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Adolescents receiving chemotherapy sleep, symptoms, and quality of life

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Adolescents Receiving Chemotherapy:

Sleep, Symptoms, and Quality of Life

By

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ABSTRACT

TITLE: Adolescents Receiving Chemotherapy: Sleep, Symptoms, and Quality of Life

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Purpose: This dissertation describes nocturnal sleep-wake activity of adolescents receiving chemotherapy and explores relationships between sleep, disease and treatment-related symptoms, and quality of life. **Sample:** 51 adolescents (ages 10 to 19 years) with a primary, secondary, or relapse of cancer (median time since diagnosis of four months) were enrolled. All participants lived and were treated in the Pacific Northwest. **Methods:** Nocturnal sleep-wake activity was assessed using objective (i.e. actigraphy) and subjective (i.e. 7- Day Sleep Diary, Adolescent Sleep Wake Scale, Adolescent Sleep Hygiene Scale measures). Symptoms and quality of life were assessed using the Memorial Symptom Assessment Scale (MSAS 7-12) and Pediatric Quality of Life Inventory Version 4.0 Teen Report (PedsQL), respectively. **Major Findings:** Mean sleep start time was 23:11 (*SD* = 1:05) and sleep end time was 8:52 (*SD* = 1:10). The mean sleep duration was 581 minutes (*SD* = 67), mean total sleep time (TST) was 500 minutes (*SD* = 60), mean wake after sleep onset (WASO) was 80 minutes (*SD* = 29), and mean sleep efficiency was 82% (*SD* = 5%). The mean number of symptoms was 4 out of 10. The most prevalent symptoms were tiredness (67%), nausea (51%), pain (48%), and changes in appetite (48%); and the most distressing symptoms were worry (83%), pain (70%), and nausea (62%). The mean PedsQL total score was 60 (*SD* = 19) with physical health (*M* = 48, *SD* = 29) having the lowest subscale score. There were no significant correlations between sleep measures (i.e. TST, WASO) and symptoms or sleep measures and quality of life. There was, however, a significant relationship between symptoms

after treatment and quality of life (r = -.375, p = .019). **Limitations:** The study was limited by the cross-sectional design (i.e., the broad approaches to age and cancer and the potential for a response-shift). **Implications:** A primary sleep disturbance in this population may be fragmented sleep rather than the usual truncated sleep period seen in healthy adolescents. Actigraphy was useful in identifying the nature of the sleep disturbance in this population.

ADOLESCENTS RECEIVING CHEMOTHERAPY: SLEEP, SYMPTOMS, AND QUALITY OF LIFE

CHAPTER 1

Introduction

Approximately 9,000 adolescents 10 to19 years are diagnosed with cancer each year in the United States (Ries et al., 2007). Dramatic increases in survival have transformed childhood cancer from an inevitably, fatal disease to a chronic, life-threatening illness (Eiser, 1994). The cost of improved survival however, is aggressive, intense, and lengthy chemotherapy protocols often in combination with surgery, and/or radiation. Chemotherapy causes debilitating physical and social-emotional symptoms which have the potential to disrupt developmental processes and negatively influence quality of life. As such, cancer is a significant challenge for children and their families as they navigate normal development towards adulthood. As more children and adolescents survive, success is no longer measured solely in survival, but more in terms of the total morbidity experienced by the child/adolescent (Eiser, 1994). Advances in symptom management are necessary to minimize the interference of symptoms on children/adolescents' daily lives and improve their quality of life during chemotherapy treatment and beyond.

Adolescents, defined as persons 10 to19 years of age, are distinctly different from adults and younger children with cancer, though they share similarities with both groups. These distinctions, including developmental stage and common cancers, make adolescents with cancer a unique population; a population that is underserved. The most common cancers in adolescents are leukemia, lymphomas, germ cell tumors, central

nervous system (CNS) tumors, malignant bone tumors, soft tissue sarcomas, thyroid cancer, and malignant melanoma. For many of these cancers survival rates are significantly lower for adolescents ages 10 to 19 years than for younger children. With ALL, for example, the survival rate is highest for toddlers (80%), and significantly lower for adolescents 10 to 14 years (65%) and adolescents 15 to19 years (51%). Adolescents are considered high risk for treatment failure by age alone, and thus are treated with more intensive chemotherapy protocols (Smith, Gurney, & Ries, 1999; Westlake & Bertolone, 2002).

Cancer diagnosis and treatment present unique challenges for adolescents who are experiencing a period of rapid physical growth, sexual and emotional maturation, an expanding sense of personal identity, increasing independence and autonomy from parents, and exploring future possibilities. Disease and treatment-related symptoms are reported as the most distressing aspect of cancer and create the most challenging obstacles for adolescents in maintaining normal activities and achieving developmental goals (Docherty, Sandelowski, & Preisser, 2006; Enskar, Carlsson, Golsater, & Hamrin, 1997; Woodgate & Degner, 2003; Woodgate, Degner, & Yanofsky, 2003). Symptoms are associated with increased dependence on parents, missed school, and inability to participate in extracurricular and other social activities (Gibson, Mulhall et al., 2005). Research, however, indicates only a small percentage of adolescents with cancer actually experience significant psychosocial disturbances (Eiser, 1994). Therefore, it is more appropriate to view adolescents with cancer as normal adolescents coping with extraordinary circumstances. As such, the emphasis of interventions has shifted from

deficit-centered approaches to approaches focused on coping and adjustment (Eiser, 1994).

Adolescents receiving chemotherapy experience multiple acute symptoms that vary in frequency, intensity, and distress across the treatment trajectory. The most prevalent symptoms are pain, fatigue, sleep disturbance, nausea and vomiting, sadness, and worry (Collins et al., 2000). Sleep disturbance, though commonly reported and clinically relevant, has received little attention in adolescents with cancer. A review of the state of the science on sleep/wake disturbances in people with cancer emphasized the need for research on sleep issues, and noted the scarcity of studies of sleep in children and adolescents with cancer (Berger et al., 2005). While the literature on sleep disturbances in adults with cancer is growing, the experiences of children/adolescents likely are different.

Sleep is an active process regulated by behavioral, neuroendocrine, and central nervous system factors. Sleep itself is the primary brain activity of developing humans and accounts for at least 40% of children/adolescents' days (Dahl, 1996). Sleep affects every aspect of children/adolescents' physical, emotional, cognitive, and social development, and therefore needs to be part of the equation in adolescent/child research. Contrary to the beliefs of the general public, there is a biological need for more sleep, not less sleep, during pubertal development (Dornbusch, 2002). Sleep disturbances can exacerbate virtually all medical, psychiatric, developmental, and psychosocial problems in adolescents and children (Mindell & Owens, 2003). Although the exact functions of sleep are unclear, it is clearly important for health and well-being, and may be even more important for people with acute and chronic illnesses such as cancer. A description of

nocturnal sleep patterns in adolescents receiving chemotherapy was a necessary first step in understanding sleep disturbances in this population.

Most symptom research in children and adolescents with cancer has focused on single symptoms, primarily pain, nausea and vomiting, nutrition, mucositis, and fatigue (Hockenberry, 2004). While research on single symptoms provides valuable information, symptoms are rarely experienced in isolation. Research on single symptoms, therefore, is likely to overlook interactions between symptoms and contributions of single symptoms to symptom clusters (Dodd, Miaskowski, & Lee, 2004). This dissertation focused on nocturnal sleep patterns and the symptom of sleep disturbance, in the context of adolescent development, cancer, chemotherapy, and other treatment-related symptoms. In addition to providing a description of nocturnal sleep patterns and sleep disturbance in adolescents receiving chemotherapy, this study explored potential interactions between sleep disturbances and other symptoms, and potential contributions of sleep disturbances to the overall symptom experience and quality of life. This study was conducted under the assumption that sleep disturbances are likely to exacerbate other disease and treatment-related symptoms and negatively affecting quality of life. Exacerbation of other symptoms may originate from an underlying shared mechanism between sleep and concurrent symptoms, or alternatively, sleep disturbances may make coping with and managing symptoms more difficult. Hence, interventions targeted at improving sleep, may also improve symptoms and quality of life. This project was innovative because it focused on sleep and explored multiple symptoms in adolescents receiving chemotherapy within the context of adolescent development. Additionally, this study focused primarily on adolescents in outpatient settings.

