treated with six to eight months of intensive chemotherapy, followed by two or more years of maintenance chemotherapy. Pain (Collins et al., 2000; Van Cleve et al., 2004), sleep disturbance (Ljungman, Gordh, Sorensen, & Kreuger, 2000), and fatigue (Collins et al.; Davies, Whitsett, Bruce, & McCarthy, 2002;

Vivian Gedaly-Duff, DNSc, RN, is an associate professor in the School of Nursing at Oregon Health and Science University in Portland; Kathryn A. Lee, PhD, RN, FAAN, is a professor and the Livingston Chair in Nursing in the School of Nursing at the University of California, San Francisco; and Lillian M. Nail, PhD, RN, FAAN, is the Dr. May E. Rawlinson Distinguished Professor and a senior scientist in the School of Nursing, H. Stacy Nicholson, MD, MPH, is the Credit Unions for Kids Professor and Chair of the Department of Pediatrics in the School of Medicine and physician-in-chief at Doernbecher Children's Hospital, and Kyle P. Johnson, MD, is an assistant professor in the Division of Child and Adolescent Psychiatry in the School of Medicine, all at Oregon Health and Science University. *This research was supported, in part, by a postdoctoral fellowship awarded to the first author from the National Institutes of Health, National Institute of Nursing Research, 2 T32 NR07088 (K. Lee, principal investigator), and by the National Cancer Institute, K24 CA098442 (L. Nail, principal investigator). Mention of specific products and opinions related to those products do not indicate or imply endorsement by the* Oncology Nursing Forum *or the Oncology Nursing Society. (Submitted August 2005. Accepted for publication August 9, 2005.)*

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Hockenberry-Eaton et al., 1998) are problems for children with leukemia and other cancers, but little is known about the experience of the symptoms in the days immediately following outpatient chemotherapy treatments for ALL (Gedaly-Duff et al., 2005). Furthermore, no studies have examined the symptoms among parents. Therefore, the current pilot study examined pain, sleep disturbance, and fatigue during a three-day period in children with ALL after they received vincristine, a vinca alkaloid associated with neuritic pain such as muscular cramping and jaw pain as well as constipation and paralytic ileus (Margolin, Steuber, & Poplack, 2002), at their outpatient visits. The same symptoms were assessed in parents.

Conceptual Framework

The University of California, San Francisco (UCSF), Model of Symptom Management (Dodd et al., 2001) and Robinson's model of family perspective (Robinson, 1995) guided the study. The symptom model has three dynamic and bidirectional dimensions: symptom experience, management of symptoms, and outcomes. Each person's perception, evaluation of meaning, and response to a symptom or symptom cluster are influenced by personal factors (e.g., developmental, demographic, psychosocial, physiologic), environmental factors (e.g., physical, sociocultural, family), and health and illness factors (e.g., phase of treatment, health of father and mother). In the UCSF model, parents are considered an environmental factor because they are caring for their children at home. Adding Robinson's model of family perspective addresses the complexity of family-level research by describing variables such as a child experiencing symptoms, the influence of a sick and symptomatic child on the father and mother as caregivers, and the family as a group. The sick and symptomatic child is considered simultaneously with the family as a whole in Robinson's model. The current researchers assumed that fathers and mothers took responsibility for their children's care during chronic illness to help their families function (Seagull, 2000). For the current study, the family perspective of symptoms was limited to the individual experience for fathers, mothers, and children that may influence caregiving (Robinson) rather than adopting a more complex perspective such as parents' perceptions of their children's symptoms. For example, fatigued parents have reported being "edgy" and less able to comfort children who were restless and tired (Ferrell, Rhiner, Shapiro, & Dierkes, 1994). In addition, symptom research is moving from single symptoms to symptom clusters (Miaskowski, Dodd, & Lee, 2004). Clinically, children with cancer experience multiple symptoms during treatment (Collins et al., 2000), and the nature of the relationships among symptoms is not well understood. The current study describes pain, sleep disturbance, and fatigue in children with ALL and in their fathers and mothers.

