Fatigue, Physical Performance, and Carnitine Levels In Children and Adolescents Receiving Chemotherapy

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Dedication

This dissertation is dedicated to the courageous children and adolescents battling cancer who teach us so much about life. They are willing and energetic teachers for all those who are ready to learn from them. As subjects in this study, they were the key to my learning about the experience of fatigue during chemotherapy.

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Abstract

Fatigue in childhood cancer is a pervasive and distressing symptom that has a physical component described as a “lack of energy”. Fatigue, physical performance, and a micronutrient, carnitine, all relate to physical energy and may be influenced by chemotherapy. The purpose of this exploratory study was to examine the relationship between the physical performance and carnitine plasma levels and fatigue in child (ages 6 to12) and adolescent (ages 13 to 17) cohorts newly diagnosed with cancer and receiving chemotherapy. Standardized instruments were administered between day 15 and 29 of the 1st and 3rd cycle of chemotherapy. Instruments included physical performance tests (Timed Up and Down Stairs [TUDS] and 6-Minute Walk test [6MWT]), carnitine plasma levels, and the self-report Childhood Fatigue Scale (CFS) or Fatigue Scale for Adolescents (FS-A).

In the child cohort (n = 16), a Wilcoxon signed rank test showed that the TUDS appeared to improve from cycle 1 to cycle 3 of chemotherapy. The median time in seconds decreased from cycle 1 (*Md* = 15.88) to cycle 3 (*Md* = 14.04), $z = -1.71$, $p = .09$. Performance on the 6MWT also appeared to improve from cycle 1 to cycle 3. The median distance of meters walked increased from cycle 1 (*Md* = 359.05) to cycle 3 (*Md* = 406.40), $z = -1.71$, $p = .09$. Levels of free carnitine levels decreased with the median lowering from cycle 1 (*Md* = 43.0) to cycle 3 (*Md* = 32.0), $z = -2.48$, $p = .01$. Fatigue in children decreased during the first three cycles of chemotherapy. The median on the total score for the CFS decreased from cycle 1 (*Md* = 18.0) to cycle 3 (*Md* =10.5), $z = -1.99$, $p = .05$.

In the adolescent cohort (n = 14), the TUDS revealed a slight improvement in physical performance from cycle 1 to cycle 3 of chemotherapy. The median time in seconds decreased from cycle 1 (*Md* = 10.88) to cycle 3 (*Md* = 8.30). The distance on

the 6MWT evidenced little change from cycle 1 to cycle 3. Free carnitine levels were stable. There was a suggestion that fatigue in the adolescents decreased from cycle 1 to cycle 3 of chemotherapy. The median score on the FS-A decreased from cycle 1 (*Md* = 23.5) to cycle 3 (*Md* = 20.5), $z = -1.43$, $p = .15$.

Spearman's rank-order correlation was used to examine relationships between changes in variables from cycle 1 to 3. In the child cohort, when the TUDS improved, fatigue tended to decrease ($r_s = .41$, $p = .11$), and when 6MWT improved, fatigue decreased ($r_s = -.60$, $p = .01$). When free carnitine levels decreased, fatigue decreased ($r_s = .43$, $p = .13$).

In the adolescent cohort, correlations between changes in the physical performance and fatigue were small. However, when free carnitine decreased, fatigue also decreased ($r_s = .52$, $p = .06$).

Fatigue may decrease early in treatment as disease symptoms resolve. Fatigue in the child cohort was related to physical performance, which is consistent with previous studies that define fatigue in children as primarily a physical sensation. Adolescent fatigue was not related to physical performance, which supports the concept that, in adolescents, fatigue is more complex and includes mental and emotional components. In both cohorts, a decrease in carnitine levels was not associated with an increase in fatigue.

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Chapter 1

Overview

Introduction

Symptom distress in children with cancer is frequently overlooked as efforts focus on a curative approach to treatment (Docherty, 2003; Hockenberry, 2004; National Institutes of Health, 2002). Both children and adolescents with cancer have identified fatigue as one of the most distressing treatment related symptoms as well as a near-universal experience (Davies, Whitsee, Bruce, & McCarthy, 2002; Hockenberry-Eaton & Hinds, 2000; Hinds & Hockenberry-Eaton, 2001). The National Institutes of Health State of the Science on Symptom Management in Cancer: Pain, Depression, and Fatigue identified that there is a lack of knowledge about the role coexisting conditions play in the symptom of fatigue (National Institutes of Health, 2002). Studies demonstrate that conceptually, childhood fatigue is experienced differently among developmental levels (Clark-Steffen et al., 2001), and consideration of developmental stage is needed when researching children with a life-threatening illness (Hare, Hinds, & Stewart, 2004).

A working group of pediatric oncology nursing researchers identified important issues that must be considered in moving the symptom research agenda forward for children and adolescents with cancer. They stressed that biologic perspectives need to be incorporated into pediatric cancer symptom research (Hare et al. 2004). Two of the biologic mechanisms that have been proposed as contributing to cancer related fatigue include abnormalities in adenosine triphosphate (ATP) synthesis and loss of muscle mass and function (Dimeo, 2001; Gutstein, 2001; NNCN, 2008). Carnitine is a key micronutrient that is required for the conversion of fatty acids into ATP. Several chemotherapy agents have been found to deplete carnitine (Peluso et al., 2000). Alterations in muscle functioning in people with cancer contribute to reduced physical

performance (Dimeo et al., 2003; Lucia, Earnest, & Perez, 2003). In this study, the relationship between fatigue, physical performance, and carnitine will be examined among children (ages 6-12 years) and adolescents (ages 13-17 years) undergoing chemotherapy treatment for cancer.

Study Aims

The primary aims and hypotheses of this study include:

Aim 1: To determine the change in physical performance and change in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy.

Hypothesis 1.1: Children and adolescents will experience a significant decrease in physical performance from cycle 1 to cycle 3 of chemotherapy.

Hypothesis 1.2: Children and adolescents will experience a significant increase in fatigue from cycle 1 to cycle 3 of chemotherapy.

Aim 2: To determine the relationship between the change in physical performance and change in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy.

Hypothesis 2: Children and adolescents who experience a significant decrease in physical performance from cycle 1 to cycle 3 of chemotherapy will have a significant increase in fatigue.

The secondary exploratory aims and hypotheses of this study include:

Aim 3: To examine carnitine plasma levels in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) at the 1st cycle and 3rd cycle of chemotherapy.

Hypothesis 3: Carnitine plasma levels in children and adolescents will significantly decrease from cycle 1 to cycle 3 of chemotherapy.

Aim 4. To determine the relationship between carnitine plasma levels and fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy

Hypothesis 4: Children and adolescents who experience a significant decrease in carnitine plasma levels from cycle 1 to cycle 3 of chemotherapy will have a significant increase in fatigue.

Conceptual Framework.

A conceptual model entitled, *Developmental Model for Children and Adolescents with Cancer,* was developed by M. C. Hooke (2008a) as a framework for this study (Figure 1). This model incorporates both factors identified in Hockenberry and Hinds' research on fatigue in children with cancer and concepts from developmental science. Hockenberry and Hinds identified factors that could contribute to the symptom of fatigue as including treatment (and treatment side effects), environmental (inpatient/outpatient wait times, altered routines, interrupted sleep) and family/cultural/ community (behavior and expectations of others) (Hockenberry-Eaton & Hinds, 2000). These factors are incorporated in the conceptual model for this study.

In developmental science, there is recognition of the complexity of human development and the interaction of biological, social, and ecological factors over the person's life course (Magnusson & Cairns, 1996). The cognitive, psychological, physiological and physical components of the child's development involve reciprocal interactions among these components within a dynamic, continual process of development (Miles & Holditch-Davis, 2003). In a developmental framework, a change in one component of development will impact others. For example, if a child is

physiologically impacted by illness and is unable to attend school and/or have peer interactions, other parts of the child's development will be impacted. The four interacting components (cognitive, psychological, physiological and physical) comprise the core of the *Developmental Model for Children and Adolescents with Cancer* (Hooke, 2008a). External ecological factors influence developmental processes; these external factors may come from multiple systems levels including parents and family, community, and culture (Bronfenbrenner & Morris, 1998). These external ecological factors are included in the conceptual model and are placed in the concentric circles outside the core of the child's development. Cancer treatment acts as an additional ecological influence on the developmental components. Treatment influences the cancer itself (a physiological component) but its side effects can also impact the physical (i.e., decreased physical performance, increased fatigue), physiological (i.e., decreased carnitine levels, anemia), cognitive (i.e., neurocognitive late effects), and psychosocial (i.e., increased mental fatigue, depression) components.

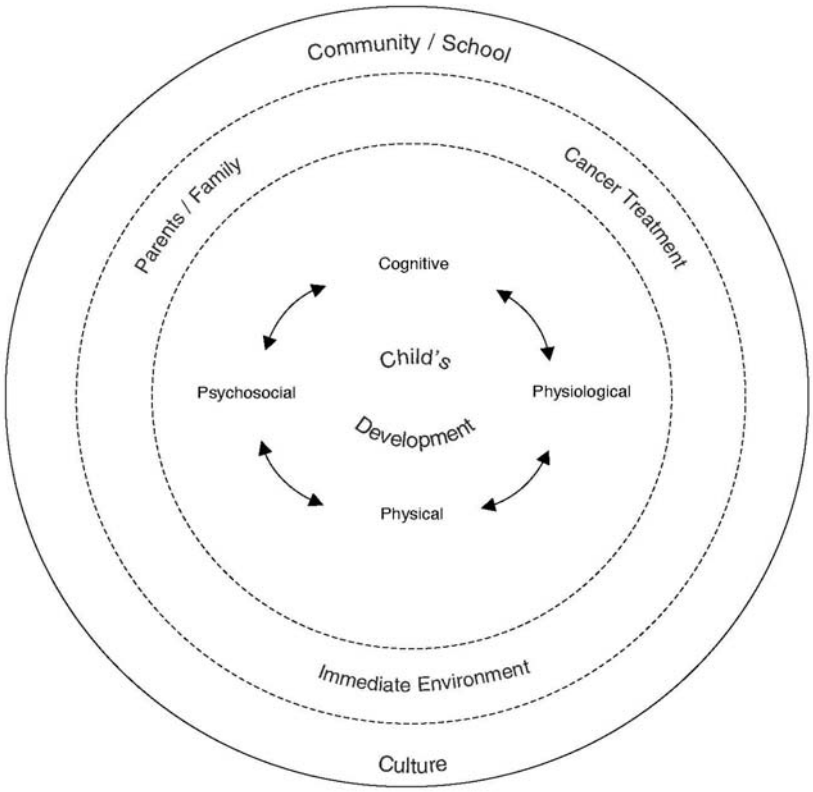

Figure 1. Developmental Model for Children and Adolescents with Cancer (Hooke, 2008a)

A developmental framework calls for the use of developmentally appropriate measures (Miles & Holditch-Davis, 2003) such as the child and adolescent fatigue instruments used in this study. A developmental model also allows researchers to conceptualize disease and treatment-related symptom experiences as an ongoing process that changes across time and developmental levels (Docherty, 2003). The influence of childhood illness on development has seldom been investigated; priority must be given to consideration of development in research on children with chronic illness including cancer (Bronfenbrenner, 2005; Hare, Hinds, & Stewart, 2004). The *Developmental Model for Children and Adolescents with Cancer* provides a conceptual framework for organizing the factors that influence the child's development and cancer

experience at specific time points and also over the continuum of cancer treatment and survival.

Summary

Remarkable progress has been made in cancer treatment for children and adolescents in the last thirty years, with cure rates approaching eighty percent (Cure Search, 2008). Attention must be given to the child or adolescent's fatigue symptom management during cancer treatment to decrease distress and provide energy for engaging in the normal developmental activities of childhood. The length of treatment for the newly diagnosed pediatric oncology patient ranges from 4 months to 3 years. The cancer experience influences the cognitive, psychological, physiological and physical components of development and can present a threat to children's ability to meet developmental challenges and milestones. These developmental achievements lay the foundation for their future development. The findings from this study will contribute to the research program on fatigue in children diagnosed with cancer. The identification of physical (physical performance) and physiological (carnitine) variables that may influence fatigue will provide direction for developing future interventions to influence the child/adolescent's quality of life and support ongoing human development and maturation.

Chapter 2

Review of the Literature

Introduction

In this review of the literature, fatigue will first be discussed. The experience of fatigue in the pediatric cancer patient will be reviewed as reported in key qualitative nursing research studies. The prevalence of fatigue, as identified in quantitative studies, will be presented, and research on the pathophysiology of fatigue will be summarized. Studies on fatigue instrument development will be discussed followed by recent studies that examined childhood cancer fatigue in relation to other symptoms. Additionally, the incidence of fatigue in childhood cancer survivors will be reviewed.

In the next section of the literature review, physical performance will first be defined and categorized into three domains. The current literature on physical performance outcomes of children during and after cancer treatment will then be organized according to these three domains. Interventional studies that sought to improve physical performance during cancer treatment will then be reviewed. Lastly, carnitine will be discussed as it relates to energy metabolism. The influence of chemotherapy agents on the carnitine system will be examined as well as current research related to carnitine supplementation.

Fatigue

The experience of fatigue from the patient and family's point of view. In developing their research program on fatigue in children and adolescents with cancer, Hinds and Hockenberry first developed a definition of fatigue in the context of the child or adolescent's experience of being a family member, being treated for cancer, and achieving developmental milestones (Hinds & Hockenberry-Eaton, 2001). The purpose of their first descriptive, qualitative study was to learn how children ages 7 to 12 and

adolescents ages 13 to 18 with cancer identified and defined fatigue. They also sought to learn what factors contribute to or alleviate this fatigue (Hinds et al., 1999). Separate focus groups of children, adolescents, parents and staff were conducted; twenty-nine focus groups were held with a total of 84 individuals. The nine focus group questions were used in parallel forms for the two patient groups (child and adolescent), parent, and staff groups. Data category codes included: descriptors of fatigue, causes of fatigue, general alleviating factors, and staff-initiated actions in response to patient fatigue. Definitions of fatigue were developed using the essential characteristics and outcome of fatigue as well as the contributory and alleviating factors.

The overarching conceptual definition of fatigue was described as a distressing, pervasive symptom with physical, mental, and emotional components characterized by a lack of energy (Hinds et al., 1999). The definition differed by developmental level. The school age group emphasized the physical sensation of feeling weak or tired, which could result in difficulties in play and concentration as well as feelings of anger and sadness. The adolescent group emphasized mental and emotional tiredness that alternated and sometimes merged with the physical sensation of fatigue. Adolescents shared that fatigue interfered with their ability to interact physically and emotionally with friends, family, and staff and prevented participation in school and activities. Both patient groups identified more causes of fatigue than alleviating factors, which indicated that they were more aware of what makes them feel fatigue than what relieves it. A conceptual model of fatigue was developed for each group that depicted the contributing and alleviating factors according to environmental, personal/behavioral, cultural/family/other, and treatment related categories. The methodology used by pediatric nursing researchers Hinds and Hockenberry in their first study in their program of fatigue research provided a strong conceptual definition of fatigue. Separate focus

groups for the developmental stages of school age children and adolescents resulted in a clearer understanding of the experience based on the patient's stage of development.

Researchers Davies, Whitsett, Bruce, and McCarthy (2002) generated a new perspective of fatigue in children with cancer in their qualitative study. Using a purposeful sampling technique, participants from two pediatric oncology treatment sites were selected. A total of 13 children, ages 5 to 15, and 12 parents were interviewed separately, and grounded theory analysis was applied to the transcribed interviews. In their findings, the researchers described energy as a core concept in the descriptions of fatigue, and managing this energy was the emergent core process. Three subjectively distinct types of fatigue were identified: *typical tiredness, treatment fatigue, and shutdown fatigue. Typical tiredness* was a normal process that was expected with normal day-to-day activities for the child's stage of development. *Treatment fatigue* was a new type of experience and the cause and onset was more difficult to identify and predict. Treatment modes (chemotherapy, radiation, surgery), environmental disruptions (interrupted sleep, hospital noise) and mental demands of interactions all contributed to this type of fatigue. *Shutdown fatigue* had increased intensity, duration, and immobilizing effects. During this undesirable and negative experience, the child shuts down from his or her environment in order to preserve energy. Children managed their dwindling energy and prevented further loss through replenishing, conserving, and preserving strategies. The children's descriptions of fatigue and management strategies included physical, mental, and emotional dimensions, which were consistent with Hinds and Hockenberry's findings. The ages of the patient sample (5 to 15 years) covered a large developmental range, but unlike Hinds and Hockenberry, Davies et al. did not discuss if or how fatigue changed across the developmental spectrum.

In their longitudinal, qualitative study, Woodgate, Degner, and Yanofksy (2003) described the childhood cancer symptom course from the perspectives of the children and their families. Thirty-nine children, ages 4 ½ to 18 with mixed cancer diagnoses, were studied over a two and a half year period during their treatment that included chemotherapy alone or chemotherapy with radiation and/or surgery and/or bone marrow transplant. Data collection methods included open-ended formal interviewing of parents and children (patients and their siblings). Through the development of the illness narratives, the paradigmatic relationships of symptom categories were confirmed. The children experienced cancer symptoms as overall feeling states. Symptoms were not singular side effects but rather multiple states with multiple layers of meaning. Quotes from at least one preschool child, school-age child, and adolescent were used to describe symptoms and demonstrate their universality across the developmental continuum. When experiencing the symptoms of fatigue, children described it as “I am wiped out… my body is just too tired for me to care” (Woodgate et al, 2003, p.810). Children felt like they were in a state of limbo; they were not in the living world, yet not in the world of the dying. Family members felt helpless in decreasing this sensation and could only wait for them to regain some energy. They described this time as being “betwixt and between” (Woodgate et al., 2003, p.811). In their discussion, Woodgate et al. identified the need for health professionals to modify how they assess and intervene in cancer symptoms through the use of valid and reliable cancer symptom assessment tools that include feeling states.

Using a qualitative approach, multiple researchers have provided clear evidence that fatigue is a distressing, frequently occurring, and sometimes overwhelming symptom in children and adolescents receiving treatment for cancer. It is a multi-dimensional experience that can be difficult to separate as a singular symptom. Fatigue

has both physical and mental components that are influenced by the child's level of development, the child's experience with treatment and other symptoms, as well as the environment, family and cultural background, and personal factors.

Prevalence of fatigue in children undergoing cancer treatment. Children with cancer, parents, and health care providers in quantitative studies have reported that fatigue is a frequent cause of distress in children and adolescents undergoing cancer treatment. In a group of 160 children with cancer, ages 10 to 18, the most prevalent symptom reported on the Memorial Symptom Assessment Scale (MSAS) was lack of energy at 49.7% (Collins et al, 2000). In a second study of a group of 149 children with cancer, ages 7 –12, over one-third (35.6%) reported "feeling tired" in the previous 48 hours in their responses to the Memorial Symptom Assessment Scale (MSAS). Fatigue was again the most prevalent symptom reported (Collins et al, 2002).

Gibson, Garnett, Richardson Edwards, & Sepion (2005) conducted a cross-sectional study using a questionnaire-based survey of 95 parents of children with cancer and 235 health care professionals (HCP) about cancer-related fatigue. Both parent and HCP groups reported patient fatigue as a frequent and disruptive symptom. Fifty-six percent of the HCP's responded that the majority of patients they cared for experienced moderate levels of fatigue and thought that fatigue was a serious issue for their patients' quality of life. The HCP perceived that fatigue influenced the patient's emotional well-being, independence, relationships with family and peers, and their ability to enjoy life and be active in play and schoolwork. Fifty-seven percent of parents reported that their child experienced fatigue at least once a week and that the fatigue had a significant impact on both the physical and the mental/emotional domains of life and was disruptive to family life.

Pathophysiology of fatigue. There is an absence of research in pediatric oncology on the physiological changes that occur in children experiencing cancer related fatigue. Literature from adult studies highlights key areas that may provide insight into the pathophysiology of fatigue in children. Ryan and colleagues (2007) examined research studies that focused on the etiology of fatigue in adults with other chronic illnesses, such as chronic fatigue syndrome and arthritis, and then extrapolated potential relationships to cancer related fatigue (CRF) in adults. From a physiological perspective, Ryan et al. defined fatigue as the inability to maintain power output. Fatigue can be categorized into two components: peripheral and central. Peripheral fatigue originates in the neuromuscular junctions and muscle tissue and occurs when the peripheral neuromuscular system is unable to respond to central stimulation. Mechanisms that trigger peripheral fatigue include defects in muscle metabolism that result in ATP dysregulation and the buildup of metabolic by-products. Central fatigue occurs in the CNS and is the result of the failure to transmit motor neuron impulses. Central fatigue is demonstrated by the inability to perform physical and mental tasks that are dependent on self-motivation even though the individual has the cognitive and motor capability to do the task (Ryan et al.). Mechanisms hypothesized to potentially influence central fatigue include serotonin dysregulation that results in an increase in brain serotonin and a reduced ability to perform physical work, a disturbance of the hypothalamus/anterior pituitary/adrenal cortex (HPA) axis that results in endocrine changes, circadian rhythm changes, and increased levels of proinflammatory cytokines that induce “sickness behavior” (Ryan et al.). Further research is needed that focuses on subjects with cancer to both advance our knowledge about the pathophysiology of cancer related fatigue in adults and to examine if these same mechanisms, or different ones, apply to children and adolescents.

In addition to the primary physiological mechanisms related to fatigue, health professionals may exacerbate the patient's fatigue by counseling them to decrease their daily activities in order to conserve energy; this advice can cause paradoxical results (Dimeo et al., 2003). When muscles become inactive, the enzyme content in the mitochondria and the density of muscle capillaries decrease; this results in a loss of oxidative metabolic capacity and dependence on the less effective anaerobic glycolysis pathway. Myofibrils become thinner indicating muscle atrophy; muscle fibers needed for endurance activities are lost. Muscles lose their power and force and become more fatigable (Al-Mauid & McCarthy, 2001; Lowe, 2004). As fatigue increases, the person with cancer becomes more sedentary which triggers a further downward spiral of physical capability and a continued increase in fatigue (Lucia, Ernest, & Perez, 2003). Multiple meta-analysis and systemic reviews have rated exercise as demonstrating the highest evidence as a safe intervention for reducing fatigue and improving physical performance in adults undergoing cancer chemotherapy and bone marrow transplant (Mitchell et al., 2005; NCCN, 2008; Knols et al., 2005, Cramp, 2008).

Measurement of fatigue in children and adolescents with cancer. In their program of fatigue research, Hinds and Hockenberry used their conceptual definitions derived from children and adolescents undergoing cancer treatment to develop and test instruments to measure fatigue. The data collected during the original focus group was used to create the 14-item Childhood Fatigue Scale (CFS) (Hockenberry et al., 2003). Children ages 7 to 12 defined fatigue as "a profound sense of being physically tired, or having difficulty with body movement," (Hockenberry et al., p. 320). Participants also described feeling mad or sad when fatigued. Review by expert pediatric oncology nurses was used to establish the content validity of the CFS and the instrument testing was completed on 149 children between ages 7 to 12 who were receiving chemotherapy.

The CFS researchers identified three subjective dimensions that conceptualized fatigue and had strong correlations between them (Hockenberry et al.). These three subscales were: lack of energy, not able to function, and altered mood. Two of these reflect the physical endurance changes children experience. One reflected emotional changes without a focus on cognitive changes. The CFS findings are consistent with findings from developmental theorists who find that children ages 7 to 12 focus on finishing physical tasks and activities rather than cognitive functioning.