The long-term goal of this research is to support the continuing development and improve the quality of life of adolescents receiving chemotherapy by focusing on symptom management. The primary purpose of this study was to describe the nocturnal sleep-wake activity of adolescents receiving chemotherapy for cancer, and secondarily to explore the relationships between sleep, treatment-related symptoms, and quality of life.

Specific Aims

Primary Aim

- Describe the nocturnal sleep-wake activity of adolescents ages 10 to 19 years receiving chemotherapy using multiple sources of data including actigraphy, a baseline sleep questionnaire, diary, Adolescent Sleep-Wake Scale (ASWS), Adolescent Sleep Hygiene Scale (ASHS), and a brief interview.

Secondary Aims

The purpose of the secondary aims was to explore relationships between variables and generate effect size estimates for future research.

- Explore the relationship between nocturnal sleep-wake activity and treatment-related symptoms in adolescents receiving chemotherapy using the Memorial Symptom Assessment Scale (MSAS) 7-12.
- Explore the relationship between nocturnal sleep-wake activity and quality of life of adolescents using the PedsQL 4.0 Generic Core.

Sleep disturbance is a distressing problem for adolescents receiving chemotherapy (Gibson, Mulhall et al., 2005). Sleep disturbance is often experienced amidst multiple other symptoms (Gibson, Garnett, Richardson, Edwards, & Sepion, 2005), which negatively affect quality of life. The causes of sleep disturbance in adolescents with

cancer are unclear, but likely result from a combination of age, pubertal development, chemotherapy and other aspects of the cancer experience. A prospective, cross-sectional study was needed to understand the variability of sleep disturbances in adolescents receiving chemotherapy and identify important variables for future research.

CHAPTER 2

Review of Literature

Conceptual Framework

This study is based on modifications of The Model for the Study of Children's Sleep proposed by LeBourgeois (2006). The background section was organized around the major components of the model which include Quality of Life, Adolescence, Cancer and Treatment (e.g. chemotherapy, radiation, and surgery), Sleep Hygiene Behaviors, and the Five Behavioral Dimensions of Sleep (i.e. Going to Bed, Falling Asleep, Maintaining Sleep, Reinitiating Sleep, and Returning to Wakefulness). Quality of life is used as a broad indicator of the effects of cancer treatment. Assessments of quality of life can be used to identify particularly demanding treatment points that can be targeted for interventions to reduce these treatment demands (Hinds, Burghen, Haase, & Phillips, 2006). Cancer diagnosis and treatment during adolescence present unique challenges for individuals who are already experiencing rapid physical, sexual, and emotional changes. Symptoms prevent and/or interfere with adolescents' normal developmental activities and negatively affect quality of life. Behavioral dimensions of sleep are important because they reflect the influences of behavioral phenomena and intrinsic biological processes on sleep-wake patterns.

The original Model for the Study of Children's Sleep (MSCS) (LeBourgeois, 2006) was developed to focus on sleep in preschool and early-school age children, emphasize the significance of development on sleep hygiene (i.e. behaviors that facilitate and inhibit sleep), and present five behavioral dimensions of sleep. The original model had three domains. The outermost oval contained four contextual variables: (a) Physical

Environment, (b) Biological-Medical Health Status, (c) Familial Functioning, and (d) Psychosocial Functioning. The middle oval contained Caretaker Behaviors which are assumed to facilitate or inhibit sleep, and the innermost oval contained the Five Behavioral Dimensions of Sleep: (a) Going to Bed, (b) Falling Asleep, (c) Maintaining Sleep, (d) Reinitiating Sleep, and (e) Returning to Wakefulness. The model was multidirectional and assumed that each domain influenced, and was influenced by other domains (LeBourgeois, 2006).

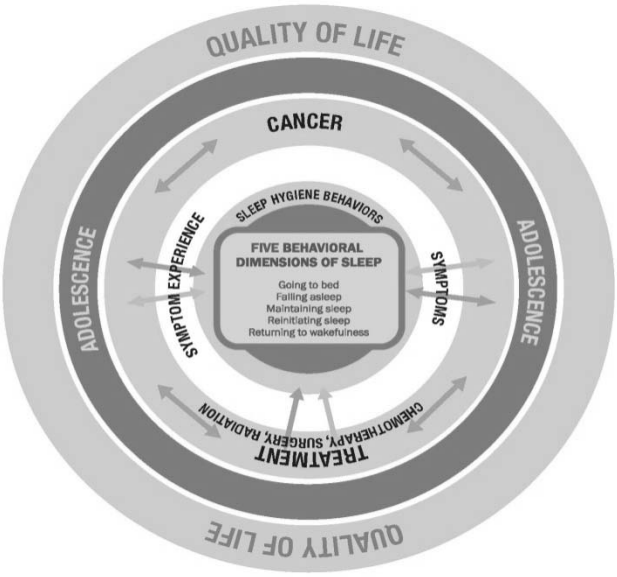

Figure 1. The Modified Model for the Study of Sleep in Adolescents with Cancer.

The original model was modified to focus on contexts relevant to adolescents with cancer, while retaining the emphasis on development and sleep behaviors. The modified Model for the Study of Children's Sleep will be referred to as the Model for the Study of Sleep in Adolescents with Cancer (see Figure 1). The outermost oval represents Quality of Life, the second oval Adolescent Development, the third oval Cancer and Treatment (e.g. chemotherapy, radiation, and surgery), the fourth oval Symptoms and Symptom Experience, and the fifth oval Sleep Hygiene Behaviors. The center square represents the Five Behavioral Dimensions of Sleep (i.e. Going to Bed, Falling Asleep, Maintaining Sleep, Reinitiating Sleep, and Returning to Wakefulness). Sleep Hygiene Behaviors (i.e. behaviors that facilitate or inhibit sleep) replaced Caretaker Behaviors in

the original model because sleep behaviors generally become less regulated by parents during adolescence (LeBourgeois, Giannotti, Cortesi, Wolfson, & Harsh, 2004). The modified model is also multidirectional and assumes that all of the variables influence and are influenced by the other variables.

Adolescence

Chronological age appears to be a clear feature of adolescence, yet little agreement exists on a definition among theorists, professional associations, federal and international agencies. Each has a different basis for their definition including age, transition, and puberty. The World Health Organization defines adolescence as ages 10 to 19 years (Lewis, Fallon, van Dongen-Melman, & Barr, 2002). The American Academy of Pediatrics and the National Institutes of Health consider children as persons less than 21 years of age, while the U.S. Food and Drug Administration defines children as persons 15 years and younger. Some professionals (e.g. physicians, epidemiologists) categorize children/adolescents in five-year intervals (e.g. 10-14 years, 15-19 years), others (e.g. psychologists, sociologists) define it according to completion of certain developmental processes and/or tasks, and still others avoid a definition altogether (Lewis et al., 2002). Developmental theorists often view adolescence as a transitional period between childhood and adulthood which can be divided into early (10 to13 years), middle (14 to16 years), and late (17 to 21 years) adolescence (McGrath & Pisterman, 1991). Puberty, the period of rapid growth and sexual maturation, generally occurs early in adolescence commencing at a mean age of 9 years in girls, 11 years in boys, and peaking at 11.5 years in girls and 13.5 years in boys in the United States. Menses for girls occur later in puberty, at an average age of 12.5 years in the U.S. Other aspects of adolescent

development (e.g. cognitive, identity) continue to expand throughout adolescence (Santrock, 2005). For the purpose of this dissertation, adolescents were defined as persons 10 to 19 years of age, reflecting broadly the biological and psychosocial period of adolescence.