Methods

Design

This prospective, descriptive pilot study examined the feasibility of collecting symptom data at home from school-age children with ALL and from their fathers and mothers and of gathering initial descriptions of pain, sleep disturbance, and fatigue experienced by the family members at home.

Procedure

Parents of children with ALL who were receiving care at the Oregon Health and Science University in Portland and living in the area of Portland, Salem, and southwest Washington were informed about the study by a nurse practitioner known to them. To be eligible, children had to be aged 8–18, in remission with no relapses, and receiving IV vincristine as outpatients. A research nurse evaluated eligibility and explained the study to parents and children. Nine of 11 families who were approached (82%) agreed to participate. After obtaining informed consent from parents and assent from children, the research nurse taught the children and parents how to record data on symptoms in their diaries, showing how each day had a different color for easier completion. The children rated their pain intensity and fatigue severity before going to bed at night and upon rising in the morning. Children and parents were asked to wear a wrist actigraph for 72 hours to obtain activity data for naps and nighttime sleep periods. Parents recorded their pain and fatigue in the evening. Data collection began at a fixed time the evening of the day a child received outpatient IV vincristine.

Instruments

Consistent with the UCSF Model of Symptom Management, data were collected on the symptoms of pain, sleep disturbance, and fatigue. Age-appropriate instruments for the children and their parents were bound together as a diary and color-coded for each day.

Children's instruments: The **Adolescent Pediatric Pain Tool (APPT)** was used to report (a) intensity of pain using a word-graphic scale; (b) quality of pain using 43 descriptors of sensation, affect, evaluation, and time; and (c) location of pain using a body outline. Reliability and validity have been established in healthy and hospitalized children aged 8–17 (Savedra, Holzemer, Tesler, & Wilkie, 1993; Savedra, Tesler, Holzemer, Wilkie, & Ward, 1989; Tesler et al., 1991; Wilkie et al., 1990).

Three-day sleep questions were used to validate the behavioral activity recorded by actigraphy. In the evening, information was requested about activities during the day, naps, medicines taken, and how the stomach felt. Morning information included sleep disturbance and dreaming. Face and content validity have been established (Franck et al., 1999).

Children's current evening and morning fatigue was assessed using the **Child Fatigue Visual Analog Scale** to examine tiredness, ease of falling asleep, inability to perform activities, and naps (Franck et al., 1999). Content and face validity have been reported (Franck et al.).

Parents' instruments: The **Short-Form McGill Pain Questionnaire,** a multidimensional instrument, was used to examine parent pain. Reliability and validity have been established (Melzack, 1987; Melzack & Katz, 1999).

Parent Three-Day Sleep Questions were used to assess self-reported sleep disturbances and to validate start and stop times for actigraphy data. In the evening, information was requested about naps, activity levels, dietary intake, meal patterns, caffeine and alcohol intake, over-the-counter medications, general health, and stress. Morning information included the time parents went to sleep, the amount of time it took to fall asleep, number of awakenings and reasons, times of getting out of bed, evaluation of sleep quality, use of sleep

medications, and number of cigarettes smoked the previous day. The diary has been used in several other studies of adults and parents (Gay, Lee, & Lee, 2004). Sleep disturbance was defined as self-report in the diary of either taking longer than 30 minutes to fall asleep or three or more night awakenings per night (Sadeh, Raviv, & Gruber, 2000), on average, across the three nights of the study.

Each parent's fatigue severity was assessed using the **Visual Analog Scale for Fatigue (VAS-F).** An average fatigue score was computed using the 0–100 mm visual analog line. The 18-item scale has established reliability and validity (Elek, Hudson, & Fleck, 1997; Lee, Hicks, & Nino-Murcia, 1991).

Wrist actigraphy (Mini Motionlogger Actigraph, Ambulatory Monitoring, Inc., Ardsley, NY), which continuously monitors wrist movement, was used to assess for objective sleep disturbances (Brown, Smolensky, D'Alonzo, & Redman, 1990). Reliability and validity have been established in children and adults (Sadeh & Acebo, 2002). Children and parents wore a waterproof actigraph continuously on their nondominant wrists for three days except when swimming, dish washing, or playing contact sports. Using standardized software, researchers determined total sleep time (TST) for 24 hours (in minutes), wake after sleep onset (WASO) or wake time as a percentage of sleep, and number of awakenings. Sleep disturbance was defined objectively as an average of less than six hours of sleep per night (TST less than six hours) or more than 15% wake time after sleep onset (WASO more than 15%) per night (Sadeh et al., 2000).