In developing the Fatigue Scale-Adolescents (FS-A), Hinds and Hockenberry and colleagues (2007a) also derived their conceptual definition of fatigue from their qualitative study of both individual and focus group interviews with adolescents ages 13 to18. Adolescents defined fatigue as “a complex changing state of exhaustion that at times seems to be a physical condition, at other times a mental state, and at other times a combination of physical, emotional and mental tiredness” (Hinds et al., 2007a, p. 609; Hinds et al., 1999, p. 282). The 14 items in the scale were designed to include one to two items from each characteristic of the conceptual definition. When the scale was tested, the four items with the highest mean scores were: “My body has felt tired,” “I want more rest,” “It is harder to keep up with my schoolwork,” and a reverse coded item, “I am able to do my usual activities” (Hinds et al., 2007a, pg 612).

Hinds and Hockenberry’s instrument development research is an excellent model of developing a quantitative measure of fatigue from a conceptual definition developed through qualitative inquiry. The researchers provide rich detail about the instrument development and testing. By using a developmental approach, the researchers were successful in developing reliable and valid assessment tools for a specific population based on that group’s developmental experience with fatigue.

Fatigue in relation to other symptoms. As knowledge about fatigue in pediatric oncology advances, additional variables and relationships are the focus of ongoing research. In their pilot study of nine children, ages 8 to18, with acute lymphoblastic leukemia, Gedaly-Duff, Lee, Nail, Nicholson, and Johnson (2006) measured the symptoms of fatigue, pain, and sleep disturbance over three days after the children received outpatient chemotherapy. All of the children reported fatigue as being prevalent at the end of the day and experienced frequent awakenings at night. Five of the children reported pain. The researchers concluded that the patient reports suggested that these symptoms might cluster together after chemotherapy treatments.

Hinds and Hockenberry continue to build on their program of fatigue research and have completed studies measuring fatigue in relationship to sleep disturbance. In a descriptive, longitudinal pilot study, Hinds and Hockenberry and colleagues measured the nocturnal awakenings and sleep environment interruptions experienced by 27 children and teens ages 7 to18 who were receiving inpatient chemotherapy over three days for treatment of solid tumors or acute myeloid leukemia (Hinds et al., 2007b). They also examined correlations between sleep duration and fatigue. Sleep in the subjects was measured by wrist actigraphy and parent documentation in a sleep diary. The staff and parents recorded sleep interruptions when they entered and exited the patient room. Fatigue was measured using these researchers' Children Fatigue Scale (CFS) and Fatigue Scale for Adolescents (FS-A). The patients experienced 0 to 40 nocturnal awakenings per night with a median of 14 awakenings. For 70% of the patients, the longest nocturnal sleep period without awakening was one hour on one to two nights. There was a significant relationship between the number of nocturnal awakenings and fatigue over the course of hospitalization ($F = 5.71$, $p = 0.027$) and between nocturnal awakenings and sleep duration ($F = 6.35$, $p = 0.014$). Hinds et al. (2007b) concluded

that their findings supported a relationship between sleep quality and hospital-related fatigue in children undergoing cancer treatment and recommended that nurses implement work procedures and staff education to minimize sleep interruptions.

In their next study, Hinds and Hockenberry and colleagues examined whether there was a significant change in sleep quality and fatigue levels measured during the five days immediately before dexamethasone compared to measures during a 5-day pulse of oral dexamethasone period (Hinds et al., 2007c, 2007d). Subjects, who served as their own controls, included 100 children and adolescents ages 5 to 18 who were undergoing maintenance chemotherapy for acute lymphoblastic leukemia at two sites. Subjects were treated on one of four risk-based treatment protocols: St Jude low risk, St Jude standard risk, COG low risk, and COG standard risk. The protocols had different total doses for the dexamethasone pulse. Sleep duration, efficiency, minutes and awakenings were measured by wrist actigraphy and parent diary during the continuous 10-day study period. Fatigue was measured on day 2 and 5 of the two 5-day periods for each cohort using the fatigue instruments for their age group that had been developed and tested by the researchers. There was a significant increase in sleep duration (total minutes in bed) ($p = 0.0003$) and a significant increase in fatigue ($p < 0.001$) from pre-dexamethasone to day 5 during the dexamethasone pulse period. Neither sleep efficiency scores ([time asleep: time in bed] x 100) nor nocturnal awakenings had significant changes before and on dexamethasone. There were significant differences between the four risk-based treatment groups in sleep efficiency, sleep minutes, and nocturnal awakenings with the greatest sleep changes occurring in the group receiving the highest dose of dexamethasone. The average sleep efficiency for each treatment group in both 5–day study periods (off and on dexamethasone) was lower than the level considered acceptable for children and adolescents. The researchers concluded that

dexamethasone pulses during maintenance therapy adversely influence sleep and fatigue, but noted that the results did not explain the precise mechanism of change (Hinds et al., 2007c, 2007d).

Fatigue in childhood cancer survivors. As treatment of childhood cancer advances, researchers have begun to identify symptoms and late effects on long-term survivors on the disease. Meeske and colleagues have focused their research on fatigue and other factors related to quality of life in cancer survivors. In 2005, Meeske, Siegel, Globe, Mack, and Bernstein examined the prevalence of fatigue in long-term survivors of ALL and identified factors related to fatigue. One hundred sixty-one subjects ages 18 to 41 who had completed childhood ALL treatment between 1975 and 1995 were interviewed by phone. Fatigue was measured using established scales. Cancer-related symptoms were assessed using the Symptom Distress Scale and depression was assessed using the Center for Epidemiological Studies Depression Scale. The incidence of fatigue was 30% and was within the general population normal limits. However, fatigue was the most frequently reported symptom on the Symptom Distress Scale and survivors who reported fatigue were 33 times more likely to be depressed than non-fatigued survivors. There was a strong correlation between off-treatment fatigue and depression ($r = 0.75$). Four of the factors that were associated with fatigue were also associated with depression; these factors were sleep disturbance, pain, obesity, and cognitive impairment (Meeske et al.)

In a second study of 86 pediatric cancer survivors ages 8 to 18, Meeske, Patel, Palmer, Nelson and Parow (2007) measured quality of life using the Pediatric Quality of Life Inventory 4.0 Generic Core Scale (PedsQL™) and fatigue using a 10-point scale. The mean time since completing treatment was 7.8 years. Fatigue was associated with poorer physical functioning ($p < 0.01$) and poorer psychosocial functioning ($p < 0.0001$),

as well as a lower Peds QL™ total score ($p < 0.001$). Fatigue was recognized as having a negative impact on physical performance, mood, cognition, school performance, and social interactions. Furthermore, fatigue was the most powerful predictor of functional status and health related quality of life (Meeske et al.).

Fatigue summary. Fatigue is clearly a distressing and complex symptom that can be described by children and adolescents and measured with developmentally appropriate data collection methods. Research has informed us about the incidence of fatigue and progressed to examining the relationship of fatigue to a limited number of other variables, such as types of chemotherapy treatments and sleep disturbance. Although it is not as prevalent in cancer survivors, fatigue is associated with poorer quality of life. The prevalence and intensity of fatigue in the pediatric oncology population and its potential for influencing the child's symptom experience support the need for further research of this symptom.

Physical Performance.

Definition. Physical performance is conceptualized as a child's ability to do developmentally appropriate muscle movements necessary for the child to ambulate and actively participate in age appropriate experiences that support ongoing development and health. Physical performance is influenced by the individual's motor function, muscle strength, and endurance. Measures of physical performance can be categorized in three domains: *physiologic capacity, functional capacity, and functional status* (Pu & Nelson, 1999). The first domain, *physiologic capacity*, refers to the body's ability to perform under physical stress (i.e., muscle strength, aerobic capacity) and is measured as a continuous, quantitative variable. The second domain of *functional capacity* theoretically refers to tasks that are performed in everyday life (i.e., walking endurance, functional mobility) that are usually assessed by a trained tester. The final domain,

functional status, corresponds to behavioral indications of disability and is often assessed through self-report scales or questionnaires (i.e., performance status). The relationship between improved *physiologic capacity* and *functional capacity,* as well as between *functional capacity and functional status,* is the focus of ongoing research. These relationships are thought to be curvilinear, in that improvements in *physiologic capacity* (i.e., muscle strength) impact *functional status* (i.e., ability to ambulate) to a certain threshold, after which function is not influenced by improvements in *physiologic capacity* (Pu & Nelson). Studies of physical performance studies in children and adolescents have focused on measuring the scope of problems in childhood cancer survivors and on children with acute lymphoblastic leukemia (ALL), the largest disease group in childhood cancer. More recent studies have examined physical performance measurements during treatment, and finally, evaluated interventions to improve physical performance.

Physiologic capacity after cancer treatment. In their meta-analysis of survivors of childhood acute lymphocytic leukemia (ALL), van Brussel, Takken, Lucia, van der Net, and Helders (2005) reviewed 17 studies that evaluated the peak oxygen uptake (VO_{2peak}). They recognized that exercise increased the physiologic capacity in adults with cancer and resulted in improved quality of life and less fatigue. Little is known about the aerobic fitness in survivors of childhood ALL. VO_{2peak}, which is measured during a graded maximal exercise to volitional exhaustion, is considered the best measurement for aerobic fitness by The World Health Organization. This standard of measurement of VO_{2peak} was one of the inclusion criteria for the meta-analysis. Additional criteria included studies of childhood ALL and healthy controls, description of the methodology for VO_{2peak} measurement, and description of subjects' characteristics. Three of the studies met their inclusion criteria and the subjects were combined into a

pool of 102 survivors. Van Brussel et al. found that VO_{2peak} was 13% lower in survivors of childhood ALL when compared to healthy control subjects (95% confidence interval: [-27, 0.004]). It was recognized that more research is needed to understand the variables in cancer survivors that could influence VO_{2peak}. These include central cardiac dynamics, sedentary habits, lung function impairments, and muscle atrophy. The researchers noted that poor physical fitness contributes to fatigue and they recognized that exercise could improve the quality of life of these patients.

Functional capacity during and after cancer treatment. Wright, Halton, Martin, and Barr (1998) evaluated the basic gross motor skills, hand grip strength, and ankle dorsilflexion range of motion in 36 survivors of childhood ALL, ages 5 to 14, who were at least 12 months past completing therapy. Using paired t-tests, the survivor group's scores were compared to a group of matched age and gender healthy controls. When the two groups were measured using the Gross Motor Function Measure, there were no significant differences in their ability to perform most basic gross motor functions, such as walking, running and climbing stairs. However, the cancer survivors performed significantly poorer on a more sensitive Bruininks-Oseretsky Test of Motor Proficiency test (BOTMP) in the components of running speed and agility, balance, and strength ($p < 0.001$ for each component). Additionally, the ALL survivor group had significantly less handgrip strength ($p = 0.007$) and less ankle dorsiflexion ($p < 0.001$). There was not a significant correlation between the BOTMP scores and the amount of time off therapy. Wright et al. acknowledged that most children treated for ALL are able to perform basic gross motor skills and so their motor performance is generally unnoticed by health care professionals because the child is not overtly disabled. The chemotherapy drugs, vincristine and prednisone, were discussed as potential contributors to the survivors' muscle weakness. The importance of physical performance ability in relation to self-

esteem, health, level of fitness and success in recreational and educational pursuits was identified by the researchers. This study represented an important first step in understanding the importance of measuring physical performance and the recognition that cancer survivors may have significant deficits.

In a later study, Wright, Galea, and Barr (2005) again focused on survivors of childhood ALL. They measured balance using the BOTMP balance subtest as well as self-perception of physical activity, and health-related quality of life in 99 subjects, ages 5 to 25, who were at least 1 year off treatment and up to 13 years post treatment. A second group of subjects, ages 5 to 31, who had not been treated for cancer were matched for age and sex to provide comparative data. The ALL survivors had significantly lower scores on the BOTMP balance test (t = -6.893, p < 0.001), on the Children's Self-perceptions of Adequacy in and Predilection for Physical Activity Scale (CSAPPA) (t = -3.178, p = 0.002), and on the Health Utility Index (HUI) measurement for quality of life (t = -4.747, p < 0.001). Predictors of lower balance scores included receiving cranial radiation treatment, being overweight, lower CSAPPA sub-score for adequacy, and lower HUI sub-score for cognition. Wright et al. discussed that the etiology of balance problems was likely to be multi-factorial and variable. Balance is important to proficiency in sports and active play. The ALL survivor group was less likely to participate in physical activities and therefore could not experience the health benefits of exercise.

In a pilot study, Gocha Marchese, Chiarello, and Lange (2003) examined the relationship between measures of strength and functional mobility in 8 children, ages 4 to 15, before and during the delayed intensification phase of treatment for ALL compared to age and gender matched controls. Knee extension strength and ankle dorsiflexion strength were measured by hand-held dynamometer. The Timed Up and Go test (TUG),

a functional capacity measurement, evaluates the time needed to stand from sitting, walk 3 meters, turn around, return to the chair and sit down. In children with ALL measured before delayed intensification, the mean measures of knee extension strength, ankle dorsiflexion strength, and TUG were significantly less than the means for the healthy matched controls ($p = 0.43$, $p < 0.001$, $p = 0.004$ respectively). Additionally, children with ALL had a significant decrease in ankle dorsiflexion strength ($p = 0.015$) from before delayed intensification to week 4 of that phase of treatment. On week 4, there was a correlation of –0.794 ($p = 0.05$) between knee extension strength and the TUG, indicating that children who were stronger in knee extension performed the TUG faster. This study contributes to the knowledge that children lose strength and functional mobility during treatment for ALL. The researchers recommended using tests such as a run/walk test to examine endurance in relation to functional mobility outcomes and identified the need for intervention studies to prevent or rehabilitate these physical changes.

Functional status during and after cancer treatment. The Childhood Cancer Survivor Study (CCSS) includes a sample of over 20,000 cancer survivors. Subjects in this study completed a 24-page baseline questionnaire that included questions about physical performance and physical activity (Robison et al., 2005). As part of the CCSS study, limitations on physical performance were assessed in a cohort of 11,481 survivors of brain cancer, leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney tumor, neuroblastoma, soft-tissue sarcoma or malignant bone tumor (Ness et al, 2005). Subjects were treated before age 21 and had survived at least 5 years since diagnosis. The 11,481 survivors were compared to a group of 3,839 siblings without cancer. There were six self-report questions that asked about experiences over the past 2 years in relation to health and vigorous activities like running, participating in strenuous sports,

and lifting level objects. The median age of cancer survivors completing the survey was 23 years, with a range of 8 to 47 years. The median age for sibling respondents was 26 years, with a range of 5 to 56 years. After the researchers had adjusted for age and sex, survivors of all cancer types (n =2253, 19.6%) were almost twice as likely to report performance limitations in comparison to siblings (n = 455, 11.8%). There was a significant difference between the physical performance mean scores of survivors and siblings ($p < 0.001$). Predictor variables (cancer type, treatment, late effects) were also analyzed with survivors of bone cancer, brain cancer, and Hodgkin disease reporting the highest levels of performance limitations. The researchers discussed that although late effects cannot always be prevented, their influence on physical performance may be lessened through more aggressive rehabilitation and fitness interventions during and after treatment.

In their study of children, ages 8 to 12, who were either undergoing treatment for cancer (n = 72) or had completed cancer treatment (n= 90), Shankar and colleagues assessed physical functioning, one of the four dimensions in the Minneapolis-Manchester Quality of Life-Youth Form (MMQL-YF) (Shankar et al., 2005). The two groups treated for cancer were compared to healthy children (n = 481). The six questions in the physical functioning sub-scale related to participation in sports, having energy, and taking part in activities. Children actively undergoing cancer treatment for leukemia (64%), lymphoma (6%), brain tumor (8%), or other solid tumors (22%) had significantly lower scores for physical functioning compared to healthy children (mean scores: 3.47 vs 4.00; $p = 0.01$). Significant differences were found for all of the diagnostic sub-groups except for other solid tumors. The cancer survivor group did not report significantly lower scores in physical functioning compared to the healthy children (mean scores: 3.99 vs 4.00; $p = 0.83$). Shankar et al. suggested that the comparable

self-report scores of cancer survivors to healthy children was the result of cancer survivor's adaptive view of life and abilities that may have developed after a life-threatening illness.

Keats, Culor-Reed, Courneya, and McBride (2006) measured physical activity in adolescents across the cancer experience with the Leisure Score Index (LSI) of the Godin Leisure Time Exercise Questionnaire. The LSI is a self-report measure that asks three questions about the frequency and duration of mild, moderate, and strenuous activity/exercise performed for at least 15 minutes in the previous week. The researchers found a significant decrease in the total LSI from pre-diagnosis to during treatment ($P < 0.0005$). Levels of activity after treatment did not return to pre-diagnosis levels ($P = 0.002$). As part of the LSI measure, each episode of activity/exercise is assigned a metabolic equivalent MET; a mild session is 3 METS, moderate is 6, and strenuous is 9. Ninety-seven subjects recalled their behaviors during three intervals: pre-diagnosis, during treatment, and after treatment; their responses for each time period were categorized as being active (27 METS per week) or inactive. Twenty-three percent of subjects were categorized as "maintainers"; they were active pre-diagnosis and continued to be active during and after treatment. "Temporary relapsers" (47.1%) were active pre-diagnosis, became inactive during treatment, but returned to activity post treatment. "Permanent relapsers" (13.8%) were active before being diagnosed, became inactive during treatment, and then stayed inactive after treatment. "Non-participants" (10.3%) were inactive during all three time periods. Five percent of the subjects were inactive pre-cancer but became active after treatment. Keats et al. discussed that cancer treatment may have a negative effect on adolescent physical activity levels; in their study, these levels rebounded somewhat after treatment but did not return to the pre-diagnosis levels. The researchers concluded that studies are needed to evaluate

interventions that increase levels of physical activity during and after cancer treatment to maximize health benefits and quality of life.

Physical performance interventions during cancer treatment. In their pioneering study, Marchese, Chiarello, and Lange (2004) examined the effects of a physical therapy intervention in children undergoing treatment for acute lymphoblastic leukemia (ALL). A sample of 28 children ages 4 to 15, who were in the maintenance phase of ALL treatment, were randomly assigned to an intervention group or a standard care control group. The physical therapy intervention consisted of five PT sessions at week 1, 2, 4, 8 and 12. Families were also directed on how to do an individualized exercise program at home. Measurements were performed at baseline and at the end of 4 months. Children in the intervention group had significantly improved ankle dorsiflexion active range of motion and knee extension strength ($p < 0.01$). There were no significant differences between the two groups for measures of ankle dorsiflexion strength, Timed Up and Down Stairs test (TUDS), 9-minute walk-run, or quality of life measures. Children in the control group did not have a significant change in their measurements indicating that functional abilities did not improve or worsen during this phase of treatment. Marchese et al. noted that children in both groups scored poorly on the 9-minute walk-run when compared to healthy norms. Further research is needed to examine outcomes of intervention earlier in treatment, in younger children, and with added focus on exercise that will increase endurance. Larger studies may provide further insight into the effectiveness of rehabilitation interventions as well.

San Juan and colleagues (2007) also studied children in the maintenance phase of ALL treatment when they evaluated the effect of a 16-week exercise program that included aerobic and resistance training. Seven children ages 4 to 7 underwent an exercise intervention consisting of 90 to 120 minute sessions in the hospital gymnasium

three times a week. The researchers were not successful in recruiting more subjects for a control group. The strength training included a series of 11 exercises that involved the major muscle groups. Aerobic exercise started with 10-minute sessions at 50% of the age-predicted maximum heart rate and advanced to at least 30 minutes at 70% HR maximum. Aerobic sessions included cycling, running, walking, and aerobic games. Adherence to the training was 85%. Measurements were performed at pretraining, post training, and after a period of detraining. Measures of functional mobility (TUDS, TUG 3 meter, TUG 10 meter) improved significantly after training but did not show a significant difference between pretraining and detraining. Measures of strength endurance (bench press, leg press, seated row) improved significantly with the intervention and remained significantly improved after detraining. Ankle dorsiflexion and passive and active range of motion did not change significantly from pretraining. Subjects $VO_{2\ peak}$ improved significantly after training and then decreased slightly with detraining; the difference from pre-training to detraining was no longer significant which indicated a partial maintenance of the improvement during detraining. Despite the limitation of a small sample size, San Juan et al. demonstrated that children undergoing treatment for ALL can safely undergo rigorous aerobic and resistance training and make significant improvements in their fitness levels.

Physical performance summary. Research on physical performance during and after treatment for childhood cancer informs us that patients have less strength and endurance compared to healthy children. They are less active and are less able to perform physically. Outcomes of physical therapy and exercise physiology interventions have been evaluated in small studies of children during ALL maintenance therapy. The ability to perform physically is important to the child's ongoing development. Further research is needed to understand how physical performance changes over the trajectory

of treatment, how changes relate to other symptoms including fatigue, and how physical performance deficits may influence development. Evidence is also needed on effective interventions that can be incorporated into the child or teen's daily life.

Carnitine

Carnitine system. Carnitine is a micronutrient that is used by the body in fatty acid metabolism. Fatty acids are a primary source of energy for humans, especially in the cardiac and skeletal systems. During digestion, insulin stimulates the process by which dietary fat is transformed into triglycerides for storage in the adipose tissue. When triglycerides are needed for energy in the muscles, they are hydrolyzed to free fatty acids and glycerol; epinephrine and glucagons regulate this lipolysis process. The long chain fatty acids travel through the circulation and enter the mitochondria through the carnitine system as acylcarnitines (Hoppel, 2003). It is the carnitine palmitoyl transferase (CPT) system that moves the long chain fatty acids through the outer and inner membranes of the muscle cell's mitochrondria (Stipanuk, 2000). The fatty acids combine with coenzyme-A to form fatty acyl-coA, which is the primary fuel for aerobic metabolism (Blei, Fall, & Kushmerick, 1999). Using β- oxidation, the fatty acids are metabolized into ATP. Additionally, carnitine also transports fatty acids back out of the mitochondria that accumulate as a result of normal and abnormal metabolism. Carnitine plasma levels are further regulated through the proximal tubules of the kidney where it is reabsorbed through a specific transport system (Peluso et al., 2000). Carnitine is stored primarily in the skeletal and cardiac muscles; these tissues use fatty acids as their primary source of energy. Deficiencies in carnitine are manifested as low energy levels and muscular weakness.

Carnitine and chemotherapy. In their review of research studies of cancer treatments that influenced the carnitine system, Peluso and colleagues (2000) noted that

animal models suggest that there is interference by anti-cancer drugs on the carnitine network. Doxorubicin is an anthracycline antibiotic chemotherapy drug that is an important agent in the treatment of many pediatric malignancies including leukemia, lymphoma, and solid tumors but has the potential for cardiotoxic side effects. Doxorubicin is thought to hinder the carnitine system by reducing heart concentrations of free carnitine, decreasing free fatty acid oxidation, decreasing creatine phosphate, and decreasing protein synthesis and oxygen uptake (Peluso et al.). In animal models, carnitine supplementation improved these metabolic changes. Yoon, Hong, Boriack, and Bennett (2003) found that rats treated with doxorubicin had a significant decrease in carnitine palmitoyl transferase (CPT) activity when compared to a control group. They concluded that doxorubicin influences the carnitine system by profoundly inhibiting the CPT activities which, in turn, inhibits fatty acid oxidation in the heart (Yoon et al.).