Adolescence and Chronic Illness: A Non-Categorical Approach

Adolescence is a unique period in human development characterized by rapid physical growth, sexual and emotional maturation, an expanding sense of personal identity, increasing independence and autonomy from parents, and exploration of future possibilities (Santrock, 2005). Chronic illness adds additional challenges that include symptoms, medications, surgery, treatment regimens, frequent medical appointments, hospitalizations, school absences, and activity limitations (Woodgate, 1998). Noncategorical approaches to research focus on commonalities, in terms of psychosocial challenges, among illnesses rather than differences. While categorical approaches, which classify children and adolescents with cancer in terms of their specific disease (e.g. leukemia, Hodgkin's lymphoma, bone tumors), are critical for biomedical interventions (Bleyer et al., 2008), other aspects of cancer are more important for understanding the impact of the disease on adolescents. This section provides a foundation for taking a noncategorical approach to studying adolescents with cancer.

Despite considerable and obvious differences among chronic health conditions, commonalities exist in the experiences of individuals and families dealing with a wide array of chronic conditions (E. C. Perrin et al., 1993). Pragmatically, it is a daunting task to study all conditions specifically, especially with the wide array of rare pediatric conditions. This leads to the inclusion of children/adolescents with conditions that are

easy to classify and occur with moderate frequency, and the exclusion of less common conditions that also significantly impact the lives of adolescents/children and their families. Noncategorical approaches assist in identifying commonalities within and variability between diagnostic groups. Rolland (2005) and Stein (1997) both advocate noncategorical approaches for classifying conditions, focusing on the developmental consequences of chronic conditions on individuals and families, rather than the disease itself. For the purposes of this research, Rolland's (2005) work was valuable for understanding noncategorical differences between conditions, or in this case, between cancer diagnoses while Stein's (1997) work was valuable in describing the broad variability within specific cancer diagnoses. Together these two researchers lend support for using a non-categorical rather than disease approach to understanding the experiences of adolescents with cancer.

Rolland (1987) developed a psychosocial typology of illness using the Family Systems-Illness Model. The purpose of the model was to provide a better link between biologic and psychosocial worlds, and to clarify relationships between chronic illness and the family life cycle. The goal of psychosocial typology of illness is to categorize chronic illnesses according to their psychosocial demands on individuals and families across the lifespan. Typologies, or illness trajectories, are classified according to onset, course, outcome, incapacitation, level of uncertainty, and change over time. Onset of illness can be classified as acute or gradual, and the course as progressive, constant, or relapsing/episodic. Outcome describes the extent to which the illness will cause death, or shorten one's lifespan. Incapacitation refers to the degree of physical or mental

impairment, disfigurement, or social stigma caused by the illness. Uncertainty is viewed as a metacharacteristic affecting all dimensions of chronic illness.

Illness trajectories are expected to change over time. The three broad time phases: crisis, chronic, and terminal, are linked by critical transition periods. The crisis phase includes the periods of time before diagnosis when symptoms are present, diagnosis itself, and the initial adjustment period. Key challenges include learning to manage symptoms, adjusting to the hospital environment and disease-related procedures, and establishing relationships with health care providers. The chronic phase primarily involves efforts to maintain a sense of normality despite the illness and heightened uncertainty. The terminal phase involves the time before death, the death itself, and the grief that follows. The crisis, chronic, and terminal phases are linked by critical transition periods where families reevaluate the appropriateness of their life structure in the face of new, illness-related, developmental demands (Rolland, 1987).

Stein (1997) developed a noncategorical conceptual framework and questionnaire for identifying children with chronic conditions to improve program planning and policy. Children, rather than conditions, were classified along a series of continua, understanding that fluidity of these classifications with time, treatment, and progression of the condition. The dimensions of the physical-mental continuum were: duration of illness, age of onset, limitation of age-appropriate activities, visibility, expected survival, mobility, physiologic functioning, communication, course of illness, and uncertainty. Using this physical-mental continuum addresses differences among children within and between specific disease categories (E. C. Perrin et al., 1993). While cancer is a disease category in itself, it is traditionally viewed in terms of specific diagnoses (e.g. leukemia,

bone tumor, brain tumor). Using a non-categorical approach to studying cancer in adolescents provides insight to the similarities and differences between adolescents with different diagnoses (e.g. leukemia and bone tumors), but also recognizes the variability within each diagnosis.

Cancer

Differences in Adolescent Cancers

Differences between cancers diagnosed in children/adolescents and those diagnosed in adults are significant because they affect treatment, disease and treatment-related symptom profiles, and likely the overall symptom experience of cancer. Cancer in children usually involves tissues of the reticuloendothelial system[1], central nervous system, muscle, or bone. Cancer cell types in children/adolescents under 15 years are usually embryonal in origin, non-epithelial (e.g. leukemia, lymphoma), and result from a genetic predisposition or early exposure to risk factors. Cancers in adults, conversely, generally are carcinomas and epithelial, occur in a specific organ (e.g. breast, lung), and result from environmental and lifestyle factors. Most children/adolescents present with distant metastases or systemic disease, while adult cancers are frequently localized (Ruccione, 2002). As a result of these differences, adult and childhood cancers are classified differently. Childhood cancers are classified by histology and primary site, using the International Classification of Childhood Cancer (ICCC) criteria, whereas adult

[1] The reticuloendothelial system, a part of the immune system, consists of phagocytic cells circulating in the blood or fixed to various connective tissues (e.g. pulmonary alveoli, liver sinusoids, skin, spleen and joints).

cancers are classified solely by primary site using the International Classification of Diseases for Oncology (ICD-O) criteria (Ruccione, 2002).

Despite its relative rarity, childhood cancer is diagnosed in approximately 9228 adolescents ages 10 to 19 years each year in the United States. About 3579 (39%) of these adolescents /children are ages 10 to 14 and 5649 (61%) are ages 15 to 19 years (Ries et al., 2007). Cancers in adolescents and young adults differ from older adults and younger children. Adolescents and young adults (AYA) are defined roughly by the National Cancer Institute, as persons 15 to 29 years. Therefore this dissertation does not pertain to the entire AYA group, but rather adolescents 15 to 19 years and younger adolescents ages 10 to 14 years.

Cancers common in young children (e.g. neuroblastoma, Wilms, retinoblastoma), and adults (e.g. carcinomas of the digestive and genitourinary tracts), are rarely seen in adolescents (Bleyer, 2002). Whereas non-epithelial cancers predominate in children, and epithelial cancers predominate in adults, they occur with equal incidence in older adolescents. The shift from a predominance of non-epithelial cancers to a predominance of epithelial cancers proceeds through the decades of adolescence and young adulthood (Wu et al., 2005). Cancers in adolescents and young adults, therefore, are not classified accurately by histology or primary site alone (Bleyer, 2002). Older adolescents (15 to 19 years) have not experienced the dramatic improvements in survival seen in younger children and older adults (Bleyer et al., 2008). Advances in cancer survival have been achieved through an integrated understanding of tumor biology and host biology, and the state of knowledge related to adolescents has lagged behind other age groups. Adolescent treatment has risen largely from treatments administered to children and older adults

without a true appreciation for the possibility of important physiological and pharmacological differences in adolescents (Bleyer et al., 2008). A combination of factors likely contribute to decreased survival among adolescents and young adults (AYA) including limited access to state-of-the-art therapy, lower participation in clinical trials, unfavorable tumor biology, variations in response to therapy, and differences in supportive care resources (Bleyer, Budd, & Montello, 2005).

Clinical trial participation is the single factor most highly correlated with outcome deficits (Bleyer et al., 2005). Dramatic improvements in pediatric cancer survival have occurred since the development of national cooperative groups, the Children's Oncology Group (COG) being the current iteration. Most pediatric cancer centers in the US are part of COG. These clinical trials provide consistent, state-of-the-art therapies to children and adolescents using aggressive treatment plans with almost universal curative intent (Pollock, 2007). While 90% of children less than 15 years are treated at COG institutions and thus have access to clinical trials, only 20 to 35% of those 15 years and older are treated in such institutions; the remainder are treated at adult centers and therefore excluded from pediatric clinical trials (Bleyer et al., 2005).

Common Cancers and Symptoms in Adolescents

Childhood cancer statistics are reported for age groups spanning five years, and thus adolescents are represented in two age groups: 10 to 14 years and 15 to 19 years. The most common cancers in adolescents (incidence rates 10 to 14 years and 15 to 19 years respectively) are central nervous system (CNS) tumors (21%/6%), leukemia (15%/ 14%), non-Hodgkin's lymphoma (9%/3%), bone and joint tumors (10%/6%), and

Hodgkin disease (9%/14%). Germ cell tumors, malignant melanoma, and thyroid cancer become more prevalent in adolescents 17 to 19 years (Ries et al., 2007).