The **Family Questionnaire** asked for information about each member living in a household, including age, gender, role in the family, occupation or employment, health status, ethnicity, family marital status, and family income. Contextual family factors that might influence symptoms of pain, sleep disturbance, and fatigue, such as joblessness, migrant or moving status, accidents, divorce, and arguing or fighting, also were included.

Results

The children's average age was 11 (seven were aged 8–12; two were aged 13–16). Four boys and five girls participated. Three had been diagnosed with leukemia less than one year, and six had been diagnosed one to two years. The sample included seven Caucasians, one Native American, and one Pacific Islander. Families were married (n = 6), in a partnered or permanent relationship (n = 2), or separated (n = 1). The average number of years married or partnered was eight (range = 3–15 years); average family income was $41,000–$50,999 (range = $11,000–$81,000).

All of the children with ALL completed their three-day diaries and wore their actigraph sleep watches for 72 hours. One family withdrew because the mother found the actigraph irritating. Another mother completed the diary but did not wear the sleep watch because of a wrist injury. Being too busy interfered with diary recording for three fathers. The total sample included nine children, six fathers, and seven mothers.

Children's Symptoms

On day one, five of the nine children reported pain in the evening using the APPT (range = 0–3 on a scale of 0 [no pain] to 4 [most pain ever]). Types of pain included headache, side ache, stomach upset "from big med," and a knee scrape from a bicycle crash. Most of the children marked one to four pain locations on body outlines.

Actigraphy showed that the children slept 6–10 hours, with frequent awakenings (see Table 1). Their diaries reported that they woke zero to five times per night. All nine children reported evening fatigue (range = 1–3 on a scale of 0 [not tired] to 4 [most tired]). Two reported fatigue twice, and seven reported it three times over the three evenings; no children reported a nap. Only one child produced a record of no activity in the day hours; however, as instructed by the research nurse, he had removed the sleep watch for swimming.

Figure 1 gives an example of a 24-hour period, from noon to noon, of a nine-year-old girl with standard-risk ALL in maintenance therapy. Her average pain was 2.8 (on the 0–4 scale) over three nights and mornings; she marked her body figure in 10 places, mostly at joints, indicating "pain from chemo." Her three-day actigraphy data showed that her average total sleep time was six hours per night, with an average of 27 awakenings. In her three-day diary, she reported an average waking of two times per night (range of one to two times per night), and sleep quality was reported as "sleeping well." Children this age typically sleep 9.5 hours and awaken one or two times per night (National Sleep Foundation, 2004). Her three-day average evening fatigue was 2.3 (range = 1–3), and her morning fatigue was 0.33 (range = 0–1).

Fathers' Symptoms

On day one, three fathers reported pain, including toothache, lower back pain, and soreness from moving 60-pound boxes.

Table 1. Summary of Selected Actigraphy Sleep Characteristics, Pain Characteristics, and Fatigue Scores Averaged Over Three Nights

Characteristic	Children (n = 9)	Fathers (n = 6)	Mothers (n = 7)
Total sleep time[a]	482 minutes (± 63.9 minutes) (8 hours); range = 367–572 minutes (6–9.5 hours)	361 minutes (± 64.4 minutes) (6 hours); range = 271–465 minutes (4.5–7.8 hours)	424 minutes (± 40.6 minutes) (7 hours); range = 357–468 minutes (6–7.8 hours)
Wake after sleep onset[a]	11.5% (± 8.6%); range = 0%–24%	14.3% (± 7.1%); range = 6%–27%	8.8% (± 4.5%); range = 3%–15%
Number of recorded awakenings (actigraphy)	19.8 (± 4.1); range = 1–37	19.7 (± 7.6); range = 5–30	16.9 (± 7.4); range = 5–26
Pain	Used description only; see narrative.	Used description only; see narrative.	Used description only; see narrative.
Fatigue	Used description only; see narrative.	50 mm (± 14.8); range = 23–63 mm	45 mm (± 12.5); range = 24–55 mm

[a] Repeated-measures analysis of variance of nights 1, 2, and 3 was conducted separately on children, fathers, and mothers. No significant time effects were found, so the three nights were averaged as estimates of selected sleep characteristics. With such small sample sizes, a larger effect size is required to detect significant differences.