Ifosfamide is an alkalating chemotherapy agent used in the treatment of some solid tumors and relapsed leukemias and lymphomas. The metabolic pathways of ifosfamide leads to formation of chloroacetyl-CoA with a decrease in CoASH levels, which is an activator of energy–providing systems. This process is not related to the drug's anti-cancer properties but is part of a potentially toxic side effect. Carnitine stored in the patient binds to the chloracetyl-CoA, detoxifies it, and then the chloro-acteyl-carnitine is excreted in the urine. This detoxification process can contribute to a secondary deficiency of carnitine in patients (Peluso et al., 2000; Marthaler, Visarius, Küpfer, & Lauterburg, 1999). An additional factor exacerbating the patient's carnitine stores can be renal tubular damage from ifosfamide that allows for increased urinary loss of carnitine. Researchers found that during one chemotherapy cycle of ifosfamide, patients lost an average of 8.5 mmol of carnitine in their urine. They estimated that is loss is equivalent to approximately 10% of the carnitine stores found in their skeletal

muscle (Marthaler et al.). Repeated cycles of the drug could contribute to symptoms of carnitine deficiency and may contribute to the adverse symptoms (fatigue, encephalopathy) associated with this chemotherapy (Marthaler et al.).

Cisplatin is a platinum-containing chemotherapy drug used in the treatment of Hodgkin lymphoma and some solid tumors. Cisplatin has adverse effects on the kidney, which causes reduction in glomerular filtration and tubular damage. Carnitine is absorbed in the body proximal to the tubular level, and patients receiving cisplatin may have an increased loss of carnitine through the kidney (Peluso et al., 2000; Chang, Nishikawa, Sato, Utsumi, & Inoue, M, 2002). Chang et al. studied whether L-carnitine administered before cisplatin protected rats from kidney and intestinal injury. Four groups included a control group, a cisplatin treated group, a carnitine prior to cisplatin group, and a carnitine only group; each group had 6 rats. Cisplatin without carnitine impaired the mitochondria in the renal tubules and small intestinal mucosal cells, while carnitine administered prior to cisplatin protected these cells from injury. Carnitine did not inhibit the tumoricidal action of cisplatin against cancer cells in the rats (Chang et al.).

Studies have shown that individual anticancer drugs in a variety of drug classes interfere with the carnitine system. Little is known about other chemotherapy drugs in these same drug classes (anthracycline antibiotics, alkalating agent, platinum compound) and further research is needed to understand the scope of the cancer treatment agents on the carnitine network in the body.

Carnitine levels in cancer patients. In an adult cancer study of 10 patients receiving cisplatin chemotherapy, subjects had normal plasma carnitine levels pre-chemotherapy when compared to healthy controls. Carnitine plasma levels increased by 39% during the 3 days of chemotherapy and then normalized 7 days after a course of

chemotherapy was completed (Heuberger, Beradi, Jacky, Pey, & Krahenbuhl, 1998). Urinary excretion increased during therapy and then stabilized on the seventh day after the course was completed. The researchers hypothesized that carnitine is released by skeletal muscle tissues into the bloodstream to replace carnitine loss through renal excretion resulting in the initial increase in plasma levels on day 3 (Heuberger et al.).

In a symptom clusters study recently completed by Hockenberry and Hooke, carnitine plasma levels were measured on day 1 before chemotherapy started and 7 days after chemotherapy was initiated. Preliminary analysis of 65 patients enrolled in the study showed a significant increase from day 1 to day 7 in total carnitine (p = .013) (Hockenberry, personal communication, May 14, 2008). This supports the observation of Heuberger et al. (1998) that carnitine levels may increase before they decrease.

In a pediatric study, total plasma carnitine levels of 51 children, ages 3 to 16 years with a variety of oncologic diagnoses and treatments, were similar in sex and age to 20 healthy controls at diagnosis (Yaris, Akyüz, Coşkun, and Büyukpamükcu, 2002). At month 3 of treatment, the children with cancer had a significant decrease in total carnitine levels (p = 0.004) and the levels were significantly different than the healthy controls (p = 0.02). The carnitine levels were not related to age, sex, type of cancer, or stage of disease. Nutritional status was classified according to the Waterlow classification and the Gomez criteria (Yaris et al.). There was not a significant relationship between carnitine levels and nutritional status either at diagnosis or at month 3. The researchers concluded that inadequate intake of carnitine was not responsible for the decreased levels and suggested that decreased levels were due to metabolic changes during chemotherapy treatment and or from the neoplastic process (Yaris et al.).

Carnitine supplementation. Administration of oral carnitine has been investigated in recent studies of adult cancer patients. In an Italian study of 50 patients who experienced fatigue and had low plasma carnitine levels while receiving cisplatin (n = 44) or ifosfamide (n = 6) chemotherapy, subjects were treated with a daily dose of 4 grams of oral levocarnitine (L-carnitine) taken for one week to restore carnitine levels. All patients achieved a normal plasma carnitine level following levocarnitine supplementation. The majority (87%) of the patients reported reduced fatigue and the difference between pretreatment and post-treatment fatigue scores was statistically significant ($p<0.001$) (Graziano et al., 2002).

In a Phase I/II, open-label trial, Cruciani et al. (2006) evaluated the safety and tolerability of the maximum tolerated dose of L-carnitine oral supplementation, and the safe dose range for future clinical trials was established. Twenty-seven adult patients met the eligibility criteria. They had advanced cancer with moderate to severe fatigue, carnitine deficiency as defined by plasma free carnitine levels, and a hemoglobin > 9g/dl. Subjects were assigned in groups of three to dose groups starting at 250mg/day administered in two daily doses and increasing by increments of 500 mg to 3000 mg/day. The highest dose achieved was 3000 mg/day and no patient experienced significant side effects or toxicities. Twenty-one patients completed the study treatment, and 17 subjects, “responders,” had increased carnitine levels at the end of their treatment period. Analysis of all subjects showed that there was a significant increase in plasma carnitine levels, significant decrease in scores on the Brief Fatigue Inventory and significant improvement in sleep and depression scores. An analysis of the 17 responders showed a significant dose-response relationship for carnitine plasma levels and fatigue scores. This group of researchers recently completed patient enrollment to a phase III randomized clinical trial that is enrolling adults with invasive cancer who have

moderate to severe fatigue (National Institutes of Health, 2008) to determine if L-carnitine replacement improves fatigue.

In animal models, carnitine has been shown to be a modulator of the glucocorticoid receptor (Alesci, De Martino, Kino, & Ilias, 2004); glucorticoids are used in the treatment of leukemia and lymphoma. Before carnitine supplementation can be considered, interactions with corticosteroids used in cancer treatment must be explored. Further research is needed to understand how carnitine plasma levels change in children and adolescents over the course of cancer treatment, what chemotherapy drugs may decrease carnitine levels, and how these levels influence other symptoms.

Relationship Between Fatigue, Physical Performance, and Carnitine Levels.

Research on children and adolescents with cancer clearly informs us that fatigue is a distressing and pervasive symptom that has a physical component, described as a "lack of energy," that becomes more complex as development advances (Collins et al., 2000, 2002; Davies et al., 2002; Hinds et al, 1999; Hockenberry et al., 2003; Woodgate et al., 2003). Until recently, measurements of physical performance in pediatric oncology have focused on cancer survivors (Wright et al., 1998). Researchers are now beginning to examine physical therapy interventions to improve strength and mobility in children undergoing cancer treatment (Marchese, Chiarello, & Lange, 2004). However, fatigue has not been evaluated as a variable in relation to physical performance. With measurements now established that nurses can use in their assessment of fatigue and physical performance, further investigation is warranted. Carnitine, a key essential nutrient, has an important role in how muscles metabolize energy (Blei et al., 1999; Stipanuk, 2000). Studies indicate that several anti-cancer drugs impede the carnitine network (Peluso, et al., 2000), which could result in a less efficient aerobic muscle metabolism. Researchers have identified that fatigue increases and physical

performance decreases in the child undergoing cancer treatment, but the change in these variables over time is not known. Carnitine plasma levels have been shown to decrease in children over the course of treatment (Yaris et al, 2002); however, its relationship to fatigue is not known. The literature supports that the variables fatigue, physical performance, and carnitine are all related to physical energy; yet, there is a gap in research on the pediatric oncology population. More research is needed to understand the relationship of fatigue, physical performance, and carnitine levels in children and adolescents over the course of treatment.

Chapter 3

Methodology

Introduction

In this exploratory pilot study, a within subjects design was used to examine the relationship between the change in physical performance and carnitine plasma levels and the change in fatigue measures between two time points in two cohorts of subjects. The treatment related factors of physical performance and carnitine were the independent variables and fatigue was the dependent variable (Figure 2). Using developmentally appropriate assessments, two cohorts of children newly diagnosed with cancer (children ages 6 to 12 and adolescents ages 13 to 17) were followed during their first and third cycle of chemotherapy. A correlational design was selected for this study because the literature supported possible connections among the study variables, but their relationships had not been evaluated in studies of children with cancer.

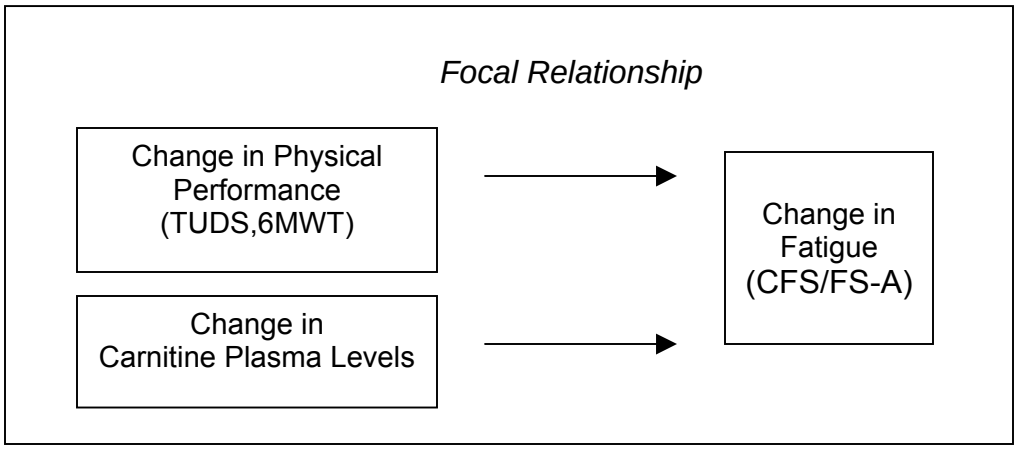

Figure 2. Study design

Sample and Setting

The study was conducted at two pediatric oncology treatment centers in the Twin Cities of Minneapolis and St. Paul, Minnesota. The study was initiated in the oncology

program at Children's Hospitals and Clinics of Minnesota that serves children on two hospital campuses, one in Minneapolis and the other in St. Paul. The pediatric oncology program at the University of Minnesota Physicians Masonic Cancer Center in Minneapolis, Minnesota was added as a second study site in the 10th month of the study to expedite subject enrollment. During the 20-month study period, eligible subjects included children (ages 6 to 12) and adolescents (ages 13 to18) who: 1) spoke English; and were 2) newly diagnosed with cancer; 3) receiving chemotherapy for a minimum of 3 cycles with at least two intravenous or intramuscular chemotherapy agents; 4) able to give assent according to institutional guidelines; and 5) who had parental consent to participate. Children and adolescents were excluded if they: 1) were receiving radiation therapy; 2) had an antecedent neurological, developmental, or genetic disorder; 3) displayed neurological deficits secondary to surgical intervention; and/or 4) were in the intensive care unit longer than 48 hours during the first two weeks of diagnosis. As newly diagnosed patients entered the oncology programs at the two study sites, they were screened for eligibility for this study by the investigator.

Rationale for inclusion criteria. Following the study's conceptual framework, the fatigue study measurements were based on their developmental sensitivity. The age ranges for the two study cohorts were based on the age criteria that were established in the psychometric testing for self-report fatigue scales for children and adolescents with cancer. The scale for adolescents had only been tested in English. A three-cycle period of chemotherapy was selected as the study time interval because, during this time, intensive chemotherapy is administered to induce and consolidate a remission in the patient. The time frame of three cycles also included the shortest treatment interval for some pediatric cancers (Wilms tumor and Hodgkin Disease), although treatment regimens for other diagnoses could continue for up to three years. Receipt of two

intravenous and/or intramuscular chemotherapy agents was selected as the criterion indicator of minimal intensity of treatment. In the pediatric cancer population, there is insufficient evidence about the relationship of symptom distress and cancer diagnosis and treatment. A wide range of diagnoses was included in this study. Adult studies have shown that "symptoms do not correspond closely with particular diseases or with the chemotherapy protocols patients undergo" (Given et al., 2004). Although animal studies indicate that three chemotherapy agents, ifosfamide, cisplatin, and doxorubicin, are associated with carnitine loss, other intravenous chemotherapy agents have not been eliminated as sources of carnitine loss. Many agents in a chemotherapeutic drug classification have similar actions on cells. For example, other agents in the anthracycline category (which includes doxorubicin) have the same toxic side effect profile. Therefore all intravenous and intramuscular chemotherapy agents were considered for the two drug criteria.

Rationale for exclusion criteria. Children and adolescents who were receiving radiation therapy during the first three months of treatment were excluded because this is an additional treatment variable that could contribute to fatigue. Children and adolescents who were hospitalized in the intensive care unit during the first two weeks of treatment were excluded because of the known relationship between intensive care and muscle atrophy. Patients with neuromuscular deficits at diagnosis were also excluded because the physical performance instruments were not appropriate for this group.

Sample size. A sample size of 40 subjects was originally selected as a sufficient number to detect meaningful differences in fatigue. A sample with one group of patients, that included both children and adolescents, was planned. The fatigue scores from the child and adolescent subjects were to be transformed to z scores to allow for standardization of this measurement. At the time of the study development, there were

no studies that examined change in fatigue during cancer treatment. The sample size calculations were based on the mean fatigue scores from the Childhood Fatigue instrument development study (Hockenberry et al., 2003). The group sample size calculations of 40 would have achieved 96% power to detect a difference in means of 7.0 in fatigue scores from a first condition mean of 7.0 at cycle 1 to a second condition mean of 14.0 at cycle 3, assuming a standard deviation of differences of 11.6 and using a paired t-test with a 0.05 two-sided significance level.

During the study enrollment period, fatigue studies conducted by Hinds and Hockenberry that utilized their fatigue instruments with children and adolescents with cancer were published (Hinds et al., 2007b; Hinds et al., 2007c). In these studies, the subjects using the Child Fatigue Scale (CFS) and the subjects using the Fatigue Scale for Adolescents (FS-A) were analyzed as separate cohorts; *z* scores for fatigue measures were not used. In consultation with both Hinds and Hockenberry, each researcher recommended that separate analyses for these two developmental age groups be conducted because the conceptual definition of fatigue is unique for each developmental group (personal communication, Hinds, April 3, 2008; personal communication, Hockenberry, April 14, 2008). Based on this consultation, the analytic plan for this study was then amended to allow for separate analysis of children and adolescents instead of the original plan of a combined analysis of children ages 6 to 17. Recruiting a sample size of 40 subjects in each developmental group was not feasible at the study sites, so enrollment was concluded when 31 subjects were entered within the 20-month enrollment period. However, for this exploratory study, effect size has been measured to provide direction for future research. Exact *p* values of significance are reported.

Subject recruitment. All subjects meeting the eligibility criteria were invited to participate in the study. Potential subjects and their parents were approached about the study in the hospital setting or outpatient cancer clinic one to two weeks after the start of their chemotherapy treatment. The investigator discussed the study, invited the patient and parents to participate, answered questions, and assessed the patient's and each parent's understanding of the study. Families were provided a minimum of 30 minutes without the investigator present to discuss the study and make their decision. Some families took the consent form home to discuss it and then completed the consenting process at the next clinic visit. Consent was obtained from a parent or legal guardian. Assent was obtained from children and adolescents according to the study site's Institutional Review Board requirements. Any child or adolescent who did not provide assent was excluded from the study.

Six potential subjects refused participation for a refusal rate of 16%. All who refused simply stated that they didn't want to do the study. One child added that he felt "too tired." There were no situations where the parent consented and then the child refused. All parents first asked their child if they wanted to participate. Subjects received a ten-dollar gift card to Target® after completing each set of measurements. During the 20-month enrollment period, 31 subjects enrolled in the study; 15 subjects were from the Children's Minneapolis campus, 14 were from the Children's St. Paul campus, and 2 were from the University of Minnesota Oncology Program. One subject was dropped from the study when his treatment plan required a bone marrow transplant; he was unavailable for the second set of measurements. Data analysis was performed on the final sample of 30 subjects; 16 were children between ages 6 and 12 and 14 were adolescents between ages 13 and 17.

Instrumentation and Measurement

Childhood Fatigue Scale (CFS). The CFS is a 14-item, two-part questionnaire that takes approximately 10 minutes for the child to complete (Hockenberry et al., 2003) (Appendix B, Figure B1). The researcher reads the scale to the child, asking for a “yes” or “no” (frequency) response regarding their experience of any fatigue-related symptoms during the past week. If the statement is true for the child, he or she is asked to rate how much the problem bothers them on a four-point adjectival scale ranging from “Not at all” to “A lot” (intensity). If the child has not experienced the particular problem and has answered with a “no” response for the question, the score is zero for that question. Multiplying the frequency with the intensity score provides the total fatigue score, which can range from 0 to 70. Higher scores correspond to greater amounts of experienced fatigue. In a psychometric instrument study of 149 children receiving chemotherapy for cancer treatment, the mean frequency score was 5.6 (range: 0-14; SD 3.04) and the mean total score was 14.0 (range: 0-55; SD 11.64) (Hockenberry et al.). The internal consistency estimate for the intensity scale of the CFS was 0.84 (Cronbach’s alpha); item to total correlations for the CFS intensity score ranged from 0.34 to 0.60. Internal consistency reliability testing for the frequency scale of the CFS yielded a Kuder-Richardson value of 0.73 (Hockenberry et. al.). The CFS was also sensitive in detecting a significant increase in fatigue frequency ($p = 0.018$) in a sub-group of 15 subjects who had two measurements during 6-week period of intensive therapy for acute lymphocytic leukemia. The researchers recognized that additional research is needed to propose cutoff scores that would merit fatigue intervention; they suggested that a score above the means in this sample for fatigue frequency (5.6) and total fatigue score (14) indicates the presence of fatigue in children.

Fatigue Scale for Adolescents (FS-A) The FS-A is a 14-item self-report scale developed to measure the perceptions of fatigue during the previous week of treatment in adolescent cancer patients *(*Hinds et al., 2007a*),* (Appendix B, Figure B2). The adolescent reads the scale and circles the description of the intensity of the fatigue for each item on a 5-point Likert type scale; scale completion requires 3 to 4 minutes. Ratings range from 14 (no fatigue symptoms) to 70 (high fatigue). Instrument content was based on a conceptual definition of fatigue that was developed from a qualitative, focus group study of adolescents with cancer. A panel comprised of adolescents and health care providers then reviewed the FS-A for face and content validity. Instrument reliability and construct validity as well as the ability to measure change over time was tested in 64 adolescents who completed the scale at two to four data points as a subject in one of four studies (Hinds et al.). Estimates for internal consistency of the FS-A ranged from 0.67 – 0.95 (Cronbach's alpha). Item to total correlations for the intensity score ranged from 0.24 to 0.92 in three of the four studies. The scale could detect significant differences between anemic and nonanemic subjects ($P < 0.01$) and also measured change over time ($t = 2.55$, $P < 0.01$) with a mean change in FS-A score of 4.37. The study sample was slightly smaller than the minimum number recommended for exploratory factor analysis and for identifying a fatigue cut-off score. The researchers are planning on following this instrument study with a larger sample (Hinds, personal communication, April 2, 2008).

The CFS and FS-A fatigue instruments have been specifically designed to use a developmental approach to measure fatigue in pediatric cancer patients (Hockenberry & Hinds, 2000). Measurement using the CFS focuses on the sensation of being physically tired as experienced by children with cancer, while the FS-A expands and elaborates on

the mental and emotional components of fatigue reported by adolescents. The instruments are brief and have not been burdensome to complete.

Timed Up and Down Stairs Test (TUDS). The TUDS is a physical performance measure of functional mobility that also requires strength and endurance (Zaino, Marchese, & Westcott, 2004). The test involves the subjects ascending one flight of 13 to 14 step stairs, turning around, and descending to the starting point. The score is measured in seconds from the "go" cue until the second foot returns to the bottom landing. The TUDS was originally developed as a test of functional mobility in the geriatric population and was later tested in a pediatric population with a convenience sample of 47 children age eight to 14 years that included 20 children with cerebral palsy and 27 with typical development. The reported intra-rater and inter-rater reliabilities of the TUDS were intra class correlation (2,1) = 0.97 and 0.98, respectively (Zaino et al.). The TUDS test-retest reliability was ICC (2,1) = 0.94. The instrument also demonstrated strong concurrent validity to three other tests of functional capacity (Zaino et al.). The TUDS has been used in studies with pediatric oncology patients (Marchese & Chiarello, 2004; Marchese, Chiarello, & Lange, 2004; Marchese, Ogle, Womer, Dormans, & Ginsberg, 2004). In these studies, all the subjects (patients in treatment for acute lymphocytic leukemia and patients who had completed treatment for osteogenic sarcoma) were able to complete the TUDS (Marchese, personal communication, February 21, 2006). To date, the TUDS measurement has not been examined in relation to the symptom of fatigue.

The 6-Minute Walk Test (6MWT). This test is a measure of maximal functional capacity and endurance of the cardiorespiratory system. The child is directed to walk as far as possible on a flat surface for six minutes. The objective is to cover as much distance as possible in this time period. A stopwatch is used to record the time, and a

distance measurement wheel is used to calculate distance in feet, which is then converted to meters. The American Thoracic Society (2002) has published practical guidelines for administering the 6MWT. A straight, flat, corridor should be used for the test with a length ranging from 50 to 160 feet; studies have found that straight courses within this range have no significant effect on the distance walked. The course should be marked with clear turnaround points and laps should be counted. Standard phases of encouragement (i.e., “You are doing a good job.”) should be offered at intervals consistent for all subjects.

The 6MWT has been used to assess performance in ill patients with cardiac or pulmonary disease, including severely ill patients awaiting heart and/or lung transplants. This test was evaluated in a convenience sample of 23 children with mild symptoms of cystic fibrosis and had good test-rest reliability ($r = 0.9, < 0.001$) (Gulmans, vanVeldhoven, deMeer, & Helders, 1996). In a separate group of 15 children with moderate symptoms of cystic fibrosis, there was strong current validity between the walking distance in 6 minutes and the maximum workload on a cycle ergometer ($r = 0.76$, $P < 0.001$) and maximum oxygen update ($r = 0.76$, $P < 0.001$) (Gulmans et al.). A study of 17 children awaiting heart and/or lung transplants demonstrated a significant correlation between distance walked and peak oxygen update ($r = 0.70$, $P < 0.001$) and physical work capacity ($r = 0.64$, $P < 0.001$) (Nixon, Joswiak, & Fricker, 1996). In a separate study of 16 children with cystic fibrosis, the 6MWT had a significant correlation with maximal expiratory pressure ($r = 0.60$, $P < 0.01$) and maximal heart rate ($r = 0.59$, $P < 0.02$) (Cunha, Rozov, deOliveria, & Jardim, 2006). The reliability and validity of the 6MWT was assessed in a group of 74 healthy adolescents ages 13 to 15. The 6MWT demonstrated strong concurrent validity to the VO_2 max during the treadmill test ($r = 0.33$, $P < 0.004$). Test-retest reliability was measured in 52 of the subjects; the intraclass

correlation coefficient (95% confidence interval) was calculated as 0.94 (0.89–0.96) (Li et al., 2005). Recently, height-specific reference standards for the 6MWT were constructed using a sample of 1,445 Chinese children ages 7 to 16 (Li, Yin, Au, Tsang, Wong, Fok, & Pak, 2007). Height was used instead of age for the development of the reference curves because, among all anthropometric measurements, height was the most discriminating with the best correlation to 6MWT distances.