Chemotherapy

Dramatic improvements in childhood/adolescent cancer survival are attributed primarily to advancements in chemotherapy. Chemotherapy is used as the primary treatment for some cancers (e.g. ALL, lymphomas), and as an adjuvant treatment (i.e. secondary to surgery/radiation) for others. Indeed, before the use of adjuvant chemotherapy, 60-95% of children with solid tumors relapsed at metastatic sites (Balis, Holcenberg, & Blaney, 2002). Understanding the basic principles of chemotherapy helps explain the often intense, unrelenting nature of symptoms and extensive monitoring experienced during cancer treatment.

Basic Principles of Chemotherapy

Chemotherapy exploits the differences between normal cells and cancer cells with the ultimate goal of eradicating cancer cells throughout the body. Cancer cells divide more rapidly than other cells in and thus chemotherapeutic agents are designed to kill rapidly dividing cells. Because children/adolescents are undergoing rapid growth and development, their cancers often are particularly responsive to chemotherapy (Ettinger, Bond, & Sievers, 2002). Unfortunately, most chemotherapeutic agents are non-specific and target macromolecules (e.g. DNA, RNA) or metabolic pathways that are critical to both normal and malignant cells, resulting in numerous undesirable, potentially severe, and toxic effects. Chemotherapeutic agents have narrow therapeutic ranges and thus can produce significant, sometimes life-threatening toxicities even at therapeutic doses (Balis

et al., 2002). The majority of symptoms are caused by cell death induced by chemotherapy (Docherty et al., 2006).

Chemotherapy doses for children/adolescents are calculated according to body surface area (BSA). The basic principles of chemotherapy are combining drugs, dose intensity and frequency. Combining chemotherapeutic agents maximizes cell death by exerting effects at different stages of the cell cycle. To reduce development of drug resistance, chemotherapeutic agents are administered at maximum tolerated doses as frequently as possible, with just enough time between doses for bone marrow recovery to begin (Ettinger et al., 2002). Dose reductions are made when severe toxicities occur with prior treatments, whereas escalations can be made if a full dose is tolerated without anticipated toxicity.

Myelosuppression (e.g. neutropenia, thrombocytopenia, anemia) is the most serious dose-limiting toxicity. The nadir (i.e. low point of blood counts) occurs at different times for different drugs, and so higher doses of all drugs can be given if their nadirs occur at different times. The patient's clinical status and blood counts are monitored closely so that supportive care (e.g. blood transfusions, antibiotics) can be provided and complications prevented. Patients and families are given strict guidelines to follow for preventing infections (e.g. avoid crowds, hand-washing, mouth care), and signs and symptoms that need to be reported immediately to health providers.

Individuals also respond differently to chemotherapy. Individual factors such as age, gender, organ function, and genetic factors, influence the pharmacodynamics and pharmacokinetics of chemotherapeutic drugs. Therefore, two adolescents with the same diagnosis, on the same treatment protocol, may respond quite differently (Ettinger et al.,

2002). Disease, treatment, and individual factors all influence the adolescent's response to treatment and symptom profiles. Managing symptoms is especially important because unrelieved symptoms can lead potentially to treatment refusal, interruption, or cessation of treatment and poorer outcomes (Docherty et al., 2006; Dolgin, Katz, Zeltzer, & Landsverk, 1989; Hinds, Quargnenti, & Wentz, 1992), and adolescents have greater influence on these treatment decisions than children.

Acute treatment will be used to describe the phases of treatment when adolescents are receiving maximal doses of chemotherapeutic drugs with short intervals of recovery prior to subsequent doses. Adolescents generally are experiencing intense symptoms and are monitored closely for toxicities. Generally they are seen in the outpatient clinic one to three days per week for blood tests and/or treatment. On scheduled treatment (i.e. out-patient or in-patient) days, blood is drawn and a clinical assessment performed, to assure adequate bone marrow recovery prior to the next dose. If blood counts are too low or toxicities are evident, treatment and/or hospitalization generally are delayed another week. Patients are also in the clinic for blood and platelet transfusion related to myelosuppression, and administration of chemotherapy. Some drugs take eight hours to infuse while others are given intravenously over five minutes. For these reasons adolescents in acute phases of chemotherapy are seen in the outpatient clinic frequently for varying amounts of time. Maintenance chemotherapy refers primarily to adolescents with Acute Lymphocytic Leukemia (ALL) who receive two to three years of maintenance chemotherapy following their acute treatment. Generally these adolescents are seen monthly for blood counts and chemotherapy. Maintenance chemotherapy generally is

tolerated well, and most adolescents are living a “new normal” with treatment as background rather than a focus.

Symptoms

Although children/adolescents experience both disease and treatment-related symptoms, the majority of symptoms result from treatment (Docherty et al., 2006). Symptom research suggests there may be a common biologic mechanism underlying symptoms across illnesses. One mechanism of particular interest is inflammation and the role of proinflammatory cytokines (Cleeland et al., 2003; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Wood, Nail, Gilster, Winters, & Elsea, 2006). The immune system has two ways of responding to an insult (e.g. any foreign substance). One is a slow and selective process (i.e. producing antibodies) while the other is rapid and generalized. The sickness response or “sickness behavior” caused by proinflammatory cytokines is a result of the rapid and generalized immune response and includes physiological, behavioral, and hormonal changes (Watkins & Maier, 2000). These changes cause non-specific symptoms including fever, fatigue, sleep disturbance, and anorexia (Dantzer & Kelley, 2007).

Despite receiving chemotherapeutic drugs with distinctly different mechanisms, people exhibit a core set of symptoms that may be related to the release of proinflammatory cytokines (Wood, Nail, Gilster et al., 2006). A mouse model has been developed to evaluate associations between chemotherapy; cytokines IL -1 beta, TNF-alpha, and IL-6; and chemotherapy-related symptoms (Wood, Nail, Gilster et al., 2006; Wood, Nail, Perrin et al., 2006). Researchers have hypothesized that activation of the p38 mitogen-activated protein kinase (p38 MAPK) may play a central role in producing

proinflammatory cytokines and inducing sickness behavior because of a common ability of many chemotherapy drugs to activate p38 MAPK. Preliminary evidence supports that etoposide, a chemotherapy drug known to activate p38 MAPK, can induce proinflammatory cytokines and sickness-like behaviors when injected in mice (Wood, Nail, Perrin et al., 2006).

Cell death may also induce the production of proinflammatory cytokines. As discussed in the previous section, chemotherapy causes cell death not only of cancer cells, but also other normal, rapidly dividing cells, particularly those in the gastrointestinal system, hair follicles, and blood cells. The immediate effects of cell death in the gastrointestinal system are nausea, vomiting, mucositis, diarrhea, and constipation; in the hair follicles, alopecia; and in the bone marrow, anemia, neutropenia, and thrombocytopenia (Docherty et al., 2006). Symptoms including pain, fatigue, anorexia, mood alterations, and sleep disturbances indeed may result from proinflammatory cytokines (Wood, Nail, Gilster et al., 2006; Wood, Nail, Perrin et al., 2006).

Symptoms in Children/Adolescents with Cancer

Disease and treatment-related symptoms have multiple dimensions that include frequency, intensity, and distress. While the literature related to symptoms in adults with cancer is burgeoning, it is not necessarily generalizable to adolescents because of significant differences in cancers, treatments, and age. Symptom distress, for adolescents with cancer, has been defined as a report or awareness of any change in function, sensation, or appearance that causes physical discomfort, mental anguish, or suffering (Hinds et al., 1992). Understanding symptom distress is important, as unrelieved symptom distress can interfere not only with developmental goals, but also result in

interruption or cessation of treatment, and poorer outcomes (Docherty et al., 2006; Hinds et al., 1992). This section will focus specifically on the symptom literature related to children/adolescents with cancer.