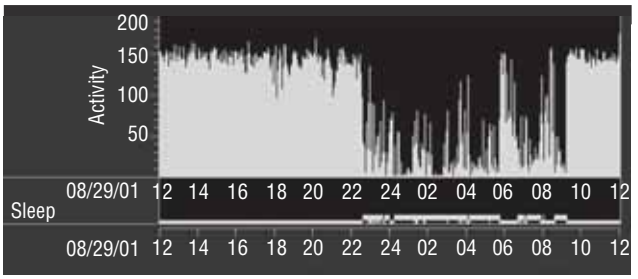

Figure 1. Sample Actigraph

Actigraphy showed that fathers slept 4.5–7.8 hours per night, with frequent awakenings. Their diaries reported waking zero to three times per night. Their average fatigue score was 50 mm (± 14.8) (VAS-F, 0–100 mm; 0 means no fatigue).

Mothers' Symptoms

On day three, three mothers reported pain, including menstrual pain, stress headache, and back pain. Actigraphy showed that mothers slept 6–7.8 hours per night with frequent awakenings. Their diaries reported waking zero to five times per night. The mothers' average evening fatigue score was 45 mm (± 12.5) (VAS-F, 0–100 mm; 0 means no fatigue).

Discussion

The results of the study demonstrate that age-appropriate, paper-and-pencil diaries and wrist actigraphy can be used to provide important symptom information about school-age and adolescent children, as well as their fathers and mothers, in the home setting. Children reported pain and fatigue and demonstrated sleep disturbances consistent with previous studies of single symptoms and retrospective surveys. For example, 26%–40% of children receiving outpatient therapy for cancer reported moderate to severe pain (McGrath et al., 1990; Miser, Dothage, Wesley, & Miser, 1987), pain and sleep disturbances were part of children's descriptions of fatigue (Davies et al., 2002; Hockenberry-Eaton et al., 1998), and parents reported sleep problems in their children (Hockenberry et al., 2003). Children who had chemotherapy for two weeks to one month (11.6% ± 6.0) had significantly more symptoms than those who had no chemotherapy in more than four months (5.2% ± 5.1; $p < 0.01$), with lack of energy and pain being the most prevalent symptoms (Collins et al., 2000).

The psychophysiologic mechanisms and interactions among pain, sleep disturbance, and fatigue are complex, not well understood (Ancoli-Israel, Moore, & Jones, 2001; Lewin & Dahl; Theobald, 2004; Vgontzas & Chrousos, 2002), and under-researched in childhood cancer (Hare & Hinds, 2004). Pain may interfere with the ability to get into deep sleep stages because it can fragment sleep with frequent awakening, activate threat-related arousal to more pain, and increase vigilance that something worse may happen (Lewin & Dahl, 1999). Childhood cancer pain may be (Berde, Billet, & Collins, 2002; Ljungman et al., 2000)

- Disease-related, sometimes called cancer- or tumor-related (e.g., pain caused by infiltration of tumors in various organs or tissues)
- Treatment- or therapy-related (e.g., pain related to chemotherapy or radiation, including mucositis and abdominal and anal pains with intestinal neuropathy related to vinca alkaloid therapy; esophageal and gastric acid pain with high doses of corticosteroids; medullary bone pain with administration of colony-stimulating factors)
- Procedure-related or diagnostic- and monitoring-related (e.g., pain from lumbar puncture, bone marrow aspiration, or removal of central venous lines)
- Related to side effects of treatment (e.g., constipation associated with codeine and morphine, physiologic withdrawal)
- Unrelated to cancer and its therapies (e.g., toothaches, exercise-induced muscle pain).