The 9-Minute Walk-Run test has been used as an assessment of physical fitness of healthy school age children and adolescents and has also been used as a measurement of children with cancer (Marchese & Chiarello, 2004; Marchese, Chiarello, & Lange, 2004; Marchese, Ogle, Womer, Dormans, & Ginsberg, 2004). In these pediatric oncology studies, all the subjects were able to complete the 9-Minute Walk-Run (Marchese, personal communication, February 21, 2006). The shorter measurement of a 6-minute walk was selected for this study to decrease the burden on subjects.

The physical performance instruments, TUDS and 6MWT, were selected for this study because they had a low subject burden, were developmentally appropriate for the age range of the subjects, and were cost-effective measures of functional capacity in terms of the muscle strength and endurance required for daily ambulation. It is noteworthy that physical performance is influenced by three inter-related concepts: motor performance, muscle strength, and endurance. In this study, instruments were used to measure one concept of physical performance, but the outcome of the measurement could be influenced by the other concepts. For example, the TUDS and 6MWT measured muscle strength and endurance that could be influenced by motor function changes that affect ambulation. Patients who are experiencing chemotherapy induced peripheral neuropathy (CIPN) with motor function changes could perform more slowly on the study measures because of foot drop. CIPN also causes muscle atrophy.

These inter-related concepts could influence each other and the child's physical performance.

Carnitine plasma levels. The physiologic measurement of carnitine plasma levels required three milliliters of blood. The sample was drawn at the time of the routine laboratory studies and placed in a green-top heparinized tube. The blood was spun by centrifuge, aliquotted and frozen in a plastic vial. Plasma samples were stored in a -70 Celsius degree freezer to allow the batch of samples to be run simultaneously. To ensure the specimen integrity, they were processed, stored, and transported according to specifications from the evaluation site, Mayo Medical Laboratories of Rochester, Minnesota.

Carnitine plasma levels are reported as several values. Free carnitine (FC) is a measure of the L-carnitine available for transporting fatty acids into the mitochondria. Total carnitine (TC) is the free carnitine (L-carnitine) plus acyl-carnitine, which is the waste product after the body has used the L-carnitine. Carnitine deficiency is defined biochemically as abnormally low plasma levels of free carnitine (FC). Carnitine plasma measurements include the ratio of the acyl carnitine (AC i.e. the total carnitine TC minus the free carnitine FC) to the free carnitine (FC ie the L-carnitine) and are reported as the AC/FC ratio (Schmidt-Sommerfeld, Werner, & Penn, 1988). Under normal physiological conditions, 80 % of total carnitine (TC) is FC and 20 % is AC. Researchers have reported that an increased ratio of AC/FC greater than 0.4 is abnormal which indicates that there is insufficient free carnitine in relation to increased metabolic needs (Sayed-Ahmad, 2007).

In this study, free and total carnitine were measured by tandem mass spectrometry (MS/MS) stable isotope dilution analysis. Hydrolysis enabled measurement of total carnitine, and esterified carnitine (acylcarnitine) was calculated as the difference

between the total and free carnitine. Reference values are shown in Appendix C, Table C1.

Upon study entry, demographic and health history data were collected from the subject's medical record including the child's age, gender, race/ethnic group, and diagnosis and risk group. On the day of a study measurement, additional information about the subject's history was abstracted from the medical record. This included the total number of inpatient hospital days, hemoglobin, and body mass index. This data was collected so that it could be considered in the analysis of potential moderators. This component of the analysis plan was amended when the sample was divided into two cohorts. The abstracted data may be used in the future for a secondary data analysis in relation to psychometrics of instruments used in the study.

Data Collection Procedures

First measurement time point. The first day of chemotherapy is day 1 of cycle 1; study measurements were obtained during the third week of their first chemotherapy cycle between day 15 and day 29 during a routine clinic visit or hospitalization. The initial study measurements were not performed before chemotherapy was initiated at diagnosis because of the stress during this diagnostic time period as well as the short time period (1 to 2 days) between the diagnosis and chemotherapy starting. During the study development period, an examination of oncology patients' outpatient visits revealed that patients frequently had appointments in weekly intervals. The open time period of two weeks (day 15-29) assured that study measurements could be done during a standard visit without requiring the family to make an additional trip to the hospital or clinic.

During this time period (15 to 29 days into the chemotherapy cycle), the patient's blood counts had reached their nadir and most had started to recover. The fatigue

instrument asked the subject to think about how they have felt the previous week. This allowed the subject to report how they felt during a period of neutropenia, which children and adolescents have reported as contributing to fatigue (Hockenberry-Eaton & Hinds, 2000). Current research informed the investigator that carnitine levels initially increase during the first week of chemotherapy (Hockenberry, personal communication, August 29, 2005). Studies have also shown that levels decrease the following week after this initial spike (Heuberger et al, 1998). Carnitine measurements were performed between days 15 and 29 with the goal of avoiding the initial increase in plasma levels and capturing the lower level.

Second measurement time point. The second study measurements (fatigue scales, carnitine plasma levels, and physical performance measures) were performed during the third chemotherapy cycle during treatment. Study measurements were again obtained between day 15 and day 29 during a routine clinic visit or hospitalization. The third cycle was chosen as the time point to assure inclusion of patients who have short chemotherapy treatment plans. In the pediatric oncology study that measured carnitine levels, significant decreases occurred three months after chemotherapy treatment was started (Yaris et al., 2002).

Although the three-cycle period was relatively short when one considers the two to three year treatment period for some pediatric cancers, it is during this time period that patients receive intense chemotherapy to “induce” a remission of their disease. The three-cycle time period also allowed for the measurement of subjects over a short trajectory of treatment while restricting the introduction of additional variables that occur over longer time periods. During longer time periods, the child’s ongoing development would need to be considered in measuring change in the study variables. For example, a significant change in height would influence stride length in the 6MWT or moving from

school age to adolescence would influence the perception and measurement of fatigue. Additionally, it is after the initial induction period of three to six cycles of chemotherapy that solid tumor patients have radiation therapy or second look surgeries to remove tumor that has been shrunken by chemotherapy. Measuring fatigue and physical performance after an invasive surgery or during radiation therapy would introduce an additional variable.

Administration of study measurements. The fatigue instrument was administered prior to the performance measures to assure that fatigue was reported from the previous week and not related to fatigue resulting from the TUDS and 6MWT. The Child Fatigue Scale was read to the child by the investigator. Adolescents were given the self-report Fatigue Scale for Adolescents, on a clipboard, to complete. All subjects were directed to think about how they had felt during the past week. They were also told that there were no right or wrong answers and that they should report how they actually felt and not how they thought the parent, investigator, or health care staff wanted them to feel. Carnitine plasma levels were drawn from the subject's central line during a routine lab draw by the nurse caring for the patient. Blood samples were collected within a ten-minute period before physical performance measurements.

The 6-Minute Walk Test (6MWT) was administered indoors on a flat, tiled floor in a long hall of the institution. A walking "loop" was identified by placing large, green arrows on the floor. The distance of one loop was measured using a measuring wheel that is typically used to measure distances at track meets. Depending on the patient location (campus, hospital or clinic), the loop distance ranged from 180 to 220 feet. The subject was directed to walk as quickly as possible, without running, to cover as much distance as they could in 6 minutes following the green arrows on the floor. The investigator said, "Ready, set, go," and started the timer. During the first lap only, the

investigator walked alongside the subject who set the walking pace. This was done to clarify the walking route. Every minute, verbal encouragement was provided (i.e., “You are doing a good job”). The subject repeated the walking loops for 6 minutes while the investigator recorded the number of loops. At 6 minutes, the alarm on the timer sounded, and the subject was directed to stop and stay at their location. A partial loop was measured using the measuring wheel. The total distance was calculated in feet by multiplying the number of loops by loop distance and adding the last partial loop distance. The total distance was then converted to meters.

The Timed Up and Down Stairs Test (TUDS) was administered within each hospital on a staircase with 12 stairs of standard height, a landing, and a handrail. Time was measured using a stopwatch. The investigator stated, “Quickly, but safely, go up the stairs, turn around on the landing and come all the way down until both feet are on the landing.” Subjects were instructed to face in the direction of movement (not sideways). They could choose any method of traversing the stairs that could include step to or foot over foot pattern, running up the stairs, skipping steps, etc. The handrail could be used and shoes were worn. The cue was given: “Ready, set, go” and the stopwatch was started. The investigator observed the subject at all times for safety, while having a thumb on the stopwatch. The stopwatch was stopped when both feet were on the lower landing. If someone else was using stairs, the investigator waited until the person passed by before starting the test. Time was recorded in seconds to the hundredth of a second.

If a subject was hospitalized at a data collection point when intravenous fluids were infusing, the child was temporarily “capped off” from the intravenous infusion pump to allow the mobility needed for physical performance measures. This procedure is standard practice for children who leave the inpatient area to go to other areas of the

hospital. No subjects received chemotherapy before the completion of measurements on a data collection day. A summary of the study variables, measurements, and collection times can be seen in the Appendix D, Table D1.

Data Analysis

The statistical analysis plan will be described for each study aim. SPSS software version 14.0 was used for data analysis. The first step in the data analysis was the examination of each variable (fatigue, physical performance, carnitine) at each of the two time points for missing data and for parametric assumptions (e.g., normality, equality of group variances, etc.). The distribution curves of the variables revealed a non-normal distribution and therefore nonparametric statistical tests were utilized.

Aim 1: To determine the change in physical performance and change in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy. A Wilcoxon signed rank test with a two-sided significance level was used to evaluate the change in each variable: child fatigue, adolescent fatigue, TUDS, 6-Minute Walk test, from cycle 1 to cycle 3.

Effect size calculations for fatigue in each age group were calculated as the ratio of the z value to the square root of N (Pallant, 2007). Effect size indicates the responsiveness of the scale in patients for whom a change is expected to occur (Fayers & Machin, 2000). Cohen (1988) criteria for effect size for the Wilcoxon signed rank test were used for interpretation with .1 = small effect, .3 = medium effect, and .5 = large effect (Pallant, 2007).

The Mann-Whitney *U* test was performed for each cohort. This technique was used to test for differences between males and females in the amount of change in physical performance and change in fatigue. The Kruskal-Wallis test was used to compare the difference in the change in physical performance and change in fatigue

between the three diagnostic groups, acute lymphocytic leukemia (ALL), lymphoma, and solid tumors, in each cohort.

Aim 2: To determine the relationship between the change in physical performance and change in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy.

Spearman's rank-order correlation was used to examine relationships between each of the physical performance independent variables (TUDS, 6-Minute Walk test) and the dependent variable, child fatigue or adolescent fatigue in each age cohort. Correlations between these variables were examined from the first set of measurements (i.e. TUDS/Fatigue, 6MWT/Fatigue at cycle 1) and from the second set of measurements. The strength of the relationship between the change in TUDS and change in subject fatigue score and between change in the 6MWT and change in subject fatigue score was measured. Cohen (1988) criteria for effect size for Spearman's rank-order correlation were used for interpretation with .1 = small effect, .3 = medium effect, and .5 = large effect (Pallant).

Aim 3: To examine carnitine plasma levels in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) at the 1st cycle and 3rd cycle of chemotherapy. A Wilcoxon signed rank test with a two-sided significance level was used to evaluate the change in carnitine plasma levels from cycle 1 to cycle 3. The Mann-Whitney *U* test was performed to test for differences between males and females in the amount of change in carnitine plasma levels. The Kruskal-Wallis test was used to compare the change in carnitine plasma levels between the three diagnostic groups, acute lymphocytic leukemia (ALL), lymphoma, and solid tumors.

Aim 4: To determine the relationship between carnitine plasma levels and fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy. Spearman's rank-order correlation was used to examine the relationship between the independent variables, carnitine plasma levels, and the dependent variable, child fatigue or adolescent fatigue in each age cohort. Correlations between these variables were examined from the first set of measurements (i.e.. carnitine/fatigue at cycle 1) and from the second set of measurements. The strength of the relationship between the change in carnitine and change in subject fatigue score was measured. Cohen criteria of effect size (1988) were applied.

Multiple regression analysis to assess for potential moderators could not be performed because each cohort sample was small in size. The 6 to 12 age group that used the Child Fatigue Scale had 16 subjects, and the 13 to 17 age group that used the Fatigue Scale for Adolescents had 14 subjects.

Chapter 4

Results

Introduction

The purpose of this chapter is to describe characteristics of the study sample and present the results of the hypotheses testing. The study sample included two cohorts: 16 children (ages 6 to 12) and 14 adolescents (ages 13 to 17). Throughout this chapter, results are presented separately for each of the two cohorts. The demographic characteristics of the sample are first defined. The descriptive statistics and distribution curves of the study variables, child fatigue, adolescent fatigue, physical performance measurements (6MWTand TUDS), and carnitine plasma levels for each cohort are presented. Each hypothesis is tested and relationships between variables are explained. Exact *p* values of significance are reported. The chapter concludes with a summary of the study findings.

Sample Characteristics

The distribution of patients by age, gender, race, and diagnostic group for each cohort is presented in Table 1. Males and females (56% vs. 44% respectively) were more evenly distributed in the child group than the adolescent group, which had predominantly males (79%). Patients in the study were predominantly Caucasian (88% of children; 88% of adolescents), which is characteristic of the pediatric oncology population in the state of Minnesota. In the child cohort, diagnoses were evenly distributed between ALL (38%), lymphoma (31%) and solid tumors (31%) and no subjects had the diagnosis of AML. Among adolescents, 50% of the subjects had the diagnosis of lymphoma with the remaining subjects having ALL (21%), AML (7%), or solid tumors (21%).

Table 1
Patient Demographic Characteristics

Characteristic	Children (*n* = 16) *n*	%	Adolescents (*n* = 14) *n*	%
Gender				
Male	9	56%	11	79%
Female	7	44%	3	21%
Age at Diagnosis				
6	4	25%		
7	1	6%		
8	3	19%		
9	1	6%		
10	3	19%		
11	1	6%		
12	3	19%		
13			4	29%
14			5	36%
15			2	14%
16			1	7%
17			2	14%
Race or Origin				
Caucasian	14	88%	12	86%
Black	1	6%	1	7%
Asian				
Native American			1	7%
Hispanic	1	6%		
Diagnostic Group				
ALL	6	38%	3	21%
AML			1	7%
Lymphoma	5	31%	7	50%
Solid tumor	5	31%	3	21%

Descriptive Data and Distribution of Study Measurements

Descriptive statistics from each of the study measurements were evaluated. The statistics for study measurements for the child cohort are listed in Table 2. In this table, statistics for the dependent variable, fatigue (measured by the CFS), and the independent variables of physical performance (measured by the TUDS and 6MWT) and carnitine plasma levels are presented. The CFS included a frequency score and a total score, and both are listed. One subject's carnitine specimen at cycle 1 was misplaced during laboratory processing and a different subject's specimen at cycle 3 was misplaced in processing so the sample size for carnitine plasma levels at each

measurement point is 15. However, the total number of child subjects who have two samples is 14.

Table 2

Descriptive Statistics for Child Variables

Study Variables	*n*	Mean	SD	Min.	Max.	Median
Dependent						
CFS Frequency – Cycle 1	16	7.1	3.8	0.0	13.0	7.0
CFS Frequency – Cycle 3	16	4.6	3.5	0.0	13.0	4.5
CFS Total – Cycle 1	16	18.0	12.7	0.0	41.0	18.0
CFS Total – Cycle 3	16	11.2	9.7	0.0	37.0	10.5
Independent						
TUDS (seconds) – Cycle 1	16	19.06	11.58	7.99	54.18	15.88
TUDS (seconds) – Cycle 3	16	14.84	7.13	6.13	35.20	14.04
6MWT (meters) – Cycle 1	16	358.60	129.36	160.93	620.57	359.05
6MWT (meters)- Cycle 3	16	422.40	95.37	262.96	601.06	406.30
Total carnitine– Cycle 1	15	51.6	18.8	17.0	89.0	49.0
Total carnitine– Cycle 3	15	38.3	9.3	22.0	51.0	40.0
Free carnitine– Cycle 1	15	44.7	17.4	13.0	80.0	43.0
Free carnitine– Cycle 3	15	32.1	8.5	18.0	45.0	32.0
Acylcarnitine– Cycle 1	15	6.9	2.2	3.0	10.0	7.0
Acylcarnitine– Cycle 3	15	6.2	3.5	2.0	14.0	6.0
AC/FC ratio– Cycle 1	15	.16	.07	.10	.30	.10
AC/FC ratio– Cycle 3	15	.18	.09	.10	.40	.20

Table 3 lists the descriptive statistics for the adolescent cohort with the same study variables. The FS-A that was used to measure fatigue in adolescents has one total score and does not have a frequency score. One subject refused to perform the TUDS at cycle 3 of chemotherapy, but the other study measurements were completed.

Table 3

Descriptive Statistics for Adolescent Variables

Study Variables	*n*	Mean	SD	Min.	Max.	Median
Dependent						
FS-A Total – Cycle 1	14	26.6	7.4	20.0	47.0	23.5
FS-A Total – Cycle 3	14	22.3	5.1	16.0	29.0	20.5
Independent						
TUDS (seconds) – Cycle 1	14	11.07	2.97	6.23	14.82	10.88
TUDS (seconds) – Cycle 3	13	10.39	4.17	6.07	18.37	8.30
6MWT (meters) – Cycle 1	14	481.77	65.05	410.26	671.80	460.55
6MWT (meters)- Cycle 3	14	452.15	117.04	118.87	624.84	461.62
Total carnitine– Cycle 1	14	48.0	27.2	23.0	135.0	40.0
Total carnitine– Cycle 3	14	39.7	15.0	21.0	78.0	37.0
Free carnitine– Cycle 1	14	40.9	24.5	20.0	112.0	35.0
Free carnitine– Cycle 3	14	33.3	11.1	18.0	58.0	32.0
Acylcarnitine– Cycle 1	14	7.1	5.1	2.0	23.0	6.5
Acylcarnitine– Cycle 3	14	6.4	4.8	1.0	20.0	5.0
AC/FC ratio– Cycle 1	14	.19	.07	.10	.30	.20
AC/FC ratio– Cycle 3	14	.19	.11	.00	.50	.20

Normality of distribution was determined by examining the histogram for each study variable. In Appendix A, the histograms for the child cohort measurements at cycle 1 of chemotherapy are found in Figures A1 through A8 and for cycle 3 in Figures A9 through A16. Histograms for the adolescent cohort measurements at cycle 1 can be seen in Figures A17 through A23 and those for cycle 3 are in Figures A24 through A30.

The histogram curves demonstrate that in the child cohort, the 6MWT at cycle 1 and free carnitine levels at cycle 3 have normal distributions. In the adolescent cohort, the TUDS at cycle 1 has a normal distribution. For both cohorts, all the remaining

distribution curves were not normal and therefore non-parametric statistics were used to test the study hypotheses.

Results for Aim 1

Aim 1: To determine the change in physical performance and change in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy. A Wilcoxon signed rank test with a two-sided significance level was used to test the hypotheses for Aim 1. Effect size was calculated for the change in fatigue and Cohen (1988) criteria of .1 = small effect, .3 = medium effect, .5 = large effect were applied. A Mann-Whitney *U* test was performed to test for differences between males and females in the amount of change in physical performance and change in fatigue. A Kruskal-Wallis test was performed to compare the change in physical performance and change in fatigue between the three diagnostic groups, acute lymphocytic leukemia (ALL), lymphoma, and solid tumors.

Hypothesis 1.1: Children and adolescents will experience a significant decrease in physical performance from cycle 1 to cycle 3 of chemotherapy.

In measures of physical performance in the child cohort, TUDS appeared to improve from cycle 1 to cycle 3 of chemotherapy. The median time in seconds decreased from cycle 1 (Md = 15.88) to cycle 3 (Md = 14.04), z = -1.71, p = .09. Performance on the 6MWT also appeared to improve from cycle 1 to cycle 3. The median distance of meters walked increased from cycle 1 (Md = 359.05) to cycle 3 (Md = 406.40), z = -1.71, p = .09.

In the child cohort, a Mann-Whitney *U* test revealed no significant difference between males (n = 9) and females (n = 7) in the amount of improvement on the TUDS (p = .84) or the 6MWT (p = .76). In this cohort, there were 6 children with ALL, 5 with lymphoma, and 5 with solid tumors. The Kruskal-Wallis test appeared to differ across

the three diagnostic groups (ALL, lymphoma, and solid tumors) in improvement in the 6MWT, χ^2 (2, *n* = 16) = 4.80, *p* = .09. The child ALL group had greater change in their median score (improvement in 6MWT distance) (*Md* = -171.75) than the lymphoma group (*Md* = -84.73) or the solid tumor group (*Md* = 26.82). A negative median score indicated that the distance in meters at the second measurement at cycle 3 of chemotherapy was greater than the distance at the first measurement at cycle 1. However, there was not a difference in improvement on the TUDS across the three diagnostic groups in the child cohort, χ^2 (2, *n* = 16) = 2.66, *p* = .26.

In the adolescent cohort, the TUDS revealed a slight improvement from cycle 1 to cycle 3 of chemotherapy. The median time in seconds decreased from cycle 1 (*Md* = 10.88) to cycle 3 (*Md* = 8.30), *z* = -1.22, *p* = .22. The distance on the 6MWT evidenced little change from cycle 1 and cycle 3. The median distance in meters remained constant from cycle 1 (*Md* = 460.55) to cycle 3 (*Md* =461.62), *z* = -.91, *p* = .36.

In the adolescent cohort, a Mann-Whitney *U* test revealed no significant difference between males (*n* = 11) and females (*n* = 3) in the amount improvement on the TUDS (*p* = .94). However, there was a slight difference in improvement on the 6MWT with females walking farther on the second measurement (*Md* = -41.76, *n* =3) than males (*Md* = 6.4, *n* =11), *U* = 6.0, *z* = -1.64, *p* = .10. A negative median score indicated that the distance in meters at the second measurement at cycle 3 of chemotherapy was greater than the distance at the first measurement at cycle 1. In this cohort, there were 3 adolescents with ALL, 1 with AML, 7 with lymphoma, and 3 with solid tumors. A Kruskal-Wallis test revealed no significant differences between the three diagnostic groups (ALL, lymphoma, and solid tumors) in the adolescent cohort in relation

to change on the TUDS (p = .59) or 6MWT (p = .69). AML was not included as a group in the Kruskal-Wallis test because only one subject had that diagnosis.

Hypothesis 1.2: Children and adolescents will experience a significant increase in fatigue from cycle 1 to cycle 3 of chemotherapy

The CFS used by the child cohort includes two scores. The “yes” or “no” responses to the scale items provide the CFS frequency score. For each “yes” response, the child rates how much the problem bothers them, which yields a fatigue intensity rating. The total score for the CFS is calculated by multiplying the frequency score by the intensity rating. In the child cohort, the frequency score for the CFS decreased from cycle 1 to cycle 3 of chemotherapy. The median frequency score for the CFS decreased from cycle 1 (*Md* = 7.0) to cycle 3 (*Md* 4.5), z = -2.08, p = .04, with a medium effect size (r = .37). The total score for the CFS decreased during the first three cycles of chemotherapy. The median score on the total score for the CFS decreased from cycle 1 (*Md* = 18.0) to cycle 3 (*Md* 10.5), z = -1.99, p = .05, with a medium effect size (r = .35). A Mann-Whitney U test revealed no significant difference between the change in total fatigue scores in males (*Md* = 4.0, n =9) and females (*Md* = 14.0, n =7), U = 27.5, z = -.42, p = .68. Using the Kruskal-Wallis test, a statistically significant difference was found in the change in total fatigue scores across the three diagnostic groups, χ^2 (2, n = 16) = 9.60, p = .01. The child ALL group had higher median score (decrease in fatigue) (*Md* = 17.5) than the lymphoma group (*Md* = 3.0) or the solid tumor group (*Md* = -3.0).