Collins and colleagues (2000, 2002) have examined the prevalence of symptoms in children/adolescents with cancer. Both studies were cross-sectional, included inpatients and outpatients, and children/adolescents who had received chemotherapy recently (i.e. in the last two to four weeks) and not so recently (≥ 4 months). The first study (Collins et al., 2000) evaluated the prevalence and characteristics (i.e. frequency, intensity, distress) of 30 symptoms in 160 adolescents (10 to 18 years) using an instrument they adapted from the adult version of the Memorial Symptom Assessment Scale (MSAS). The mean (± *SD*) number of symptoms was 12.7 ± 4.9 (range 4 to 26) for inpatients and 6.5 ± 5.7 (range 0 to 28) for outpatients. The most common symptoms (i.e. those with prevalence rates greater than 30%) were lack of energy, pain, drowsiness, nausea, cough, lack of appetite, sadness, nervousness, worrying, irritability, itching and insomnia. Prevalence, however, did not necessarily reflect the frequency, severity, or distress of symptoms. The most distressing symptoms (rated as “quite a bit” or “very much” by ≥ 40% of those who experienced them) were difficulty swallowing, insomnia, mouth sores, “I don’t like myself”, hair loss, skin changes, vomiting, and problems with urination. More than half of the symptoms were reported to have higher frequencies than distress. Inpatients experienced more symptoms than outpatients, and adolescents with solid tumors reported significantly more symptoms than those with hematological or central nervous system malignancies (Collins et al., 2000).

The second study (Collins et al., 2002) evaluated the prevalence and characteristics of 8 symptoms in 149 children (7-12 yrs), testing the reliability and validity of the MSAS (7-12), an instrument modified for younger children from adult and child (10-18 years) versions. The 8 symptoms were selected because they were highly prevalent and reflected both physical and psychological symptoms. The mean number of symptoms was 1.9 (*SD* = 1.6). As with older children and adolescents, the most prevalent symptoms were not necessarily the most distressing. The most prevalent symptoms[2] were tiredness (36%), pain (32%), and trouble sleeping (31%); most frequent[3] were tiredness (64%), pain (56%), and itch (56%); most intense[4] were sadness (60%), pain (56%), and itch (56%), and most distressing[5] were nausea (65%), sadness (50%), and trouble sleeping (39%) (Collins et al., 2002).

Ljungman and colleagues (1999) described the extent and causes of pain for 55 hospitalized children/adolescents (0-19 years) with cancer in treatment for one month after diagnosis to 3 months post treatment. They found that 60% of children/adolescents with cancer had pain at diagnosis and 36% reported pain occurring “often” or “very often.” Treatment-related (49%), procedure-related (38%), and disease-related pain (13%) were considered most problematic. Treatment-related pain was caused by

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[2] Three symptoms with the highest reported prevalence rates.

[3] Frequency of symptom was rated as “a medium amount” or “almost all the time” by the highest percentage of participants who experienced the symptom.

[4] Intensity of symptoms was rated as “medium” or “a lot” by the highest percentage of participants who experienced the symptom.

[5] Distress rated as “quite a bit” or “very much” by the highest percentage of participants who experienced the symptom.

mucositis, limb pain, abdominal and anal pain, dyspepsia, and conjunctivitis. Procedure-related pain was caused by subcutaneous and intramuscular injections, and lumbar punctures (Ljungman, Gordh, Sorensen, & Kreuger, 1999).

Hedstrom, Ljungman, and von Essen (2005) investigated perceptions of distress among 56 adolescents (13 to 19 years) recently diagnosed with cancer. Using structured interviews, they asked adolescents to identify aspects of distress they had experienced since diagnosis. These aspects then were categorized by the investigators as physical concerns, personal changes, feelings of alienation, and disease and treatment-related worries; and adolescents were asked to identify one aspect in each category that had been "most distressing." The "most distressing" aspects of cancer (i.e. with prevalence rates over 50%) were "losing hair" (91%), "missing leisure activities" (84%), "weight loss/gain" (80%), "fatigue" (62%), "worry about missing school", and mucositis (54%). Finally, participants were asked to identify the "overall worst aspect" of cancer since diagnosis. The "overall worst aspects," were "worry about not getting well", mucositis, nausea, pain from procedures/treatment, and "worry about missing school" (Hedstrom, Ljungman, & von Essen, 2005).

Adolescence has a major influence on the cancer experience in adolescents and distinguishes them from adults and younger children (Larouche & Chin-Peuckert, 2006). Intensive treatment regimes, frequent clinic appointments, hospitalizations, and distressing symptoms are all aspects of the cancer experience that can prevent adolescents from participating in normal developmental activities. Indeed symptoms create some of the greatest challenges for adolescents with cancer striving to reach developmental

milestones and maintain normalcy (Enskar et al., 1997; Gibson, Mulhall et al., 2005; Hinds et al., 1999; Larouche & Chin-Peuckert, 2006).

Although the effects of cancer and symptoms during adolescence have not been explored specifically, they can be gleaned by reviewing from the literature from a developmental perspective. Four publications illustrated the impacts of symptoms on adolescent development particularly well. Woodgate (2005) described how symptoms impacted adolescents' perceptions of themselves and their "ways of being in the world". Gibson et al. (2005) described the effects of fatigue on adolescents' well-beings and abilities to maintain normal activities. Larouche and Chin-Peuckert (2006) explored adolescents' perceptions of body image during cancer treatment and the impacts of their perceived body image on daily life, and Hinds et al. (1999) examined the concept of hopefulness in adolescents.

Woodgate described how childhood cancer and the symptom course were interpreted by 39 children (4 to 18 years) and their families. The findings of this study, detailed in several publications, are presented throughout this section. Woodgate (2005) described how symptoms impacted the lives of 15 adolescents (12 to 18 years), their perceptions of themselves and their "ways of being in the world." Life as a klutz was experienced when the body seemed particularly unruly and unreliable due to trembling fingers, weak muscles, and other symptoms. Life as a prisoner was experienced when symptoms made them feel more dependent on others and their condition called for more vigilant monitoring; life as an invalid was experienced when symptoms worsened, making them feel "really sick", and helpless in a world of illness. Life as an alien was experience when the body was distorted due to symptoms such as hair loss, a round and

puffy face, weight gain or loss, and unusual emotional feelings. When feeling alien they only vaguely recognized themselves and felt more conspicuous to others. Life as a zombie described the experience of a "tired body" resulting from fatigue or lingering symptoms and was described as having "no energy for anything." Life as a kid was experienced only when symptoms were minimal, usually between cycles or after treatment was completed (Woodgate, 2005).

Changes in physical appearance are especially difficult for adolescents with cancer, not only in relation to the way they perceive themselves, but also how others (e. g. parents, siblings, friends, strangers) respond to them and their changing bodies (Larouche & Chin-Peuckert, 2006; Woodgate, 2005). Larouche and Chin-Peucket (2006) explored the body image perceptions of 5 adolescents (14 to 17 years) receiving treatment for cancer. Two common perceptions of body image during cancer treatment were: 1) "I don't look normal" and 2) "People look at me." The perception "I don't look normal" was attributed to physical factors such as hair loss, round and puffy faces, implanted ports, scars and pale complexions. All expressed "looking sick" while some actually expressed "looking ugly" as a result of physical changes. Both "looking sick" and "looking ugly" led to feelings of exposure and vulnerability conveyed in the perception "People look at me". Adolescents tried to maintain normality by minimizing physical changes, wearing hats to conceal hair loss, wearing shirts with higher necks to conceal subcutaneous ports, and using enhancers such as trendy clothes, accessories, and make-up to distract from other changes (Larouche & Chin-Peuckert, 2006).

Gibson and colleagues (2005) described the effects of fatigue on well-being and abilities to maintain normal activities in 8 adolescents (16 to19 years). Fatigue and other

symptoms made previously simple activities (e.g. bathing, dressing) challenging, and created undesired dependence on others. Illness, treatment, and symptoms caused frustration related to dependence on others and the dramatic changes in their lives. Many adolescents reported living active lives prior to diagnosis, participating in sports and other physical and social activities that were no longer possible (Gibson, Mulhall et al., 2005).