Children in the current sample reported pain associated with chemotherapy medications and pain unrelated to cancer from a bicycle accident. Parents had chronic pain such as back pain and episodic pain such as muscle soreness from moving boxes.

In addition to chemotherapy medications, worry and changes in family life to accommodate demanding treatment schedules also may contribute to disturbed sleep in children with ALL and their parents. Glucocorticoids, a cornerstone of chemotherapy in ALL, may alter sleep structure and lead to arousal and sleeplessness (Fehm et al., 1986; Vgontzas & Chrousos, 2002; Young, Sharpley, Campling, Hockney, & Cowen, 1994). From children's and parents' perspectives, diagnosis of cancer may threaten their sense of safety and security and restful sleep (Dahl & Lewin, 2002). The researchers did not address other side effects such as nausea, vomiting, diarrhea, or urinary frequency that may disturb sleep (Lee, Cho, Miaskowski, & Dodd, 2004). All of the children were in the maintenance phase of chemotherapy and may have adjusted to the medications.

Some studies have shown more anxiety during diagnosis than during other phases of treatment (Sawyer, Antoniou, Toogood, & Rice, 1997; Sawyer, Antoniou, Toogood, Rice, & Baghurst, 2000), but uncertainty may continue throughout the course of treatment (Woodgate & Degner, 2002). Animal studies have found that corticotrophin-releasing hormone expressed during stress increased secretion of corticotrophin and wakefulness (Vgontzas & Chrousos, 2002). Also, family sleep routines may change to accommodate appointments. One father told of driving to his brother's home so that he and his daughter would be nearer to the clinic for a morning appointment. His wife, who had the health insurance, stayed at the family home so she could go to work. Sleeping arrangements that facilitated family members' sleep-wake patterns were altered. The actigraphy findings showed children, fathers, and mothers waking 16 times or more per night on average, but their diary reports were in the range of zero to five. This suggests that children, fathers, and mothers may be under-reporting their actual sleep loss.

Fatigue and sleep disturbance seem to be linked. Children with cancer have been able to differentiate typical tiredness from chemotherapy-related fatigue (Davies et al., 2002). Children receiving cancer treatments have reported feeling "wiped out . . . exhausted" (Woodgate, Degner, & Yanofsky, 2003). Although anemia and metabolic changes may contribute to fatigue, sleeping poorly at night may be another important factor (Ancoli-Israel et al., 2001; Lee et al., 2004). Fatigue in children with cancer may lead to daytime sleepiness and napping, which, in turn, may lead to sleep problems at night because of fragmented desynchronized sleep-wake cycles (Ancoli-Israel et al.). None of the children or parents reported,

nor did the actigraphy data show, children or parents napping. However, the researchers did not ask about daytime sleepiness, participating in daytime physical activity, or missing school or work.

In summary, sleep disturbances may affect the quantity and quality of pain and fatigue, and pain and fatigue may affect the quantity and quality of sleep-wake cycles. Phases of chemotherapy include induction, consolidation, interim maintenance, delayed intensification, and maintenance (Margolin et al., 2002). Longitudinal studies that examine symptom data timed at the complete blood count nadir of a chemotherapy drug such as cyclophosphamide and specific days during a treatment phase will help link symptoms with treatment side effects. In addition, collecting symptom variation information associated with time of day (e.g., morning versus evening) and day of the week (e.g., weekday versus weekend) will examine the symptoms in relation to sleep-wake rhythms. Determining the incidence and changes of symptoms over time, exploring the strength of symptoms in relation to others, and investigating the synergistic effects of symptom clusters on children's and parents' outcomes will lay the foundation for intervention development (Miaskowski et al., 2004; Nail, 2004). Children's, fathers', and mothers' health outcomes may be increased with better understanding and management of the symptoms and symptom clusters.

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Author Contact: Vivian Gedaly-Duff, DNSc, RN, can be reached at gedalyv@ohsu.edu, with copy to editor at ONFEditor@ons.org.

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