The score for adolescents on the FS-A suggested a decrease in fatigue from cycle 1 to cycle 3 of chemotherapy. The median score on the FS-A decreased from cycle 1 (*Md* = 23.5) to cycle 3 (*Md* = 20.5), z = -1.43, p = .15, with a small to medium effect size (r = .27). A Mann-Whitney U test revealed no significant difference in the

change in fatigue in males (*Md* = 1.0, *n* =11) and females (*Md* = 12.0, *n* =3), *U* = 13.5, *z* = -.47, *p* = .64. Using the Kruskal-Wallis test, there was not a statistically significant difference in the change in fatigue in adolescents across the three diagnostic groups, χ^2 (2, *n* = 13) = 2.45, *p* = .30. The decrease in fatigue median for the ALL group (Md = -2.0) was not significantly different from the lymphoma group (Md = 6.0) or the solid tumor group (Md = 7.0).

Results for Aim 2

Aim 2: To determine the relationship between the change in physical performance and change in fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy. Spearman's rank-order correlation with a two-sided significance level was used to test the hypothesis for Aim 2. Cohen (1988) criteria of .1 = small effect, .3 = medium effect, .5 = large effect were used to assess the strength of the relationship.

Hypothesis 2: Children and adolescents who experience a significant decrease in physical performance from cycle 1 to cycle 3 of chemotherapy will have a significant increase in fatigue.

Child cohort. Correlations between the variables of physical performance and fatigue at each of two individual study time points were first examined. Correlations for the child cohort at cycle 1 can be seen in Table 4. The CFS frequency scores are a subset of the CFS total scores and a strong correlation was expected between these scores. At cycle 1, the correlation between a shorter time on the TUDS and lower CFS total score was small to medium. There was a large negative correlation between performance on the 6MWT and both CFS scores with greater distance walked associated with lower levels of fatigue. The two measures of physical performance,

TUDS and 6MWT, have a large negative correlation with a greater distance walked associated with lower times on the TUDS.

Table 4

Spearman's Rank-Order Correlations Between Child Variables: Fatigue and Physical Performance at Cycle 1 of Chemotherapy

Variables		CFS Frequency	CFS Total	TUDS	6MWT
1. CFS Frequency	r_s	—			
	p	—			.
2. CFS Total	r_s	.87	—		
	p	.00	—		
3. TUDS	r_s	.35	.25	—	
	p	.18	.36	—	
4. 6MWT	r_s	-.63	-.68	-.61	—
	p	.01	.00	.01	—

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

In the child cohort at cycle 3 of chemotherapy, the correlations can be seen in Table 5. At this second time point, there was no longer a large correlation between performance on the 6MWT and measures of fatigue. As in the first cycle of chemotherapy, the correlation at the third cycle between the TUDS and fatigue scores was small. The relationship between the 6MWT and the TUDS again shows a large negative correlation.

Table 5

Spearman's Rank-Order Correlations Between Child Variables: Fatigue and Physical Performance at Cycle 3 of Chemotherapy

Variables		CFS Frequency	CFS Total	TUDS	6MWT
1. CFS Frequency	r_s	—			
	p	—			
2. CFS Total	r_s	.88	—		
	p	.00	—		
3. TUDS	r_s	.15	.20	—	
	p	.57	.46	—	
4. 6MWT	r_s	-.09	-.25	-.57	—
	p	.74	.34	.02	—

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

The relationships between change in physical performance and change in fatigue in the child cohort from cycle 1 to cycle 3 of chemotherapy are seen in Table 6. There was a large correlation between change in the CFS Frequency score and change in the CFS Total score; this again was expected because the CFS Frequency score is a subset of the total score. There was a medium to large relationship between the change in the TUDS score and the change in CFS total score with a decrease in time on the TUDS being associated with a decrease in fatigue. There was a large negative relationship between change in 6MWT and change in CFS total score with an increase in the distance walked associated with a decrease in fatigue. Additionally, a decrease in the TUDS time from cycle 1 to cycle 3 had a large correlation with an increase in the 6MWT distance.

Table 6

Spearman's Rank-Order Correlations Between Child Variables: Change in Fatigue and Change in Physical Performance

Variables		Change in CFS Frequency	Change in CFS Total	Change in TUDS	Change in 6MWT
1. Change in CFS Frequency	r_s	—			
	p	—			
2. Change in CFS Total	r_s	.87	—		
	p	.00	—		
3. Change in TUDS	r_s	.31	.41	—	
	p	.24	.11	—	
4. Change in 6MWT	r_s	-.49	-.60	-.69	—
	p	.06	.01	.00	—

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

Adolescent cohort. Correlations between the variables of physical performance and fatigue at cycle 1 of chemotherapy for the adolescent cohort can be seen in Table 7. The relationship between the TUDS and fatigue was small but negative in direction indicating that longer time on the TUDS had a small relationship with lower fatigue scores. Relationships between the 6MWT and fatigue and between the TUDS and 6MWT were not evident.

Table 7

Spearman's Rank-Order Correlations Between Adolescent Variables: Fatigue and Physical Performance at Cycle 1 of Chemotherapy

Variables		FS-A	TUDS	6MWT
1. FS-A	r_s	—		
	p	—		
2. TUDS	r_s	-.16	—	
	p	.58	—	
3. 6MWT	r_s	.02	-.03	—
	p	.95	.91	—

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

For the adolescent cohort at cycle 3, correlations between variables can be seen in Table 8. There was a medium relationship between the TUDS and fatigue with longer times on the TUDS associated with higher fatigue. There was a strong negative relationship between the 6MWT and fatigue, with greater distance walked associated with lower fatigue. There was a small to medium negative relationship between the 6MWT and the TUDS with greater distance walked associated with lower times on the TUDS.

Table 8

Spearman's Rank-Order Correlations Between Adolescent Variables: Fatigue and Physical Performance at Cycle 3 of Chemotherapy

Variables		FS-A	TUDS	6MWT
1. FS-A	r_s	—		
	p	—		
2. TUDS	r_s	.45	—	
	p	.12	—	
3. 6MWT	r_s	-.67	-.30	—
	p	.01	.33	—

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

The relationships between change in physical performance and change in fatigue in the adolescent cohort from cycle 1 to cycle 3 of chemotherapy are seen in Table 9. There was a small to medium relationship between the change in the TUDS score and the change in fatigue scores with a decrease in time on the TUDS associated with a decrease in fatigue. There was a medium relationship between change in 6MWT and change in fatigue with an increase in the distance walked associated with a decrease in fatigue. Additionally, a decrease in the TUDS time from cycle 1 to cycle 3 was moderately correlated with an increase in the 6MWT distance.

Table 9

Spearman's Rank-Order Correlations Between Adolescent Variables: Change in Fatigue and Change in Physical Performance

Variables		Change in FS-A	Change in TUDS	Change in 6MWT
1. Change in FS-A	r_s	—		
	p	—		
2. Change in TUDS	r_s	.28	—	
	p	.36	—	
3. Change in 6MWT	r_s	-.32	-.37	—
	p	.27	.21	—

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

Results for Aim 3

Aim 3: To examine carnitine plasma levels in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) at the 1st cycle and 3rd cycle of chemotherapy. A Wilcoxon signed rank test with a two-sided significance level was used to test the hypothesis for Aim 3.

Hypothesis 3.1: Carnitine plasma levels in children and adolescents will significantly decrease from cycle 1 to cycle 3 of chemotherapy.

In the child cohort (n = 14), the total carnitine plasma level decreased during the first three cycles of chemotherapy, with the median at cycle 1 (Md = 49.0) becoming lower at cycle 3 (Md = 40.0), z = -2.52, p = .01. Free carnitine levels also decreased in the child cohort, with the median lowering from cycle 1 (Md = 43.0) to cycle 3 (Md = 32.0), z = -2.48, p = .01. The measures of acylcarnitine lowered slightly, with the median lowering from cycle 1 (Md = 7.0) to cycle 3 (Md = 6.0), z = -1.39, p = .17. The AC/FC

ratio was constant, with the median remaining stable from cycle 1 (*Md* = 0.10) to cycle 3 (*Md* = 0.20), *z* = -.63, *p* = .53.

In the child cohort, a Mann-Whitney *U* test revealed no significant difference between males (*n* = 9) and females (*n* = 7) in the change in total carnitine levels (*p* = .76) or free carnitine levels (*p* = .76). A Kruskal-Wallis test showed a significant difference across the three diagnostic groups, ALL (*n* = 7), lymphoma (*n* = 6), and solid tumors (*n* = 6), in change in total carnitine, χ^2 (2, *n* = 16) = 6.96, *p* = .03, and change in free carnitine, χ^2 (2, *n* = 16) = 8.39, *p* = .02. The child ALL group had greater median decrease in total carnitine levels (*Md* = 26.0) than the child lymphoma group (*Md* =13.0) or the child solid tumor group (*Md* = 0). This group also had greater a median decrease in free carnitine levels (*Md* = 25) than the lymphoma group (*Md* =12.5) or the solid tumor group (*Md* = -.1).

In the adolescent cohort, the inter-related measures of carnitine plasma levels evidenced little change during the first three cycles of chemotherapy. The total carnitine plasma level remained nearly constant, with the median at cycle 1 (*Md* = 40.0) and cycle 3 (*Md* = 37.0) showing little change, *z* = -.53, *p* = .59. Free carnitine levels were stable, with the median changing little from cycle 1 (*Md* = 35.0) to cycle 3 (*Md* = 32.0), *z* = -.63, *p* = .53. Acylcarnitine levels were slightly lower, with the median remaining stable from cycle 1 (*Md* = 6.5) to cycle 3 (*Md* = 5.0), *z* = -.67, *p* = .50. The AC/FC ratio was unchanged, with the same median at cycle 1 (*Md* = 0.20) and cycle 3 (*Md* = 0.20), *z* = -.12, *p* = .90.

In the adolescent cohort, a Mann-Whitney *U* test revealed no significant difference between males (*n* = 11) and females (*n* = 3) in the change in total carnitine levels (*p* = .46) or free carnitine levels (*p* = .86). A Kruskal-Wallis test showed no

significant difference across the three adolescent diagnostic groups, ALL (n = 3), lymphoma (n = 7), and solid tumors (n = 3), in change in total carnitine (p = .68) or change in free carnitine (p = .70).

Results for Aim 4

Aim 4: To determine the relationship between carnitine plasma levels and fatigue in a cohort of children (ages 6 to 12) and a cohort of adolescents (ages 13 to 17) from cycle 1 to cycle 3 of chemotherapy. Spearman's rank-order correlation with a two-sided significance level was used to test the hypothesis for Aim 4. Cohen (1988) criteria of .1 = small effect, .3 = medium effect, .5 = large effect were used to assess the strength of the relationship.

Hypothesis 4: Children and adolescents who experience a significant decrease in carnitine plasma levels from cycle 1 to cycle 3 of chemotherapy will have a significant increase in fatigue.

Child cohort. Correlations between the variables of carnitine plasma levels and fatigue at each of two individual study time points were first examined. Correlations for the child cohort at cycle 1 can be seen in Table 10. There was a strong correlation between total carnitine plasma levels and CFS scores with higher levels of total carnitine associated with higher levels of fatigue. This was also evident in the strong relationship between higher free carnitine plasma levels and higher CFS total scores. The relationship between acylcarnitine, the waste product of carnitine metabolism, and CFS total scores was small. There was a large negative relationship between the AC/FC ratios and fatigue with lower ratios associated with higher CFS total scores.

Table 10

Spearman's Rank-Order Correlations Between Child Variables: Fatigue and Carnitine Plasma Levels at Cycle 1 of Chemotherapy

Variables		CFS Frequency	CFS Total
1. CFS Frequency	r_s	—	
	p	—	
2. CFS Total	r_s	.87	—
	p	.00	—
3. Total carnitine	r_s	.32	.51
	p	.25	.05
4. Free carnitine	r_s	.37	.57
	p	.17	.03
5. Acylcarnitine	r_s	-.06	.19
	p	.82	.68
6. AC/FC ratio	r_s	-.47	-.58
	p	.08	.03

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

The correlations between the child variables, carnitine plasma levels and fatigue, at cycle 3 of chemotherapy can be seen in Table 11. Relationships were not evident between total carnitine and CFS total scores and between free carnitine and CFS total scores. Acylcarnitine has a small relationship with CFS total scores. The AC/FC ratio has a medium relationship with CFS total scores with higher ratios associated with higher total fatigue scores.

Table 11

Spearman's Rank-Order Correlations Between Child Variables: Fatigue and Carnitine Plasma Levels at Cycle 3 of Chemotherapy

Variables		CFS Frequency	CFS Total
1. CFS Frequency	r_s	—	
	p	—	
2. CFS Total	r_s	.88	—
	p	.00	—
3. Total carnitine	r_s	.19	.01
	p	.50	.99
4. Free carnitine	r_s	.15	-.08
	p	.59	.78
5 Acylcarnitine	r_s	.15	.27
	p	.61	.34
6 AC/FC ratio	r_s	.24	.48
	p	.40	.07

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

The relationships between change in carnitine plasma levels and change in fatigue in the child cohort from cycle 1 to cycle 3 of chemotherapy can be seen in Table 12. There were medium strength correlations between change in total and free carnitine plasma levels and change in CFS total scores with a decrease in total and free carnitine levels associated with a decrease in CFS total scores. The correlation between a change in acylcarnitine levels and change in CFS total scores was small. A small negative correlation was also seen between change in AC/FC ratio and change in CFS total scores.

Table 12

Spearman's Rank-Order Correlations Between Child Variables: Change in Fatigue and Change in Carnitine Plasma Levels

Variables		Change in CFS Frequency	Change in CFS Total
1. Change in CFS Frequency	r_s	—	
	p	—	
2. Change in CFS Total	r_s	.85	—
	p	.00	—
3. Change in Total carnitine	r_s	.33	.44
	p	.30	.11
4. Change in Free carnitine	r_s	.29	.43
	p	.32	.13
5. Change in Acylcarnitine	r_s	.12	.29
	p	.67	.31
6. Change in AC/FC ratio	r_s	-.19	-.19
	p	.53	.52

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

Adolescent cohort. Correlations between the variables of carnitine plasma levels and fatigue at cycle 1 of chemotherapy for the adolescent cohort can be seen in Table 13. There was a medium relationship between total carnitine plasma levels and adolescent fatigue and free carnitine levels and fatigue at cycle 1 of chemotherapy with higher carnitine levels associated with higher FS-A scores. A small relationship was evident between acylcarnitine and FS-A scores and a small negative relationship was evident between the AC/FC ratio and fatigue.

Table 13

Spearman's Rank-Order Correlations Between Adolescent Variables: Fatigue and Carnitine Plasma Levels at Cycle 1 of Chemotherapy

Variables		FS-A
1. FS-A	r_s	—
	p	—
2. Total carnitine	r_s	.33
	p	.25
3. Free carnitine	r_s	.36
	p	.21
4. Acylcarnitine	r_s	.13
	p	.66
5. AC/FC ratio	r_s	-.11
	p	.71

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

In the cycle 3 measurements for the adolescent cohort, correlations among variables can be seen in Table 14. Total carnitine levels had a small relationship with FS-A scores and free carnitine levels were not associated with adolescent fatigue scores. Acylcarnitine had a strong relationship with fatigue scores with higher acylcarnitine levels associated with higher FS-A scores. The AC/FC ratio had a negative medium relationship with adolescent fatigue. Lower AC/FC ratios were related to higher fatigue in adolescents.

Table 14

Spearman's Rank-Order Correlations Between Adolescent Variables: Fatigue and Carnitine Plasma Levels at Cycle 3 of Chemotherapy

Variables		FS-A
1. FS-A	r_s	—
	p	—
2. Total carnitine	r_s	.21
	p	.47
3. Free carnitine	r_s	.05
	p	.88
4. Acylcarnitine	r_s	.64
	p	.01
5. AC/FC ratio	r_s	-.49
	p	.08

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

The relationships between change in carnitine plasma levels and change in fatigue in the adolescent cohort from cycle 1 to cycle 3 of chemotherapy can be seen in Table 15. There was a medium to large correlation between change in total carnitine plasma levels and change in FS-A scores with a decrease in total carnitine levels associated with a decrease in adolescent fatigue scores. There was a large correlation between change in free carnitine levels and change in fatigue with a decrease in free carnitine associated with a decrease in fatigue. A small correlation was present between change in acylcarnitine and change in FS-A, and change in AC/FC ratio and change in FS-A.

Table 15

Spearman's Rank-Order Correlations Between Adolescent Variables: Change in Fatigue and Change in Carnitine Plasma Levels

Variables		Change in FS-A
1. Change in FS-A	r_s	—
	p	—
2. Change in Total carnitine	r_s	.47
	p	.09
3. Change in Free carnitine	r_s	.52
	p	.06
4. Change in Acylcarnitine	r_s	.22
	p	.46
5. Change in AC/FC ratio	r_s	.17
	p	.55

r_s = Spearman's correlation, *p* = Probability value, 2-tailed

Summary of Findings

In summary, the findings supported the study's exploratory aims. However, testing of the study hypotheses revealed that only one hypothesis was supported. Aim 1 sought to determine the change in physical performance and change in fatigue in each of the study cohorts, children and adolescents. The direction of change was specified in Hypothesis 1.1, which predicted that physical performance would decrease in the each cohort, from cycle 1 to cycle 3 of chemotherapy. Physical performance appeared to improve in children during this time period and adolescents experienced little change. Hypothesis 1.2 predicted that fatigue would increase in each of the two age cohorts,

from cycle 1 to cycle 3 of chemotherapy. Children experienced a decrease in fatigue with a medium effect size. Adolescents appeared to experience a decrease in fatigue but with a small effect size. The first aim examining change in physical performance and change in fatigue was supported in the child cohort. In the adolescent cohort, change in fatigue was supported while change in physical performance was not. The direction of change in fatigue and physical performance predicted in the first hypotheses was not supported in children or adolescents.

Aim 2 sought to determine the relationship between change in physical performance and change in fatigue in the two study cohorts. Hypothesis 2 predicted the direction of change and specified that children and adolescents who experienced a significant decrease in physical performance from cycle 1 to cycle 3 of chemotherapy would have a significant increase in fatigue. The relationship identified in Aim 2 was supported in the study cohorts but in the opposite direction predicted in Hypothesis 2. Children who had an increase in physical performance had a decrease in total fatigue scores. There was a medium relationship between faster TUDS times and decreased total fatigue scores. A strong relationship was evident between an increase in 6MWT distance and decreased fatigue. In adolescent cohort, there was a small relationship between a decrease in time on the TUDS and a decrease in fatigue. There was a medium relationship between walking farther distance on the 6MWT and a lowering of the fatigue score.

Aim 3 sought to examine carnitine plasma levels in the two cohorts at cycle 1 and cycle 3 of chemotherapy. Hypothesis 3 predicted that carnitine plasma levels would decrease in each cohort from cycle 1 to cycle 3. In the child cohort, total carnitine and free carnitine plasma levels decreased significantly. Total carnitine and free carnitine

plasma levels in adolescents were stable and demonstrated little change from cycle 1 to cycle 3. Hypothesis 3 was supported in the child cohort but not in the adolescent cohort.

Finally, in Aim 4, the relationship between carnitine plasma levels and fatigue in a cohort was determined for each cohort. Hypothesis 4 predicted that children and adolescents, who experienced a decrease in carnitine plasma levels between cycle 1 and 3 of chemotherapy, would have an increase in fatigue. In the child cohort, when carnitine levels decreased, fatigue also decreased. There was a medium strength correlation between the decrease in total carnitine plasma levels and decrease in total fatigue scores and a small correlation between the decrease in free carnitine and decrease in total fatigue. In the adolescent cohort, a decrease in carnitine levels was also associated with a decrease in fatigue. There was a medium to large correlation between a decrease in total carnitine and a decrease in adolescent fatigue scores and a large correlation between a decline in free carnitine levels and decline in fatigue. The study results supported Aim 4; there was a relationship between change in carnitine levels and change in fatigue. The direction of the change as stated in Hypothesis 4 was not supported because children and adolescents who had a decrease in carnitine experienced a decrease, not increase, in fatigue levels.

Chapter 5

Discussion

Introduction

In this chapter, the important study findings will be discussed in their relationship to existing research studies and their contribution to our knowledge about fatigue and related variables. Experiences related to recruiting subjects and administering the selected study measurements will be considered and limitations of the study will be presented. Implications for future research including study questions and designs will be discussed.

Discussion of Important Findings

Change in fatigue. The outcomes of this exploratory study provide new insight into the symptom of fatigue in newly diagnosed children and adolescents with cancer during the first three cycles of chemotherapy. Previous research in children and adolescents has focused on measuring fatigue at one time point during treatment (Hockenberry et al., 2003, Collins et al., Collins et al, 2000; Collins et al., 2002) or during two time points in one treatment cycle of days to weeks (Hockenberry et al., 2003; Gedaly-Duff, 2006; Hinds et al., 2007a; Hinds et al., 2007b; Hinds et al., 2007d). When measured within a treatment cycle, fatigue has increased over time.

In this study, fatigue was measured over a natural treatment course from the first cycle of chemotherapy treatment through the third cycle. The child cohort experienced a decrease in fatigue levels with a medium effect size. The effect size in the child cohort demonstrated both the magnitude of change in fatigue and the responsiveness of the CFS instrument to detect the change in fatigue experienced by the subjects. Although the size of the child cohort was small (n = 16), there was a significant decrease in the total fatigue score (p = .05). The direction and magnitude of change in fatigue in the

child cohort during the trajectory of three treatment cycles was an unexpected and important finding.

In the adolescent cohort, there was a tendency towards a decrease in fatigue with a small to medium effect size. The change in fatigue was not as significant (p = .15) as the change in the child cohort. In this smaller adolescent group (n = 14) however, the direction of change was consistent with the child cohort. The smaller effect size indicated that the magnitude of change was less as measured by the FS-A. For future studies using the FS-A, a larger sample size is needed to identify a significant change in fatigue.

The decrease in fatigue that occurred without a specific fatigue intervention must be considered in future study designs. A fatigue intervention study would need to include a control group to allow for the comparison to the natural trajectory of this symptom during treatment. A potential reason for the decrease in fatigue could be that at the first measurement point (cycle 1 of chemotherapy), patients experienced fatigue as a side effect of chemotherapy as well as an initial disease symptom that alerted youth or their family members to the fact that they were ill. At the second measurement point, all of the patients were in remission. A potential source of fatigue, the cancer itself, had been eliminated.