Hinds and colleagues (1999) examined the concept of hopefulness in 78 adolescents (12 to 19 years) newly diagnosed with cancer over the first six months of treatment as a part of an experimental study related to self-care and coping. Hopefulness was identified as an important feature of their experience (Hinds et al., 1999). Their degree of hopefulness affected their sense of well-being and commitment to treatment, and thus indirectly their biological status and treatment outcome. Specific hopes adolescents identified reflected their developmental stage and highlighted the impact of cancer on their lives. The most frequently identified hopes were “to be healthy again” and “normalcy.” First they hoped to recover from their illness, avoid relapse and recurrence, and then to return to their previous way of living with normal functional abilities. While more than half of their hopes were related to cancer and treatment; other frequently identified hopes related to social and family relationships, academic and career opportunities, and possessions (e.g. car, driver’s, pilots’ license) (Hinds et al., 1999). These hopes are consistent with the developmental goals of adolescence: increased independence, greater reliance on peer relationships, and exploration of future possibilities.

Woodgate and Degner (2003, 2004), in another publication, described the meaning of symptoms for children and adolescents with cancer. Children and parents had expectations about cancer symptoms and their relief, regardless of the child's age or developmental stage. Five major beliefs and expectations about symptoms were: (a) "short-term pain for long-term gain" (b) "you never get used to them" (c) "they all suck" (d) "it sort of helps" and (e) "they are all the same, but all different." Children and their parents believed that suffering was necessary and, therefore, treatment-related symptoms were expected. Regardless of how long they had symptoms, they never got used to them. Symptom management strategies only "sort of helped", and although complete symptom relief was not expected, they were willing to try anything and everything to alleviate their symptoms (Woodgate & Degner, 2003).

Children/adolescents perceived their symptoms as "overall feeling states," with associated meanings rather than individual symptoms or combinations of symptoms. For example, "I have a sick stomach…I feel sick, bad" reflected a physical feeling of being sick, but not "too" sick. Feeling "sick" made the cancer feel real and was a sign the cancer was being beaten. On the other hand, "I feel yucky, crappy, shitty…really sick, really bad" made the prospect of dying more real, and signified things might not be going well. Other feeling states reinforced the suffering, controlling, and uncertain natures of cancer. Each child/adolescent experienced the "overall feeling states" in their own unique way (Woodgate et al., 2003).

Families consistently identified symptoms as "major rough spots" along the illness course, and referred to the child's illness trajectory inclusively as a cancer symptom trajectory. "Passage through transition periods" was a core category which

described how children and families integrated personal meanings about symptoms into their daily lives for the purposes of surviving and maintaining a "sense of spirit." Each transition period was associated with a dominate cancer stage, beliefs about symptoms and their relationship to cancer, and a family's "way of being in the world." For example, "It is just the flu" was associated with the pre-diagnosis period. Symptoms were not associated with the threat of cancer but were viewed within the context of a normal, healthy child and therefore the family's way of being was unchanged. "It hits home", on the other hand, was associated with being "really sick" and usually occurred during intense treatment courses. Symptoms were viewed as an integral part of getting through cancer, and became a guide for understanding the stages of cancer. The family's way of being was focused on the child's needs and fighting the cancer. "It is not so bad…" was associated with periods between treatment courses or during milder courses and symptoms were viewed as a part of a "healthy" child with cancer. The family's way of being was more like their pre-cancer life (Woodgate & Degner, 2004). Woodgate and Degner's research highlights the centrality of symptoms in the cancer experience, and their effects on the quality of life of children/adolescents and their families.

Fatigue has been identified as one of the most prevalent and distressing symptoms of cancer treatment for adolescents/children with cancer and has recently become a focus of research (Gibson, Mulhall et al., 2005; Hinds, Hockenberry, Tong et al., 2007; Whitsett, Gudmundsdottir, Davies, McCarthy, & Friedman, 2008). A definition of cancer-related fatigue was qualitatively induced from focus groups which included 15 adolescents (13 to 18 years). Cancer-related fatigue was defined 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., 2007, p. 609). Causes of fatigue identified by children/adolescents were treatment, pain, low blood counts, being active, sleep changes, and the hospital environment. The qualitative definition of fatigue, induced from the first study, with data from focus groups, was used to develop a quantitative measure of cancer-related fatigue that would show change over time. This instrument, the Fatigue Scale-Adolescent (FS-A), was tested in 64 adolescents (13 to 18 years). Causes of fatigue most frequently endorsed by adolescents were treatment-related and included treatment itself, being hospitalized, and boredom.

Gibson and colleagues (2005) described the phenomenon of fatigue in 8 adolescents (16 to19 years) receiving active cancer treatment. Their definition of fatigue was an "absolute and complete exhaustion experienced after therapy that prevented all normal activity and left them weak, inactive, and unmotivated with aching and painful limbs" (Gibson et al., 2005, p. 654). Adolescents rarely used the word fatigue, but rather, described feelings of being "knackered, knocked out, shattered, or whacked" (Gibson, Mulhall et al., 2005). Fatigue and other symptoms also changed social interactions for adolescents with cancer, often curtailing social activities. Outings with friends required determination and effort, and activities that were previously enjoyable felt more like endurance events. While adolescents sometimes felt the motivation to socialize, they didn't have the physical stamina to do so. At times adolescents pushed themselves to do things that required tremendous effort for fear of being excluded (Gibson, Mulhall et al., 2005).

Whitsett and colleagues (2008) prospectively examined the experience and impact of chemotherapy-related fatigue in 12 children/adolescents (7 to 17 years). All of the children/adolescents reported feeling some degree of fatigue while receiving chemotherapy. When they felt most fatigued they reported multiple related symptoms such as depression, nausea, vomiting, and sleepiness (Whitsett et al., 2008).

Sleep

Sleep-wake patterns emerge from a complex interplay of maturational and developmental processes, behavioral phenomena, and intrinsic biological processes (Carskadon, 2002a). This section will discuss the influences of behavioral phenomena and intrinsic biological processes on sleep-wake patterns and how they relate to the Five Behavioral Dimensions of Sleep (i.e. Going to Bed, Falling Asleep, Maintaining Sleep, Reinitiating Sleeping, and Returning to Wakefulness) in the Modified Model for the Study of Sleep in Adolescents with Cancer. Finally findings related to sleep in healthy adolescents, and sleep in children/adolescents with cancer will be summarized.

Behavioral Phenomena. Alterations in sleep patterns are one of the many changes that occur during adolescence. While physiological processes play a role in adolescent sleep-wake patterns, the rapidly changing psychosocial milieu alters behaviors that influence sleep patterns (Carskadon, 2002a). Adolescents are challenged to balance sleep need with changing academic demands, altered parent-child relationships, new social pressures, part-time employment, extracurricular activities, and sports (Wolfson, 2002).

Sleep hygiene (i.e. behavioral practices that facilitate or inhibit sleep), sleep quality, sleep duration, and daytime alertness, also change during adolescence. Sleep hygiene behaviors that appear to facilitate sleep in adolescents include avoiding late-

afternoon naps, tobacco, alcohol, and caffeine prior to bedtime; following a bedtime routine; avoiding physiologically, cognitively, and emotionally stimulating activities within an hour of bedtime; sleeping alone, sleeping in a comfortable, quiet, toxin-free environment; maintaining a regular sleep schedule (LeBourgeois et al., 2004); and regular exercise (Wolfson, 2002). Adolescents are known to engage in sleep hygiene behaviors that inhibit rather than facilitate sleep such as engaging in stimulating activities including watching television, using the computer, playing video games, talking on the phone, and text-messaging before bed ("Sleep in America Poll," 2006). Additionally sleep schedules become less regulated by parents as children get older and large discrepancies frequently develop between bedtimes and wake-times on weekdays and weekends (Carskadon, Wolfson, Acebo, Tzischinsky, & Seifer, 1998).

A delayed sleep phase is a phrase used to describe sleep patterns that show considerable delays in sleep schedules between weekends and weekdays (i.e. going to bed $\geq$ 2 hours later on weekends) (Carskadon & Acebo, 1993). While a delayed sleep phase is a normal developmental feature of adolescence, it is also a clinical syndrome. This dissertation refers to delayed sleep phase only as a developmental feature of adolescence, and not as a syndrome. The delayed sleep phase observed in adolescents, were thought to result primarily from changes in psychosocial milieu and environmental constraints such as early school start times, work hours, and extracurricular activities. During puberty, however, changes also occur in the intrinsic biological processes regulating sleep (see next section). Later school start times for adolescents has been advocated by sleep specialists and researchers to reduce deficits in adolescent sleep, but these efforts have met with great resistance from educational systems and have not been

implemented on a large scale (Wahlstrom, 2002). Without removing environmental constraints, improving adolescent sleep requires teaching adolescents sleep hygiene measures to counteract daytime sleepiness. Potential countermeasures include: (a) keeping consistent, regular bedtimes and rise times throughout the week to minimize sleep loss, (b) planned naps for 25-45 minutes to improve alertness and performance, (c) a pre-sleep routine to help unwind and relax before going to bed, (d) reducing the amount of light exposure in the evening including light from televisions and computers, (e) avoid alcohol, nicotine, and other substances that disrupt sleep, and (f) regular exercise earlier in the day.

Intrinsic Biological Processes

Two intrinsic biological processes, the homeostatic and circadian processes, are primarily responsible for the biological regulation of sleep-wake activity in humans. Together these processes determine the distribution, patterning, and timing of sleep-wake cycles. By early school age sleep-wake cycles are highly consolidated and sleep requirements decrease gradually from 10 to 11 hours in school-age children, to 9.25 hours in adolescents, and eventually to 8 hours in adults (Mindell & Owens, 2003). The increased sleep needs during pubertal development frequently are not understood (Dornbusch, 2002).

The homeostatic process is driven primarily by prior sleep-wake behavior. Sleep pressure begins building upon awakening, and accumulates throughout the day until the next sleep period ensues. As such, sleep pressure, or tendency to fall asleep, is lowest immediately following a consolidated sleep period, and highest just prior to the next sleep period. If sleep needs are not met, sleep pressure accumulates above the sleep debt and

the tendency to fall asleep occurs earlier, in direct proportion to sleep debt. Sleep debt continues to accumulate until it is recovered (Dement & Vaughn, 1999).

The relative alertness or sleepiness experienced during the day is related not only to the homeostatic process, but also the clock-like circadian process. The circadian process produces predictable peaks and troughs in wakefulness throughout the 24 hour period. Two periods of maximal alertness and two periods of maximal sleepiness occur over the 24 hour period. The two periods of maximal alertness are in the early morning and in the evening, initially assisting waking, and later sustaining alertness despite rising sleep pressure. The circadian process consists of the circadian pacemaker (or biological clock), inputs which affect the pacemaker (i.e. age, environment, behavior, genetics, drugs), and outputs of the pacemaker (i.e. rhythms in physiological variables such as hormone levels, neurobehavioral performance, homeostatic, and ultradian structures of sleep). The circadian pacemaker's defining characteristics include (a) an endogenous rhythmicity that persists independent of intermittent changes in the external environment (e.g. traveling to another time zone), (b) a period close to 24 hours, and (c) the timing relative to the time of day that can be modified or reset by environmental inputs. Exposure to bright light is the most robust resetting agent for the circadian process (Czeisler & Khalsa, 2000).

The homeostatic and circadian processes are highly coupled and operate simultaneously to produce consolidated sleep and wake periods. Sleep pressure begins building upon awakening. The increasing tendency to fall asleep is opposed by the clock-dependent peaks of maximal alertness and troughs of maximal sleepiness. The two periods of maximal sleepiness occur in the late afternoon and middle of the night. The

latter assists in sustaining the sleep period despite falling sleep pressure, and the former helps create a period where some cultures "siesta" and other cultures endure or attempt to counteract the sleepiness with caffeine, exercise, or the like (Jenni & LeBourgeois, 2006) (see Figure 2).

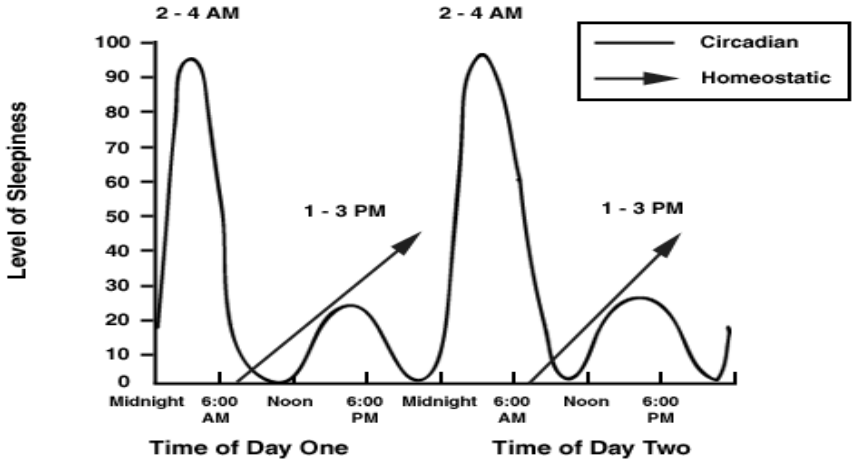

Figure 2. Homeostatic and Circadian Rhythms of Sleepiness over Two Days

Behavioral Dimensions of Sleep.

Returning to the Modified Model for the Study of Sleep in Adolescents with Cancer (see Figure 3), the Five Behavioral Dimensions of Sleep (i.e. Going to Bed, Falling Asleep, Maintaining Sleep, Reinitiating Sleep, Returning to Wakefulness) are important because they reflect the influences of both behavior and biology on sleep patterns. For example, homeostatic sleep pressure, circadian alerting, and sleep hygiene behaviors affect

Figure 3. Modified Model for the Study of Sleep in Adolescents with Cancer.

going to bed and falling asleep. Intrinsic biological processes, sleep hygiene, and school start time affect returning to wakefulness. Looking at sleep in terms of behavioral dimensions can help identify where sleep disruptions occur and what behavioral and/or pharmacological interventions may be necessary to improve sleep.

Healthy Adolescent Sleep Patterns

A delayed sleep phase (i.e. delay in weekend versus weekday sleep patterns) is the most consistent finding in adolescent sleep research (Carskadon et al., 1980; Carskadon, Vieira, & Acebo, 1993; Jenni & Carskadon, 2004). Adolescents go to sleep and rise later than younger children. School start times, however, get earlier as children get older. A review of adolescent sleep research (Crowley, Acebo, & Carskadon, 2007) found differences between weekend and school-night bedtimes (i.e. weekend bedtime delay) among adolescents averaging one to two hours, usually later in older than younger adolescents. Similarly, adolescents' weekend rise times were later than school rise times (i.e. weekend rise time delay), averaging 1.5 to 3 hours in 10-13 year olds, and 3 to 4 hours for 14-19 year olds (Crowley et al., 2007). The delay in sleep phase, coupled with early school start times, causes decreased total sleep time and daytime sleepiness on weekdays. Large differentials between school-night and weekend sleep schedules further compromise sleep-wake patterns, producing a "jet-lag" effect (Jenni & Carskadon, 2004). Insufficient sleep and daytime sleepiness are problematic due to significant negative effects on mood, cognitive functioning, behavior, family functioning (Mindell & Owens, 2003), and risk-taking behaviors (Mindell & Owens, 2003; "Sleep in America Poll," 2006).

Multinational, epidemiological studies have found total mean sleep times for healthy adolescents ranging from 7.3 to 7.8 hours on weeknights and 8.9 to 9.2 hours on weekends (Fredriksen, Rhodes, Reddy, & Way, 2004; Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002; O'Brien & Mindell, 2005; Wolfson & Carskadon, 1998) , despite an estimated sleep need of 9.25 hours (Carskadon, Acebo, & Jenni, 2004). Thus adolescents accumulated between 7 and 9.5 hours of sleep debt during the school week, equivalent to an entire night's sleep. Although adolescents slept adequately on weekends, they did not compensate for sleep loss during the week. Inadequate sleep affects many aspects of healthy adolescents' waking lives. Reduced total sleep times and irregular schedules have been associated with lower self-esteem scores and academic grades, higher levels of depressive symptoms (Fredriksen et al., 2004), more behavior difficulties including oversleep and later arrival to school, daytime sleepiness (Wolfson & Carskadon, 1998), and suicidal behavior (Liu, 2004).