The small size of the cohorts limited use of multiple regression analysis to evaluate the influence of potential moderators, such as diagnosis/treatment and gender, on the relationship between change in physical performance and change in fatigue. However, a Mann-Whitney U test found that there was no significant difference between males and females in the amount of change in fatigue in either cohort. The Kruskal-Wallis test revealed a difference in the change in fatigue between the three diagnostic groups (acute lymphocytic leukemia (ALL), lymphoma, and solid tumors) in the child

cohort but not in the adolescent cohort. The children with ALL had a significant improvement in their fatigue that may have influenced the significant decrease in fatigue found in the entire child cohort. The first measurement point for children with ALL was during induction therapy. The induction phase of treatment included high doses of corticosteroids. Side effects of corticosteroids can include muscle atrophy and fatigue. Chemotherapy at cycle 3 did not include corticosteroids, so this acute side effect would be expected to diminish. In designing future studies, it will be important to recognize the potential influence that diagnosis and treatment have on the experience of fatigue when calculating the sample size and developing the data analysis plan.

In the adolescent group, the small cohort size combined with the uneven distribution of gender and diagnosis within the cohort limited the non-parametric tests of differences between independent groups. However, an interesting finding was that even with a small number of adolescents with ALL, fatigue did not decrease in this subgroup after corticosteroids were no longer administered in the third chemotherapy cycle. Perhaps the side effects of corticosteroids are experienced differently in children and adolescents.

While administering the study measurements, I had the opportunity to interact with the subjects and observe them with their families and staff. An additional variable that was not included as a measure in this study was the positive coping that I observed which developed between cycle 1 and cycle 3 of chemotherapy. I observed positive coping in subjects' verbal and non-verbal behaviors. Patients appeared less anxious and more engaged over time as evidenced by making eye contact, being quicker to leave their parents to do study measurements, and engaging in spontaneous conversations with me. The treatment environment and staff seemed to be less foreign and frightening and treatment was becoming more predictable. Haase (2004) defines positive coping as

an adaptive response that includes confrontive and optimistic strategies; positive coping contributes to resilience during the cancer experience. In her Adolescent Resilience Model (ARM), Haase has also linked symptom distress, including fatigue, to resilience. Further research is needed to understand how protective factors such as positive coping can buffer the effects of symptom distress (Haase). This may be especially important in the adolescent population. This age group reports that fatigue includes a mental and emotional tiredness that influences everyday interactions. Coping and resilience may have a protective influence on the psychological dimensions of fatigue. Standardized measures of coping should be included in future studies of the trajectory of fatigue in youth with cancer.

Change in physical performance. The child cohort in this study demonstrated an improvement in both measures of physical performance (TUDS and 6MWT). The adolescent cohort revealed a slight improvement in the TUDS measurement, but had no change in the 6MWT. There was one previous study that measured physical performance over the natural trajectory of treatment. In a randomized clinical trial, Marchese and colleagues (2004) measured physical performance in children, ages 4 to 15, during the maintenance phase of treatment for ALL. They compared a control group (n = 15) to an intervention group (n = 13) that received a 12-week home exercise program. The control group did not have significant changes in the TUDS or the 9-minute walk during the study time period. The results from the control group in the Marchese et al. study are consistent with the results of the adolescent cohort in this study, although the measurement time-point in Marchese et al.'s control group was later in therapy.

In the child cohort, a Mann-Whitney U test revealed that males and females did not differ in the amount of improvement on the TUDS or the 6MWT. A Kruskal-Wallis

test showed a tendency for children with leukemia to have greater improvement in the 6MWT than children with lymphoma or solid tumors. This was consistent with the difference in fatigue found among the child diagnostic groups and again, might be due to the influence of corticosteroids on the cycle 1 measurement and absence of corticosteroids on the cycle 3 measurement. A difference in improvement on the TUDS was not found between the three diagnostic groups in the child cohort.

In the adolescent cohort, the uneven distribution of subjects in both gender and diagnostic groups again limited the analysis of differences among the groups. Although there was no significant difference between males and females in the amount of improvement on the TUDS, a Mann-Whitney U test showed a tendency for adolescent females to walk farther than males on the second 6MWT. However, there were only three females in the adolescent cohort. A greater gender balance in a larger adolescent cohort might have revealed a significant difference with females demonstrating a greater improvement than males. There were no significant differences among the three diagnostic groups in the adolescent cohort in improvement on the TUDS or 6MWT.

When comparing the amount of improvement on the 6MWT between children and adolescents with ALL, the change in the sub-group of children with ALL (n = 6) (Md = -171.75) was much greater than the change in the sub-group of adolescents with ALL (n = 3) (Md = -26.82). Again, a larger negative number for the median indicated a greater distance walked during the second measurement. This was consistent with differences in improvement in fatigue that were more evident in children with ALL than in adolescents with ALL. This developmental difference merits further investigation in studies with larger samples of each developmental group.

Another potential explanation for the improvement in physical performance in the child cohort compared to the stable performance in the adolescent cohort could be a

developmental difference in subjects' motivation to perform the measures. Other potential variables that could influence physical performance that were not measured in this study include the level of physical activity before the diagnosis of cancer and the patient's own perception of their competence (self-efficacy). During a study of physical activity in adolescents (n = 97) during cancer treatment, Keats and colleagues (2006) found that 77% of the teens reported that they were inactive during treatment. However, 23% of the teens recalled that they were active before treatment and continued to be active during treatment. Several of the patients in each cohort of this study volunteered information about their participation in sports (hockey, football, swimming, and soccer) before diagnosis and their return to sports during treatment. Exercise researchers have also found relationships between the person's belief in their ability to be successful in an exercise behavior and their perception of the amount of exertion required. Children and adolescents with high levels of self-efficacy perceive exercise as a more positive experience than those with lower self-efficacy (Pender, Bar-Or, Wilk, & Mitchell, 2002). In directing subjects on the physical performance measures, I provided the same directions to all of the subjects: "Do the best you can, but the activities are not a contest. There isn't a winner or a loser." I observed that some subjects were competitive and eager to perform, while others were more hesitant and less engaged. Perhaps the levels of activity, motivation, and self-efficacy were higher in the child cohort than the adolescent group. The patients' histories in relation to their stage of development, exercise and self-perception may provide important insight into their physical performance during cancer treatment and merit further investigation.

Relationship between change in physical performance and change in fatigue. In this discussion, the focus will be on the relationship between the changes in each variable. The correlations between fatigue and physical performance at each single

measurement point were provided in the study results section. These correlations must be considered in the context of the subject's physical development. For example, a taller child or adolescent would be expected to walk farther on the 6MWT. This did not mean, however, that they would have more or less fatigue. Of interest was how individual changes in performance were related to changes in fatigue. In the child cohort, there was a strong correlation between an increase in distance on the 6MWT and a decrease in the total fatigue score. There was also a medium correlation between an increase in speed on the TUDS and a decrease in total fatigue. In the adolescent group, there was a medium correlation between an increase in meters walked on the 6MWT and a decrease in fatigue scores and a weaker correlation (small to medium) between an improved time on the TUDS and a decrease in fatigue.

These study findings are consistent with Hinds and Hockenberry's conceptual definition of fatigue in children with cancer (Hinds et al., 1999). In their qualitative research, they found that fatigue was described as a distressing, pervasive symptom with physical, mental, and emotional components characterized by a lack of energy. The subjective experience of fatigue differed by developmental level as the school age group emphasized the physical sensation of fatigue while the adolescent group emphasized mental tiredness that alternated and at times merged with the physical sensation of fatigue. The fatigue instruments for both cohorts included statements about physical, mental, and emotional components of fatigue. Strong relationships between measures of change in physical performance and fatigue were found in the child cohort, while the relationships in the adolescent cohort were less evident. Children with cancer experience fatigue primarily as a physical sensation; therefore, its correlation with physical performance is logical. Developmental scientists recognize that symptom experiences are different across developmental levels (Docherty, 2003). The complexity

of the fatigue experience increases as development advances, so the adolescent's fatigue might have a weaker relationship with the physical domain as the mental and emotional components of fatigue evolve. This is the first study to examine relationships between physical performance and fatigue over multiple cycles of chemotherapy. The results provide new insight into how these variables relate to each other and may be influenced by the developmental level of the patient.

Change in carnitine plasma levels. This discussion will focus on changes in the free carnitine levels in the plasma. Free carnitine (FC) is a measure of the L-carnitine available for transporting fatty acids into the mitochondria. Carnitine deficiency is defined biochemically as abnormally low plasma levels of free carnitine (FC). In the child cohort, there was a significant decrease in free carnitine levels from cycle 1 to cycle 3. This decrease is consistent with the Yaris et al.'s findings (2002) in 51 children with cancer, ages 3 to 16. The subjects in Yaris et al.'s study experienced a significant decrease in carnitine levels between diagnosis and the third month of chemotherapy treatment. However, the adolescent cohort in this study differed from the Yaris et al study because they did not experience a large change in free carnitine levels.

In the child cohort, a Mann-Whitney *U* test revealed no significant difference between males and females in the change in total carnitine levels. A Kruskal-Wallis test revealed that children with ALL had significantly greater loss in total and free carntine compared to children with lymphoma or solid tumors. These differences indicate potential differences in the influence of different diagnosis-related chemotherapy regimens on carnitine levels. The adolescent gender groups and diagnostic groups did not have significant differences between the groups in amount of change in carnitine levels.

The difference between the child and adolescent cohorts in the change in carnitine levels may be due to differences in carnitine metabolism and/or chemotherapy drug metabolism. Some drugs (doxorubicin, ifosfamide, and cisplatin) are known to interfere with the carnitine network and could have been administered to more patients in one group than the other group. Although treatment regimens were assessed and documented, analysis of a specific chemotherapy regimen as a potential moderator was limited by the small number of subjects in each cohort of this study. Additional research is needed in larger pediatric oncology samples to provide insight into the patterns of change in carnitine plasma levels over the trajectory of treatment in relation to age and chemotherapy regimen.

Relationship between change in carnitine levels and change in fatigue. In both the child and adolescent cohorts, the decrease in free carnitine plasma levels from cycle 1 to cycle 3 was associated with a decrease in fatigue. In adult oncology studies, subjects were only included if they had both a deficiency in carnitine and high levels of fatigue (Graziano et al., 2002; Cruciani et al., 2006). Supplementation with oral carnitine provided significant improvements in both fatigue and carnitine levels. The pediatric subjects in this study did not have carnitine deficiencies at either study measurement. To date, studies have not examined relationships between changes in carnitine levels and changes in fatigue levels over the trajectory of treatment. The decrease in both free plasma carnitine levels and fatigue levels was a finding that merits further investigation. The mean free carnitine level in the child cohort at cycle 3 was 32.1 and the median was 32.0. The adolescent mean free carnitine level at cycle 3 was 33.3 and the median was 32.0. The reference values for free carnitine in children and adolescents are 22 to 65. Perhaps fatigue does not emerge as a symptom associated with carnitine levels until there is a carnitine deficiency. It may take a longer duration of chemotherapy for

carnitine stores in the skeletal muscle to be used up by the carnitine network during chemotherapy metabolism. Measuring carnitine plasma levels for a longer duration of treatment may provide insight into its ongoing relationship to the symptom of fatigue.

Subject Recruitment and Completion of Study Measurements.

This exploratory study demonstrated that children and adolescents are willing to participate in a study that measures fatigue and physical performance and can verbalize their understanding of assent. Only 6 potential subjects refused participation for a refusal rate of 16%. With the low refusal rate, it did not appear that only active patients assented to participation. Although parents verbalized their interest in helping to advance knowledge about symptom experiences as the reason they consented to study participation, children and teens freely verbalized that they were primarily interested in receiving the Target® gift card that was given to thank the subjects for their effort.

The fatigue instruments, the measures of physical performance, and the measurement of carnitine plasma levels were found to be feasible to use in this clinical population. All subjects completed the fatigue measurements within several minutes. Blood samples were easily collected from the patient's central line during standard laboratory blood draws. All subjects were able to complete the 6MWT, and only one subject refused to do the TUDS at the cycle 3 point of measurement. In 2006, additional research on the 6MWT was published that constructed height-specific standards for the 6MWT for children ages 6 to 16 (Li et al., 2006). However, there are no published norms for the TUDS. The normative curves for the 6MWT allow for a subject's performance to be plotted and compared to healthy norms. A secondary data analysis of 6MWT results demonstrated that children and teens receiving chemotherapy become severely deconditioned. At cycle 3, 8 of 10 girls (80%) and 18 of 20 boys (90%) were below the 3rd percentile when compared to healthy children (Hooke, 2008). Although the children

and adolescents with cancer were ambulatory, their physical performance was clearly impacted by their disease and its treatment. Using the 6MWT in this study allowed for measurement of change in physical performance over time as well as examining children with cancer in relation to healthy peers. In future studies, the 6MWT could also be used to predict Peak $V0_2$ with an established equation that also includes measures of the patient's heart rate and blood pressure at the end of the 6 minutes (American College of Sports Medicine, 2006).

Recruiting the subjects, completing the informed consent and assent process, and administering the study measurements provided valuable experience in conducting research, observing subjects, and developing insights in how to design future study measurements and interventions.

Study Limitations

It is recognized that symptoms are temporal in nature. The experience of fatigue is subjective and there may be a wide variation within a day, week, and/or month. A subject's recall of the fatigue over the past week may not be an accurate measurement of the subject's experience within that time frame. Physical performance is dependent on muscle physiology and is less likely to have rapid shifts in a short time period. However, physical performance is influenced by motivation and a disinterested subject may have performed less well on the study measurements. Additionally, the initial study measurements (between day 15 and 29 of the first cycle of chemotherapy) were not a true pre-treatment baseline. Access to subjects is always a challenge at diagnosis due to the brief time period between diagnosis and the initiation of treatment.

The small sample size for the study presented additional limitations. During the study enrollment period, the data analysis plan was amended. This was in response to the need to analyze the subjects who were ages 6 to 12 and those who were ages 13 to

17 as two separate cohorts based on recent findings by Hinds and Hockenberry. The fatigue scales used for these two age groups are distinctive for each developmental level. In their 2007 publications, Hinds and Hockenberry analyzed their child and adolescent fatigue scores as separate groups (Hinds et al., 2007b; Hinds et al., 2007d). In my consultation with these fatigue measurement experts, Hinds and Hockenberry recommended that fatigue measurements not be combined into one set using *z* scores. As a result of needing to separate the sample into two separate cohorts, the original sample size of 40 subjects was amended. It was not feasible to enroll 40 patients in two cohorts from the pediatric oncology population in this geographic region in a reasonable period of time. The resulting decreased sample size included a cohort of children (n = 16) and a cohort of adolescents (n = 14). The smaller sample in each cohort limited the implementation of the original plan to explore the potential moderators of age, gender, diagnosis group, or hemoglobin.

It is also recognized that there are many other variables that were not measured that could influence fatigue, physical performance, and carnitine plasma levels and the relationships between the study variables. These may include, but are not limited, to the individual's behaviors (i.e., exercise behaviors) and characteristics (i.e., self efficacy) before the cancer diagnosis, coping and resilience since receiving the diagnosis, physiologic characteristics (i.e., height, weight, and metabolism), symptoms of the individual's cancer, and the chemotherapy drugs given for different diagnoses and risk groups and their side effects. The young person is also influenced by his/her family's support, coping styles and culture, support from the larger community, and the quality and quantity of time in the environment of the home, hospital, and outpatient clinic. The complexity of the potential interactions of these variables is recognized in the *Developmental Model for Children and Adolescents with Cancer* (Hooke, 2008a).

Finally, this study was also limited by having two measurement points. With only two points, the trajectory of change is assumed to be linear. When there are three or more points, non-linear change can be detected which provides further insight into the trajectory of the cancer experience (Lyons, 2006). This exploratory study provided insight into fatigue, physical performance, and carnitine levels during the first cycles of chemotherapy and provided a foundation for moving forward in future studies of fatigue in children and adolescents undergoing cancer treatment.

Implications for Future Research

This exploratory study provides insight into the relationship between the variables of physical performance and fatigue and the variables of carnitine plasma levels and fatigue. In the future, a larger, multi-site study would allow for more rapid accrual of subjects as well as multivariate analysis of the potential moderators of age/developmental group, diagnostic group/treatment regimens, body mass index percentile for age, and hemoglobin. Potential questions to consider in future studies include: What is the influence of positive coping and resilience on fatigue? What is the relationship of exercise levels pre-diagnosis to physical performance during treatment? Does self-efficacy influence physical performance during cancer treatment?

The addition of three or more measurement points in future study designs would provide a more informative view of the trajectory of fatigue and its relationship to physical performance and to carnitine plasma levels. In a current study being conducted with Hockenberry, the relationship between carnitine plasma levels and fatigue is being examined over 8 cycles of chemotherapy with study measurements every other cycle. Additional knowledge about this physiologic measure is needed before carnitine can be considered as an intervention for fatigue.

Research in the adult oncology population has provided strong evidence of the effectiveness of exercise as an intervention for fatigue. The outcomes of this study support the relationship between improvement in physical performance and a decrease in fatigue levels. It is now time to evaluate the efficacy of exercise interventions to improve physical performance and decrease fatigue in children and adolescents. It will be important to use a control group to differentiate between a decrease in fatigue due to the natural trajectory of the symptom and a decrease in fatigue due to an exercise intervention. Exercise interventions will need to be tailored to the patient's developmental level as well as interest, physical performance pre and post diagnosis, and family resources. Additional symptoms to be measured as study outcomes include sleep disturbance and mood, as both symptoms have also improved in adults with cancer after exercise interventions.

Conclusion

Children and adolescents diagnosed with cancer experience fatigue as a symptom of disease and also as a side effect of treatment. Although it appears to lessen as disease burden decreases, fatigue continues to be reported by children and teens. As development advances, fatigue appears to become a multi-dimensional experience with the psychological distress of fatigue merging with the physical sensation. These study findings inform us about the relationship between physical performance and fatigue and provide a foundation for developing exercise interventions for fatigue. Decreasing the burden of this symptom is important for improving quality of life during treatment and for providing energy for engaging in positive life experiences that advance children along the developmental continuum to a long and healthy future.

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Appendix A

Histograms for the Child and Adolescent Cohort Measurements

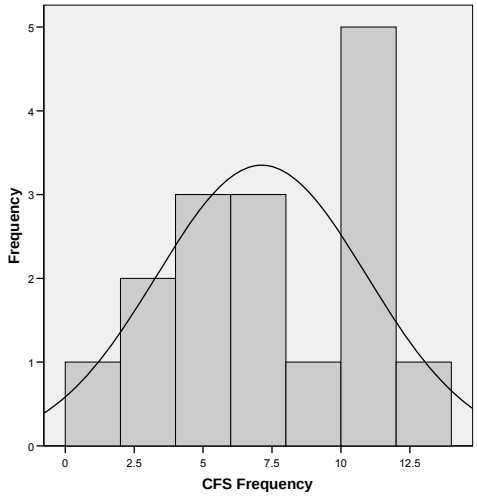

Figure A1. Child CFS frequency at cycle 1

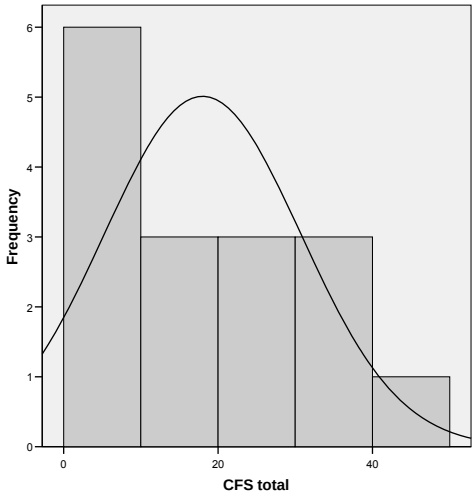

Figure A2. Child CFS total score at cycle 1

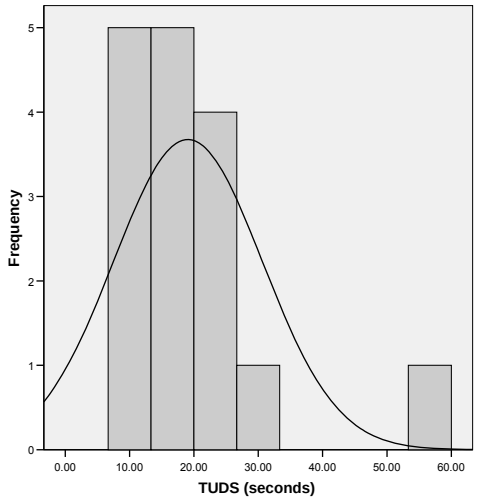

Figure A3. Child TUDS at cycle 1

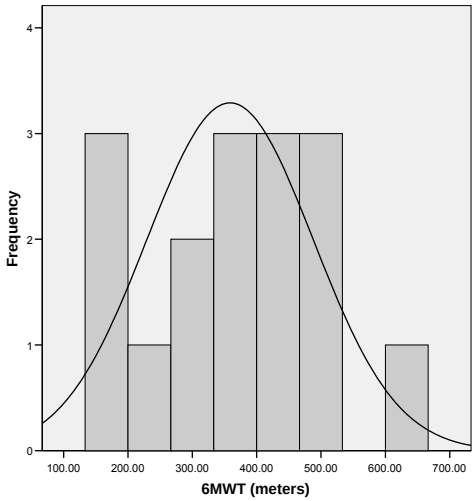

Figure A4. Child 6MWT at cycle 1

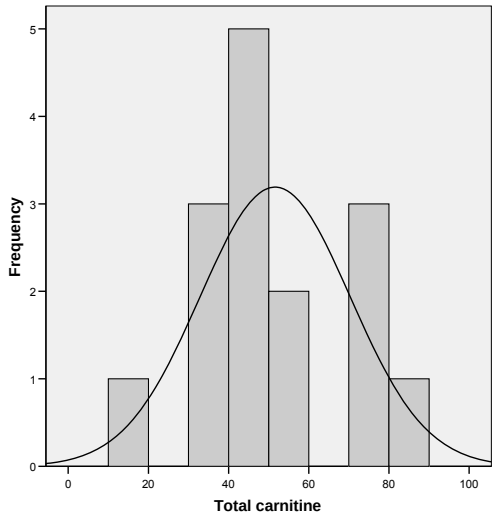

Figure A5. Child total carnitine at cycle 1

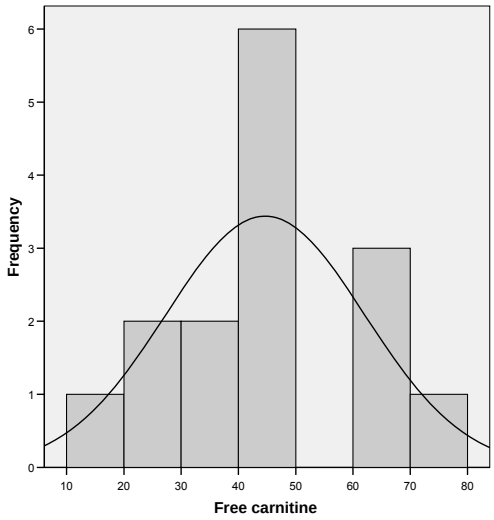

Figure A6. Child free carnitine at cycle 1

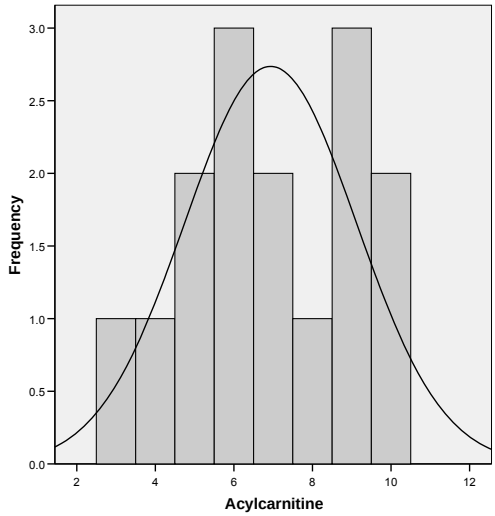

Figure A7. Child acylcarnitine at cycle 1

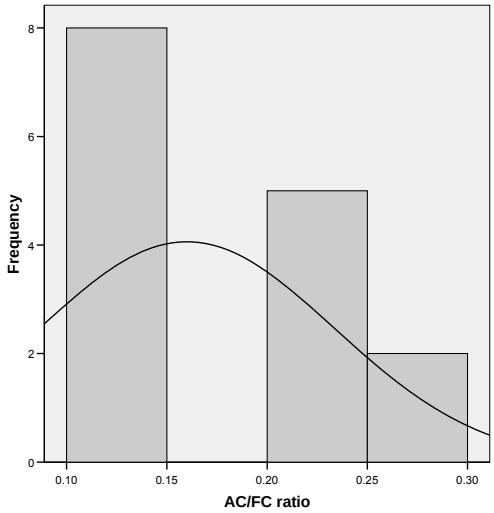

Figure A8. Child AC/FC ratio at cycle 1

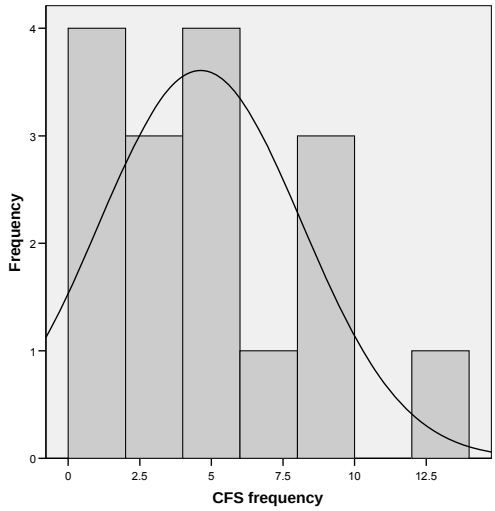

Figure A9. Child CFS Frequency at cycle 3

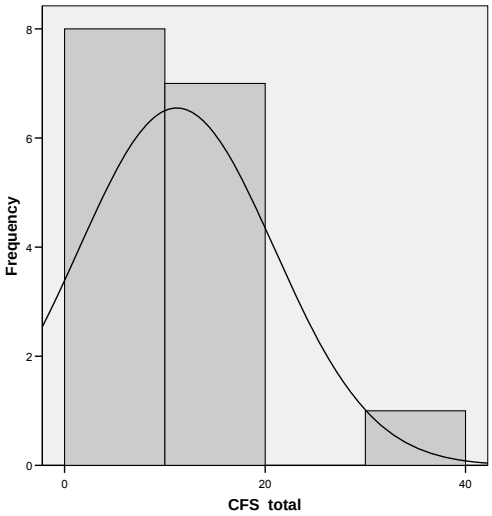

Figure A10. Child CFS total at cycle 3

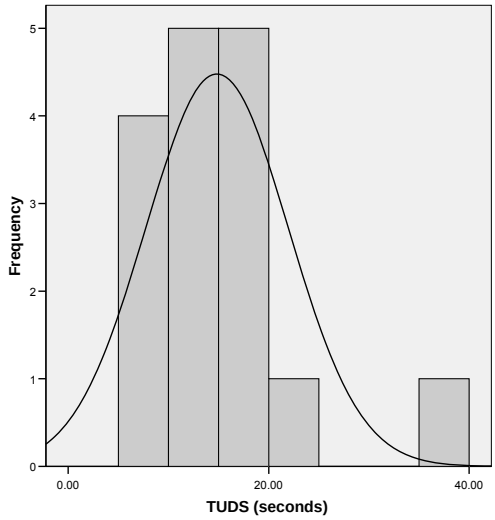

Figure A11. Child TUDS at cycle 3

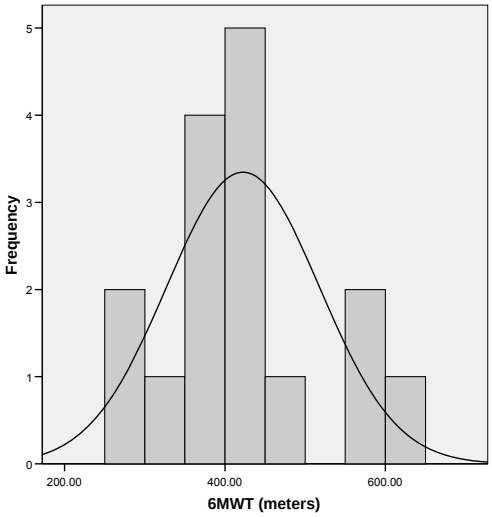

Figure A12. Child 6MWT at cycle 3

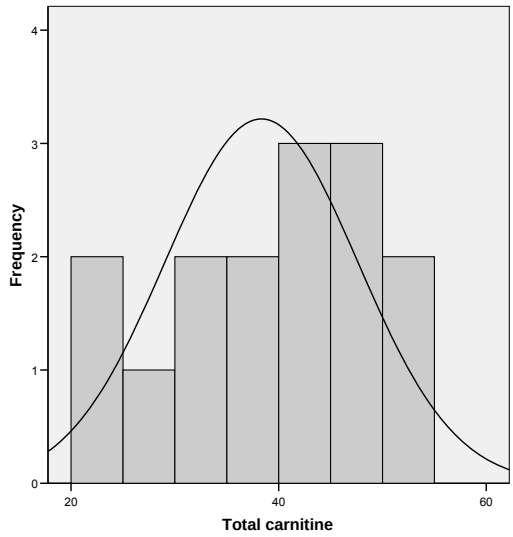

Figure A13. Child total carnitine at cycle 3

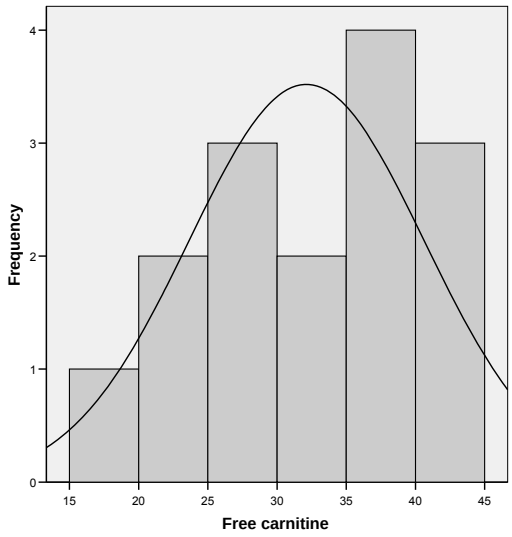

Figure A14. Child free carnitine at cycle 3

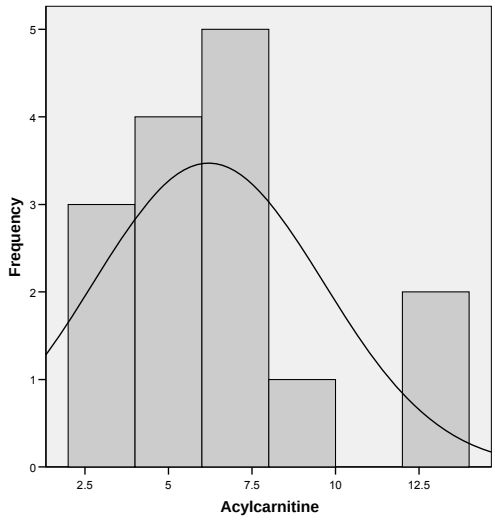

Figure A15. Child acylcarnitine at cycle 3

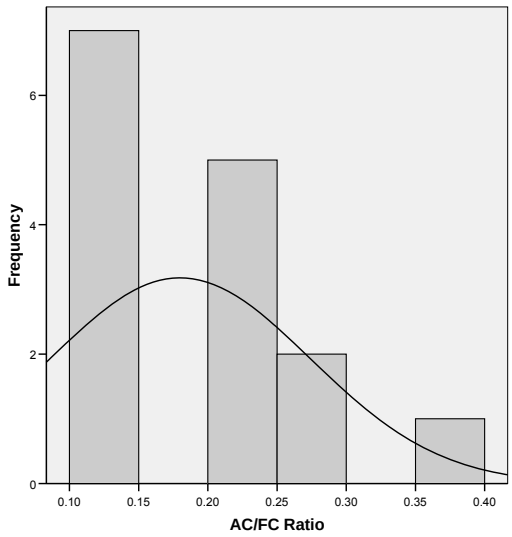

Figure A16. Child AC/FC ration at cycle 3

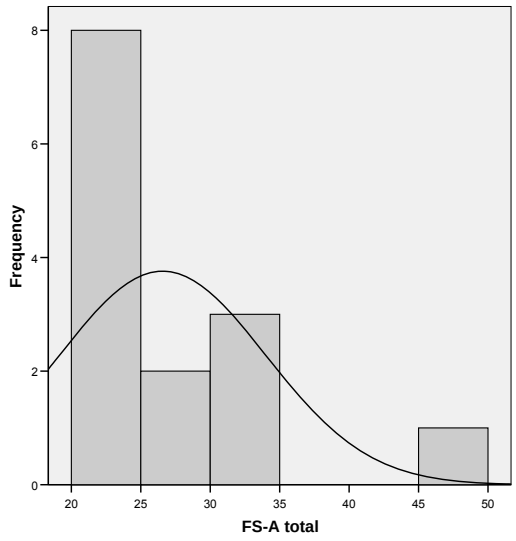

Figure A17. Adolescent FS-A total at cycle 1

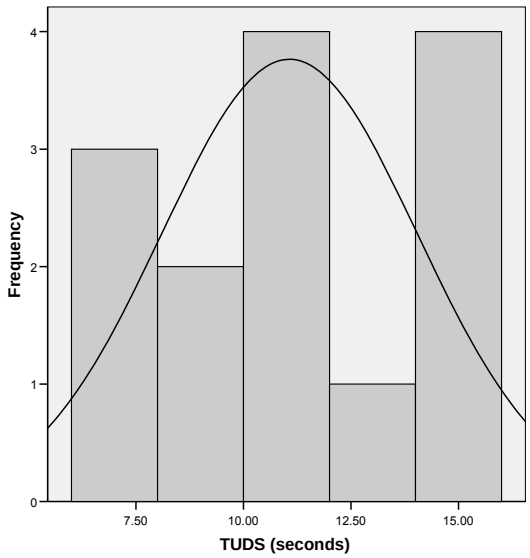

Figure A18. Adolescent TUDS at cycle 1

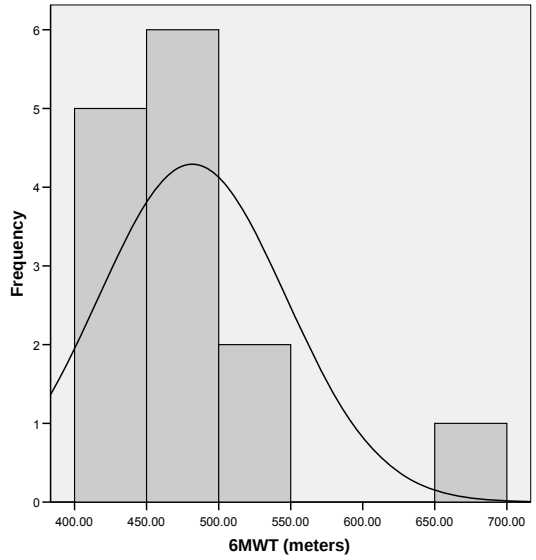

Figure A19 Adolescent 6MWT at cycle 1

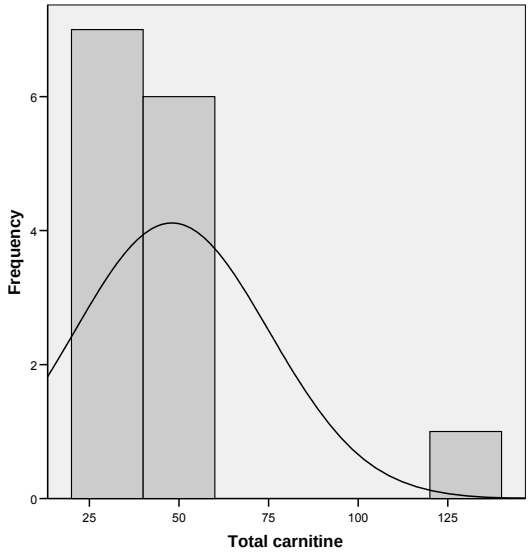

Figure A20. Adolescent total carnitine at cycle 1

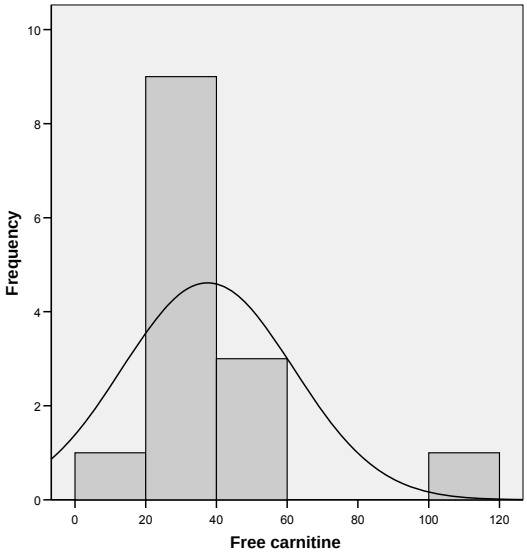

Figure A21. Adolescent free carnitine at cycle 1

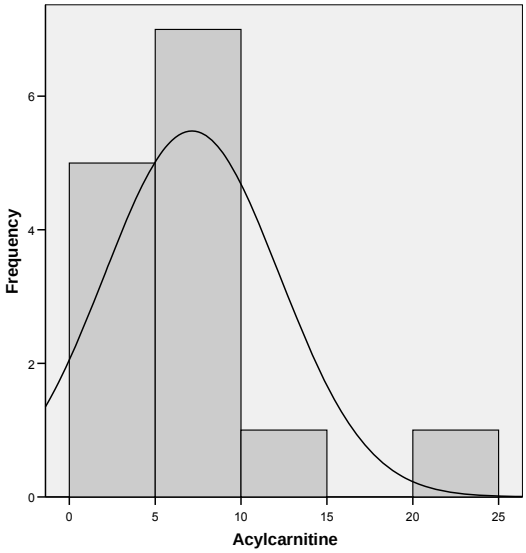

Figure A22. Adolescent acylcarnitine at cycle 1

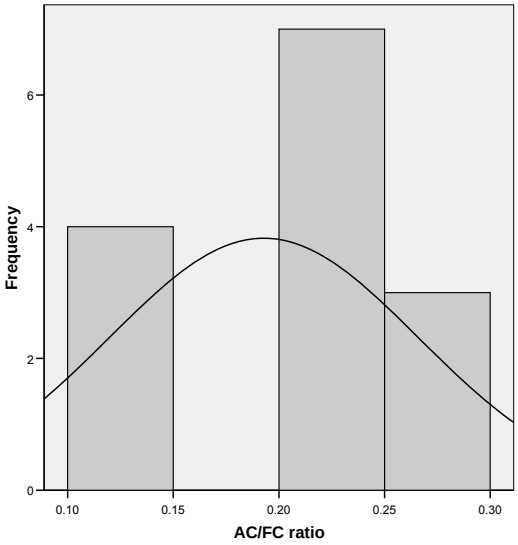

Figure A23. Adolescent AC/FC ratio at cycle 1

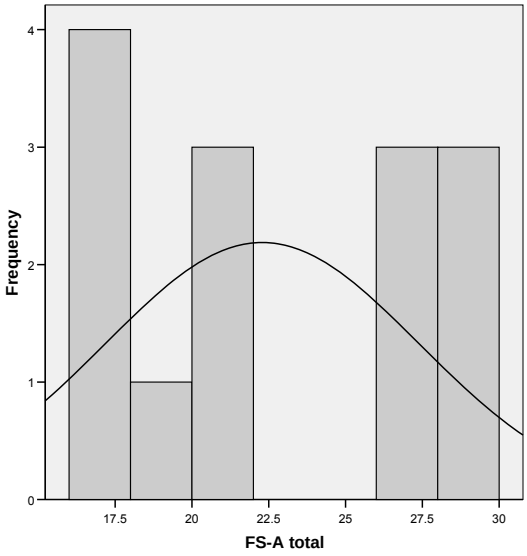

Figure A24. Adolescent FS-A total at cycle 3

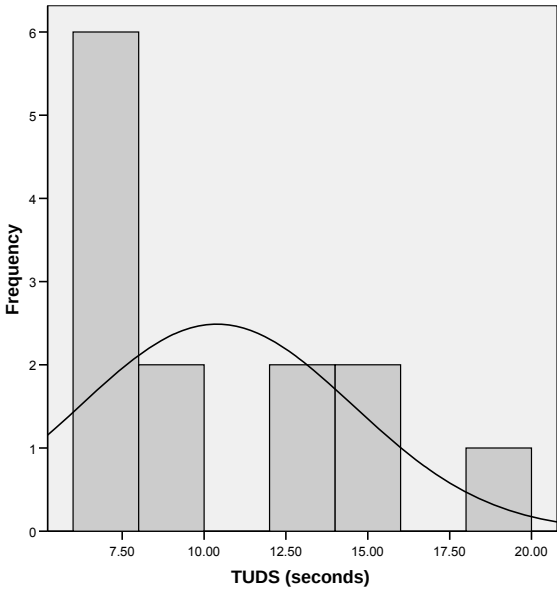

Figure A25. Adolescent TUDS at cycle 3

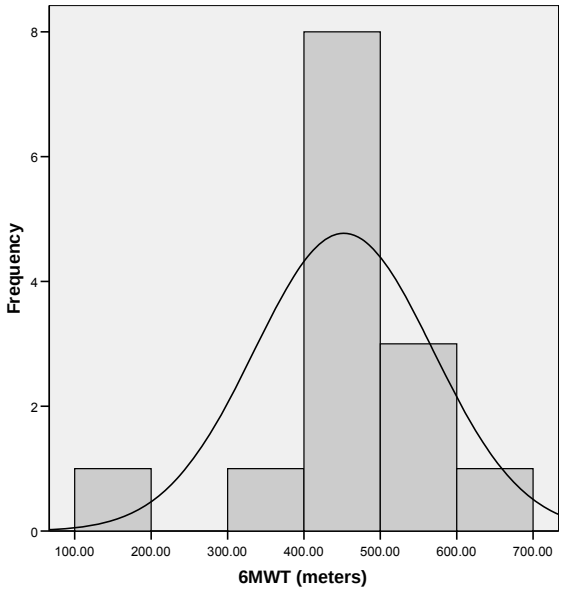

Figure A26. Adolescent 6MWT at cycle 3

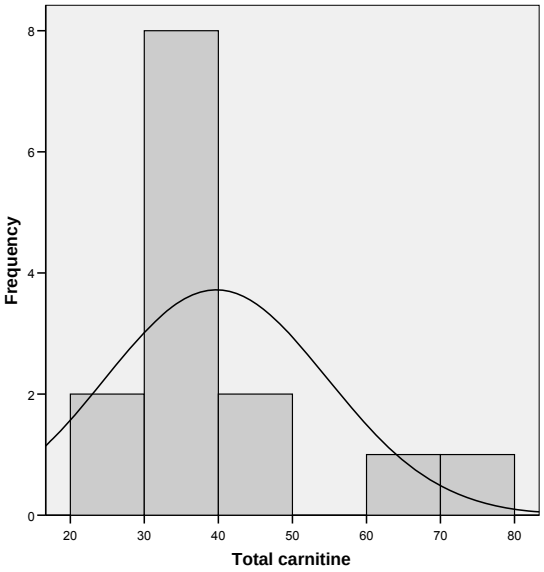

Figure A27. Adolescent total carnitine at cycle 3

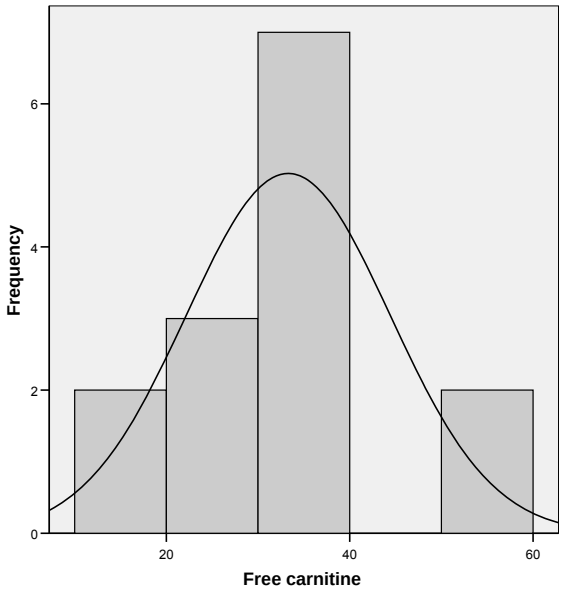

Figure A28. Adolescent free carnitine at cycle 3

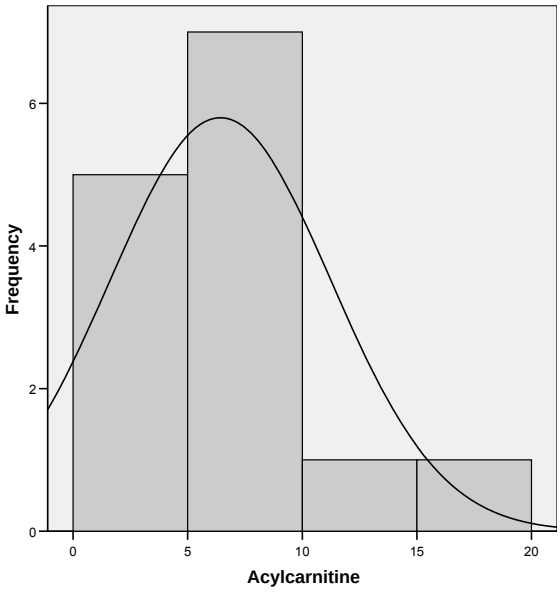

Figure A29. Adolescent acylcarnitine at cycle 3

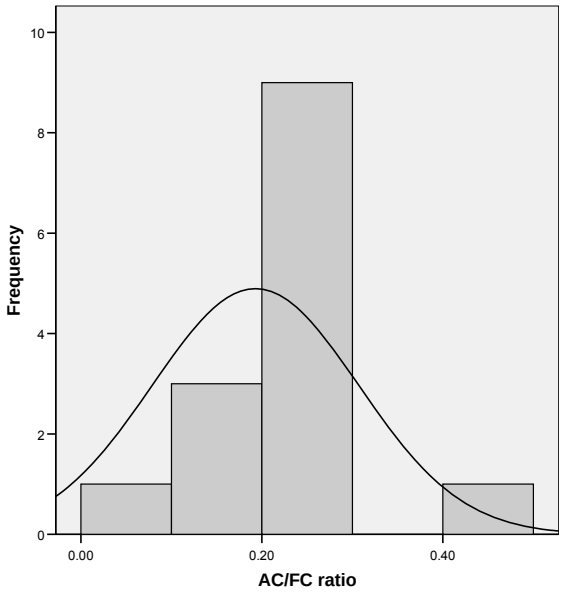

Figure A30. Adolescent AC/FC ratio at cycle 3

Appendix B

Child and Adolescent Fatigue Scales

CHILD FATIGUE SCALE (WEEKLY SCALE)

If the answer is no, go to the next question. If the answer is yes, circle how much it bothers you.

FREQUENCY			INTENSITY				
HOW HAVE YOU BEEN FEELING DURING THE PAST WEEK?			HOW MUCH DOES IT BOTHER YOU				
			Not at all	A Little	Some	Quite A Bit	A lot
1. I have been tired.	Yes	No	1	2	3	4	5
2. My body has felt different.	Yes	No	1	2	3	4	5
3. I have been tired in the morning.	Yes	No	1	2	3	4	5
4. I have needed a nap.	Yes	No	1	2	3	4	5
5. I've been too tired to play.	Yes	No	1	2	3	4	5
6. I have been lying around.	Yes	No	1	2	3	4	5
7. I have been sad.	Yes	No	1	2	3	4	5
8. I have been mad.	Yes	No	1	2	3	4	5
9. I have had to stop and rest when walking.	Yes	No	1	2	3	4	5
10. I've been too tired to do my usual activities.	Yes	No	1	2	3	4	5
11. I've been too tired to run.	Yes	No	1	2	3	4	5
12. It has been hard to keep my eyes open.	Yes	No	1	2	3	4	5
13. I slept more at night.	Yes	No	1	2	3	4	5
14. I have trouble thinking.	Yes	No	1	2	3	4	5

Figure B1. Childhood Fatigue Scale (Hockenberry et al., 2003)

THE FATIGUE SCALE FOR 13-TO 18- YEAR-OLDS (FS-A)
(Weekly Scale)

How have you been feeling during **the past week**? Please circle the **one** choice for each statement below that tells how true the statement is for you.

1. My body has felt tired.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
2. My mind has felt worn out.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
3. I move more slowly.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
4. I want to rest more.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
5. I sleep more often.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
6. It's harder to keep up with schoolwork.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
7. I don't feel like doing much.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
8. My body hasn't kept up with others.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
9. I am able to do my usual activities.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
10. I have felt angry.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
11. I have not felt like talking.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
12. I need help to do my usual activities.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
13. I don't feel like being with others.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time
14. I have to work harder to do my usual activities.	Not At All	A Little	About Half the Time	Quite a Bit	All the Time

Figure B2. Fatigue Scale for Adolescents (Hinds et al., 2007a)

Appendix C

Table C1.

Carnitine Reference Values

Age Group	Total	Free	Acylcarnitine	AC/FC Ratio
6 years	35-84	24-63	4-28	0.1-0.8
7-10 years	28-83	22-66	3-32	0.1-0.9
11-17 years	34-77	22-65	4-29	0.1-0.9
18 years or older	34-78	24-54	5-30	0.1-0.8

*Values expressed as umol/L (Schmidt-Sommerfeld, Werner, & Penn, 1988)

Appendix D

Table D1.

Study Measures and Collection Times

Study Measures	First cycle of chemotherapy	Third cycle of chemotherapy
Fatigue: CFS/FS-A	1 measurement between day 15 & 29	1 measurement between day 15 & 29
Carnitine Plasma Level	1 measurement between day 15 & 29	1 measurement between day 15 & 29
TUDS	1 measurement between day 15 & 29	1 measurement between day 15 & 29
6MWT	1 measurement between day 15 & 29	1 measurement between day 15 & 29

Appendix E

Consent Forms

Children's Hospitals and Clinics
2525 Chicago Avenue, South **347 North Smith Avenue**
Minneapolis, MN 55404 **St. Paul, MN 55102**

RESEARCH CONSENT FORM
Parent Form

Fatigue, Physical Performance, and Carnitine Plasma Levels in Children with Cancer

This is a research study. Research studies include only patients and families who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to take part in this study because you have recently been told that your child has cancer and your child is receiving IV chemotherapy to treat it.

WHY IS THIS STUDY BEING DONE?

Children and teens with cancer report that fatigue is one of the most distressing symptoms related to cancer treatment. In this study, we want to find out if fatigue increases during the first three months of cancer treatment. The ability to perform physical skills (called physical performance) will also be studied. The researcher wants to find out if there is a relationship between physical performance and the patient's level of fatigue. When physical performance skills decrease, does fatigue increase?

In this study, levels of a micronutrient called carnitine will also be measured. Carnitine is important in the process of how muscles make energy to move. We want to know if carnitine decreases during chemotherapy. When carnitine levels are low, does fatigue increase? Knowledge gained in this study will help in developing future treatments for distressing symptoms.

The purpose of this study is to:

1. **Find out how physical performance and fatigue change in children/teens during the first three months of chemotherapy treatment.**
2. **Find out if children/teens who have decreased physical performance experience more fatigue.**
3. **Examine the level of carnitine in the body and see if it changes in relation to fatigue.**

The study will be conducted at Children's Hospitals and Clinics in Minneapolis and St. Paul. It will be conducted by Casey Hooke, RN. This is her dissertation study for obtaining her PhD degree in nursing.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 40 patients will take part in the study.

WHAT IS INVOLVED IN THE STUDY?

The study focuses on the first three months of treatment when the patient is receiving IV chemotherapy.

The patient will be asked to complete study measurements during the first month of treatment and the third month of treatment. All measurements and blood specimens will be collected during routine clinic visits or during hospital admissions.

Fatigue is measured by a questionnaire. Physical performance is measured two ways. One way it is measured is by the 6-minute walk test. The patient is asked to walk continually for 6 minutes. The amount of distance that the person walks is then measured. The patient would walk in the halls of the hospital or clinic. The second way physical performance is measured is by the Timed-Up-and Down-Stairs test. During this measurement, the patient is timed as he or she walks up and down a flight of 14 steps. The person can use the hand-rail. Carnitine is measured by obtaining a ½ teaspoon of blood and measuring it in the laboratory. The blood sample would be obtained when routine labs are being drawn from the patient's central line.

The study measurements can be seen on the table below.

Study Measure	How measured?	How long does this take?	When is it measured?
Fatigue	Questionnaire completed by patient (read to patient less than age 12)	10 minutes	Between day 15 and 29 during month 1 and month 3 of treatment
Carnitine (nutritional substance)	½ tsp of blood	2 minutes	Between day 15 and 29 during month 1 and month 3 of treatment
6 minute walk	Patient walks as far as possible on 1 floor of the hospital for 6 minutes	6 minute	Between day 15 and 29 during month 1 and month 3 of treatment
Timed Up and Down Stairs Test	Patient walks up and down a flight of 14 steps in the hospital	5 minutes	Between day 15 and 29 during month 1 and month 3 of treatment

Information obtained for the study will not be given to the patient or family and will not be part of the patient's medical record. Information about the patient's diagnosis, age, gender, ethnic background, treatment, and blood counts will also be collected for the study.

HOW LONG WILL I BE IN THE STUDY?

Your child will be in the study for approximately three months. The measurements are done between day 15 and 29 during the child's first month of treatment and third month of treatment. Between the measurements, patients will not be asked to do anything related to the study.

WHAT ARE THE RISKS OF THE STUDY?

There are some minimal risks with being in this study. There might be some stress with completing the study measurements. Patients may feel tired during or after the 6 minute walk or the Timed-Up-and Down-Stairs test. Patients could trip or fall during the walking or while going up and down stairs. A spotter will be present during the Timed-Up-and Down-Stairs test. Patients will be given time to rest between study measurements.

The two blood samples will be drawn during routine lab draws. The removal of the total amount (1 teaspoon) of blood is of minimal risk to the patient.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There is no direct benefit for patients who take part in this study. We hope the information learned in this study about fatigue and physical performance during chemotherapy will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not have your child take part in the study.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information might be disclosed if required by law.

Each patient will be given an ID number. Only the patient's ID number will be placed on study forms. Information about the patient's age, diagnosis, gender, ethnic background and chemotherapy treatment, and blood counts will also be collected on a data form.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:
Faculty at the University of Minnesota who are part of the researcher's dissertation committee
Children's Hospitals and Clinics Institutional Review Board
University of Minnesota Institutional Review Board

WHAT ARE THE COSTS?

There are no costs to you for being in this research study.

WHAT HAPPENS IN THE EVENT OF AN INJURY DURING THIS STUDY?

In the event that this research activity results in an injury, please contact the researcher, Casey Hooke, RN, at 612-813-6972. Treatment will be available, including first aid,

emergency treatment and follow-up care as needed. Payment for any such treatment must be provided by you or your third party payer, if any (such as health insurance, Medicare, etc.). By signing this Consent Form, you/your child are not waiving any rights that you otherwise may have. In the event that your child is not covered by insurance please call the Family Relations Liaison at 612-813-7393, who will help you with your/your child's rights.

WILL I BE COMPENSATED FOR BEING IN THE STUDY?

Patients will be given a $10 Target gift card after each set of the two study measurements. If the patient does both measurements, he or she would receive a total of $20 in gift cards. This is to thank them for their time and effort in participating in the study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You or your child may decide not to take part in the study. If your child starts the study, you or your child can decide to stop any time. Patients can stop during a study measurement or between study measurements.

Being or not being in the study will not change your child's medical treatment in anyway. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

You will be told about new information that might affect your child's health, welfare or your willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact Casey Hooke, RN, at 612-813-6972.

If you have any questions about your/your child's rights as a research participant or any complaints that you feel you cannot discuss with the investigators, you may call Elizabeth Kipp Campbell, Ph.D., Children's Hospitals and Clinics IRB Administrator at (651) 220-5818.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Family Relations Liaison

- **in St Paul at (651) 220-6888**
- **in Minneapolis at (612) 813-7393**

WHERE CAN I GET MORE INFORMATION?

The *Oncology Family Notebook* has information about specific cancers, tests, treatment side effects and managing these side effects, adjusting to cancer and resources.

The *Family Resource Center* at the hospital can assist you in searching for more information.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

You will get a copy of this form.

SIGNATURE

The nurse researcher, Casey Hooke, RN, may contact me in the future to ask me to (allow my child to) take part in another study about fatigue and cancer treatment.

YES NO _____
initials and date

I agree to take part in this study.

Participant_____Date _____

Patients 18 years of age or older are required to sign. Patients less than 18 may choose to sign or this may be left blank. Assent is required for patient's ages 7 - 17 – please see separate assent form.

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Researcher_____Date _____

Children's Hospitals & Clinics of Minnesota IRB# 0603-014 IRB Approved: 3/14/2007
University of Minnesota IRB # 0602M82646 IRB Approved: 2/22/2007

CONSENT FORM

Parent Form

Fatigue, Physical Performance, and Carnitine Plasma Levels in Children with Cancer

You are invited to participate in a research study about fatigue during cancer treatment. You were selected as a possible participant because you have recently been told that your child has cancer and your child is receiving IV chemotherapy to treat it. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Casey Hooke, RN. This is her dissertation study for obtaining her PhD degree in nursing at the University of Minnesota. It is funded by the Pine Tree Apple Tennis Classic Foundation.

Study Purpose
Children and teens with cancer report that fatigue is one of the most distressing symptoms related to cancer treatment. In this study, we want to find out if fatigue increases during the first three months of cancer treatment. The ability to perform physical skills (called physical performance) will also be studied. The researcher wants to find out if there is a relationship between physical performance and the patient's level of fatigue. When physical performance skills decrease, does fatigue increase?

In this study, levels of a micronutrient called carnitine will also be measured. Carnitine is important in the process of how muscles make energy to move. We want to know if carnitine decreases during chemotherapy. When carnitine levels are low, does fatigue increase? Knowledge gained in this study will help in developing future treatments for distressing symptoms.

The purpose of the study is to:

1. Find out how physical performance and fatigue change in children/teens during the first three months of chemotherapy treatment.
2. Find out if children/teens who have decreased physical performance experience more fatigue.
3. Examine the level of a carnitine in the body and see if it changes in relation to fatigue

Study Procedures

If you agree to participate in this study, the patient will be asked to complete study measurements during the first month of treatment and the third month of treatment. All measurements and blood specimens will be collected during routine clinic visits or during hospital admissions.

Fatigue is measured by a questionnaire. Physical performance is measured two ways. One way it is measured is by the 6-minute walk test. The patient is asked to walk continually for 6 minutes. The amount of distance that the person walks in then measured. The patient would walk in the

halls of the hospital or clinic. The second way physical performance is measured is by the Timed-Up-and Down-Stairs test. During this measurement, the patient is timed as he or she walks up and down a flight of 14 steps. The person can use the hand-rail. Carnitine is measured by obtaining a ½ teaspoon of blood and measuring it in the laboratory. The blood sample would be obtained when routine labs are being drawn from the patient's central line.

The study measurements can be seen on the table below.

Study Measure	How measured?	How long does this take?	When is it measured?
Fatigue	Questionnaire completed by patient (read to patient less than age 12)	10 minutes	Between day 15 and 29 during month 1 and month 3 of treatment
Carnitine (nutritional substance)	½ tsp of blood	2 minutes	Between day 15 and 29 during month 1 and month 3 of treatment
6 minute walk	Patient walks as far as possible on 1 floor of the hospital for 6 minutes	6 minute	Between day 15 and 29 during month 1 and month 3 of treatment
Timed Up and Down Stairs Test	Patient walks up and down a flight of 14 steps in the hospital	5 minutes	Between day 15 and 29 during month 1 and month 3 of treatment

Information obtained for the study will not be given to the patient or family and will not be part of the patient's medical record. Information about the patient's diagnosis, age, gender, ethnic background, treatment, and blood counts will also be collected for the study.

Risks of Study Participation

The study has the following risks. There might be some stress with completing the study measurements. Patients may feel tired during or after the 6 minute walk or the Timed-Up-and Down-Stairs test. Patients could trip or fall during the walking or while going up and down stairs. A spotter will be present during the Timed-Up-and Down-Stairs test. Patients will be given time to rest between study measurements.

The two blood samples will be drawn during routine lab draws. The removal of the total amount (1 teaspoon) of blood is of minimal risk to the patient.

Benefits of Study Participation

There is no direct benefit for patients who take part in this study. We hope the information learned in this study about fatigue and physical performance during chemotherapy will benefit other patients in the future.

Alternatives to Study Participation

You may choose to not have your child take part in the study.

Study Costs/Compensation

There are no costs to you or your child for being in this research study. Patients will be given a $10 Target gift card after each set of the two study measurements. If the patient does both measurements, he or she would receive a total of $20 in gift cards. This is to thank them for their time and effort in participating in the study.

Research Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that your child has suffered a research related injury, let the researcher, Casey Hooke, RN, know right away at 612-813-6972.

Confidentiality

The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify your child as a subject. Your child's record for the study may, however, be reviewed by:

- Faculty at the University of Minnesota who are part of the researcher's dissertation committee
- Children's Hospitals and Clinics Institutional Review Board (another place that the study is being conducted)
- Departments at the University with appropriate regulatory oversight.

To these extents, confidentiality is not absolute.

Protected Health Information (PHI)

Your child's PHI created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

Voluntary Nature of the Study

Participation in this study is voluntary. Your decision whether or not to participate in this study will not affect you or your child's current or future relations with the University or with the Pediatric Oncology Department at the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

Contacts and Questions

The researcher conducting this study is *Casey Hooke, RN*. You may ask any questions you have now, or if you have questions later, **you are encouraged to** contact her at 612-813-6972. You may also contact her advisor, Ann Garwick, RN, PhD at 612-624-1141.

If you have any questions or concerns regarding the study and would like to talk to someone other than the researcher(s), **you are encouraged to** contact the Fairview Research Helpline at telephone number 612-672-7692 or toll free at 866-508-6961. You may also contact this office in writing or in person at University of Minnesota Medical Center, Fairview-Riverside Campus, #815 Professional Building, 2450 Riverside Avenue, Minneapolis, MN 55454.

You will be given a copy of this form to keep for your records.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature of Parent/Guardian_____

Date_____

Signature of Investigator_____

Date_____

IRB Code # 0602M82646
Version Date: 1/24/07

Appendix F

Assent Forms

Children's Hospitals and Clinics

Assent Form for Child/Teenager (Ages 7– 17)

Fatigue, Physical Performance, and Carnitine Plasma Levels in Children with Cancer

You are being asked to be in a study. The study is being done by Casey Hooke, RN. She is a nurse researcher.

We want to learn more about how kids feel when they are getting IV chemotherapy. We want to know if they feel tired. The feeling of being tired is called fatigue. We also want to know how they do in physical activities like walking and going up and down stairs. We are trying to learn how a substance in your blood might be related to fatigue.

If you decide you want to take part in this study, we would ask you to do the things in the list below. We would do them once during your first month of treatment. We would repeat them once again during your third month of treatment. Each time takes about 30 minutes. Here is what you would be asked to do on this study:

1. Answer questions about fatigue or feeling tired. This takes about 10 minutes.
2. Allow an extra ½ teaspoon of blood to be drawn. This would be done during routine lab draws from your portacath or hickman catheter.
3. Walk as far as you can for 6 minutes. The research person will show you where to walk in the hall of the hospital or the clinic. We would measure how far you walked in 6 minutes.
4. Climb up and down a flight of 14 steps. This test would be done in the stairs in the hospital or clinic. We would measure how long it takes to go up and down a flight of stairs safely. You could use the handrail and a spotter will be close to you also.

The study lasts for three months. You can decide to take part in the study and then change your mind anytime. You could decide to stop the study during a measurement. You could decide to stop between measurements or between month 1 and 3. That would be ok. No one would be mad at you.

Each person on the study is assigned a number. Your name would not appear on any study forms. Your answers to questions would only be known by the researcher doing the study. If the study results are shared with others, only group information would be given. We hope this study helps us learn more about how patients feel when they are getting chemotherapy.

Patients who take part in the study and complete the study activities will be given a $10 Target® gift card. One card would be given after month 1 activities. Another card would be given after the month 3 activities. These gift cards are given to thank the patient for their time and their effort.

If you do not want to be in this research project, you do not have to sign. No one will be mad at you if you say no.

_____ _____

Assent by child/teenager *Date*

To the professional:

If the child *does not* sign the form but you believe the child has *actively assented*, please document on this form. State the specific behaviors *(child shook head yes, child said "OK" after I described procedure, etc.).*

_____

_____

_____

_____

_____ _____

Researcher *Date*

Children's Hospitals & Clinics of Minnesota IRB# 0603-014 IRB Approved: 3/14/2007
University of Minnesota IRB # 0602M82646 IRB Approved: 2/22/2007

Assent Form for Child/Teenager (Ages 8– 17)

Fatigue, Physical Performance, and Carnitine Plasma Levels in Children with Cancer

You are being asked to be in a study. The study is being done by Casey Hooke, RN. She is a nurse researcher.

We want to learn more about how kids feel when they are getting IV chemotherapy. We want to know if they feel tired. The feeling of being tired is called fatigue. We also want to know how they do in physical activities like walking and going up and down stairs. We are trying to learn how a substance in your blood might be related to fatigue.

If you decide you want to take part in this study, we would ask you to do the things in the list below. We would do them once during your first month of treatment. We would repeat them once again during your third month of treatment. Each time takes about 30 minutes. Here is what you would be asked to do on this study:

1. Answer questions about fatigue or feeling tired. This takes about 10 minutes.
2. Allow an extra ½ teaspoon of blood to be drawn. This would be done during routine lab draws from your portacath or hickman catheter.
3. Walk as far as you can for 6 minutes. The research person will show you where to walk in the hall of the hospital or the clinic. We would measure how far you walked in 6 minutes.
4. Climb up and down a flight of 14 steps. This test would be done in the stairs in the hospital or clinic. We would measure how long it takes to go up and down a flight of stairs safely. You could use the handrail and a spotter will be close to you also.

The study lasts for three months. You can decide to take part in the study and then change your mind anytime. You could decide to stop the study during a measurement. You could decide to stop between measurements or between month 1 and 3. That would be ok. No one would be mad at you.

We hope this study helps us learn more about how patients feel when they are getting chemotherapy.

Patients who take part in the study and complete the study activities will be given a $10 Target® gift card. One card would be given after month 1 activities. Another card would be given after the month 3 activities. These gift cards are given to thank the patient for their time and their effort.

If you do not want to be in this research project, you do not have to sign. No one will be mad at you if you say no.

Signature of participant _____

Signature of the person explaining the study _____

Date _____

IRB Code # 0602M82646
Version Date: 1/24/07

Appendix G

IRB Approval Letters

Children's
HOSPITALS AND CLINICS
of Minnesota

345 North Smith Avenue
St. Paul, Minnesota 55102

(651) 220-6000
www.childrensmn.org

To: Mary C. Hooke, R.N.
Hematology / Oncology

From: Elizabeth Kipp Campbell, Ph.D.
IRB Administrator

Date: April 11, 2006

Subject: **IRB #0603-014 Fatigue, Physical Performance, and Carnitine Levels in Children and Adolescents Receiving Chemotherapy**

Thank you for your recent submission of the revised consent form and the HIPAA form for the above-referenced study. You have met the stipulations of the IRB, and the above-referenced study is **APPROVED** (as of the above date). This approval is contingent on our review of any changes (now or in the future) which other IRBs stipulate.

The Board requested progress reports on this protocol every 12 months. The approval for this study will expire **March 21, 2007**. Please be reminded that you are required to inform this office of any changes, additional risks, adverse events (including patient deaths), unanticipated problems, or termination of this research protocol in the interim.

With regard to HIPAA, your Authorization form has been reviewed and approved.

As noted on the attached form, departments that may be most directly affected by this study are being notified of its approval. We wish you success with your research.

Encl.

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Research Subjects' Protection Programs
Institutional Review Board: Human Subjects Committee (IRB)
Institutional Animal Care and Use Committee (IACUC)

Mayo Mail Code 820
D-528 Mayo Memorial Building
420 Delaware Street S.E.
Minneapolis, MN 55455

612-626-5654
Fax: 612-626-6061
irb@umn.edu
iacuc@umn.edu
http://www.research.umn.edu/subjects.htm

04/26/2006

Mary C Hooke
15803 Quebec Circle
Eden Prairie, MN 55346

RE: "Fatigue, Physical Performance, & Carnitine Plasma Levels in Children and Adolescents Receiving Chemotherapy"
IRB Code Number: **0602M82646**

Dear Ms. Hooke:

The Institutional Review Board (IRB) received your response to its stipulations. Since this information satisfies the federal criteria for approval at 45CFR46.111 and the requirements set by the IRB, final approval for the project (protocol received date February 27, 2006) is noted in our files. Upon receipt of this letter, you may begin your research.

IRB approval of this study includes the parent consent form, research consent form, and the assent form all received on April 18.

The HIPAA Authorization received April 18, 2006, has been approved.

The IRB would like to stress that subjects who go through the consent process are considered enrolled participants and are counted toward the total number of subjects, even if they have no further participation in the study. Please keep this in mind when calculating the number of subjects you request. This study is currently approved for 60 subjects. If you desire an increase in the number of approved subjects, you will need to make a formal request to the IRB.

For your records and for grant certification purposes, the approval date for the referenced project is March 23, 2006, and the Assurance of Compliance number is FWA00000312 (Fairview Health Systems Research FWA00000325, Gillette Childrens Specialty Healthcare FWA00004003). Research projects are subject to continuing review and renewal; approval will expire one year from that date. You will receive a report form two months before the expiration date. If you would like us to send certification of approval to a funding agency, please tell us the name and address of your contact person at the agency.

As Principal Investigator of this project, you are required by federal regulations to inform the IRB of any proposed changes in your research that will affect human subjects. Changes should not be initiated until written IRB approval is received. Unanticipated problems or serious unexpected adverse events should be reported to the IRB as they occur.

The IRB wishes you success with this research. If you have questions, please call the IRB office at (612) 626-5654.

If you have questions concerning this particular letter, please call (612) 626-2890 for Andrew.

Sincerely,

Felicia Mroczkowski, CIP
Research Compliance Supervisor
FM/aa
CC: Ann Garwick