In summary, research supports the following developmental trends in healthy adolescent sleep patterns: (a) Delays in bedtimes from early to late adolescence, (b) delays in wake times especially on weekends and during vacation periods, but to a lesser extent on school days, (c) declines in sleep duration on weekdays, less on weekends, and (d) increasing discrepancies between weekday and weekend sleep patterns (Carskadon, 2002b). These sleep pattern changes exist within the context of an educational system that requires earlier school start times in older rather than younger children. Together, the changing patterns of adolescent sleep and earlier school start times result in insufficient sleep for many adolescents (Carskadon et al., 2004).

Effects of Cancer and Chemotherapy on Adolescent Sleep

Sleep plays a significant role in health and illness and may be particularly important for adolescents with cancer. Adolescents with cancer are facing a life-threatening illness and a period of brain maturation, two occasions where sleep may be particularly important. Increasing evidence links sleep with natural killer cell activity and raises the possibility that sleep is also important for immune defense against tumor cells (Davidson, MacLean, Brundage, & Schulze, 2002; Theobald, 2004). Evidence suggests that sleep may sustain the activity of certain immune cells and chemicals which are important in fighting cancer. Studies have shown levels of interleukin-1 and tumor necrosis factor (TNF), a potent killer of cancer, rise during the night and drop upon awakening (Dement & Vaughn, 1999). Therefore, sleep is not only important for development, psychosocial functioning, and managing symptoms, but may also be important for fighting cancer. Although we have a basic understanding of sleep patterns in healthy adolescents, little is known about sleep patterns in adolescents with cancer; whether they mirror those of healthy adolescents or are different as a result of cancer and chemotherapy. Further, consequences of insufficient or disturbed sleep in adolescents with cancer are unknown.

Sleep-wake disturbances are commonly reported by adults with cancer with prevalence rates of 30 to 80%. Persistent sleep-wake disturbances appear to affect physical and psychosocial functioning, mood, symptom distress, QL, and survival (Clark, Cunningham, McMillan, Vena, & Parker, 2004). Sleep disturbances in children/adolescents with cancer are beginning to be examined. Currently there are four published studies that examine sleep-wake disturbances in children/adolescents receiving

chemotherapy. Two studies involved hospitalized children/adolescents exclusively (Hinds, Hockenberry, Rai et al., 2007; Jacob, Hesselgrave, Sambuco, & Hockenberry, 2007), one was a pilot study examining sleep in school-age children and their parents at home (V. Gedaly-Duff, K. A. Lee, L. M. Nail, H. S. Nicholson, & K. P. Johnson, 2006b), and the other study looked at the experience of a single adolescent during her first three months of chemotherapy (Docherty et al., 2006).

Hinds et al. (2007) described the patterns of nocturnal awakenings (using actigraphy) and sleep environment in 29 hospitalized children/adolescents 7-18 years with solid tumors or AML. The number of nocturnal awakenings were significantly related to sleep duration and fatigue (Hinds, Hockenberry, Rai et al., 2007). Jacob et al. (2007) secondarily examined the relationships between pain and perceptions of sleep and activity in 49 hospitalized children/adolescents 8-17 years with a variety of cancer diagnoses. A numeric rating scale (0 = did not sleep at all, 10 = slept a lot) was used to determine the amount of sleep perceived by the child/adolescent. Although there were no significant relationships between the amount of pain and perceptions of sleep, 25% of the sample reported sleep scores $\leq$ 5 regardless of pain ratings (Jacob et al., 2007). Docherty et al. (2006) presented a case study of a 16 year old during the first three months of chemotherapy for Hodgkin's lymphoma. Sleep efficiency was measured using actigraphy and scores ranged from 30 to 89% with a mean of 69%. A high degree of variability was found in sleep efficiency with no clear patterns (Docherty et al., 2006). While these studies did examine sleep and support a relationship between sleep disturbances and other symptoms, the sleep wake patterns of adolescents receiving chemotherapy in out-patient settings have not been described.

Sleep disturbances also are revealed in studies of children/adolescents with cancer that do not examine sleep directly (Collins et al., 2000; Collins et al., 2002; Docherty et al., 2006; Woodgate & Degner, 2003). Insomnia was a commonly reported in both of Collins' et al. (2002, 2000) symptom prevalence studies. Insomnia had moderate prevalence (31%), but high intensity (67%) and distress (59%) ratings. "Lack of energy" and "drowsiness" might also indicate disturbed sleep. Both of these symptoms were highly prevalent (50% and 49%) and intense (62% and 64%), but less distressing (21% and 19%) (Collins et al., 2000). Gibson et al. (2005) found sleep disturbances common among adolescents with cancer who reported difficulties falling asleep precipitated by worry, and fitful sleep related to discomfort and frequent urination (Gibson, Mulhall et al., 2005). Sleep was considered valuable for a temporary escape from reality and respite from symptoms (Woodgate & Degner, 2003). Adolescents also reported changes in sleep patterns after being diagnosed with cancer. Homebound education led to staying up late at night and sleeping late in the morning (Hockenberry-Eaton & Hinds, 2000).

Chemotherapy likely contributes to sleep disturbances. Three commonly used chemotherapeutic agents, corticosteroids (i.e. prednisone and dexamethasone), methotrexate, and vincristine will be used to explore these contributions. Corticosteroids are hormonal chemotherapeutic agents that interfere with protein synthesis and cellular metabolism. Common side effects include mood changes, depression, increased appetite, weight gain, and sleep disturbance. Methotrexate acts during DNA and RNA synthesis, so is cyotoxic specific during the S-phase of the cell cycle. Common side effects include nausea and vomiting, mucositis, diarrhea, increased risk of sunburn, and loss of appetite. Vincristine, a plant alkaloid, acts by binding to microtubules in cells, causing them to die

in metaphase. Common side effects include constipation, hair loss, and numbness/tingling in hands and feet related to peripheral nerve irritation (American Cancer Society, 2004). While sleep disturbance is a known side effect of prednisone, the physical symptoms (i.e. nausea and vomiting, mucositis, diarrhea, constipation, numbness/tingling in hands and feet) and the psychological symptoms (i.e. mood changes, depression) of these and other medications are also likely to contribute to sleep disturbances. Further, the side effects of weight gain and hair loss affect body image, which is exceedingly important to adolescents, and may be a source of rumination at bedtime or during nighttime awakenings. Other aspects of cancer treatment likely to disturb sleep include symptom management medications, changes in routines for appointments, hospitalizations, surgery, and radiation can also affect sleep (K. Lee, Cho, Miaskowski, & Dodd, 2004).

An adaptive link is thought to exist between sleep and perceptions of threat/safety that may have particular relevance for adolescents with cancer. Sleep induces a loss of awareness and responsiveness to the environment and thus requires a perception of safety. When threats to safety exist, vigilance and responsiveness prevail, and falling asleep is more difficult (Dahl & Lewin, 2002). Adolescents with cancer have unique concerns that are often intensified by the diagnosis and experience of cancer. Cognitively, adolescents have increased abilities to consider alternative possibilities, to think in multidimensional ways, to engage in metacognition, to think in relative terms vs. absolutes (Decker, Phillips, & Haase, 2004), and to think about the future (Piaget, 1955). Cancer and its treatment present many potential threats to safety which are likely to create threat-related arousals that will interfere with sleep. Four broad categories of

concerns among adolescents with cancer include 1) treatment/side-effects, 2) uncertainty—present and future (e.g. recurrence, survival, fertility) 3) social issues (e.g. relationships with family and friends, maintaining normality), and 4) personal/emotional issues (e.g. managing stress, taking control). Indeed, adolescents may have difficulty falling asleep if bedtime becomes consumed by rumination about their concerns, the possible outcomes of cancer and treatments, and the potential impacts on their own and their families' lives (Decker et al., 2004).

Spielman and Glovinsky proposed that etiologic factors involved in the development of insomnia in cancer patients could be characterized as predisposing, precipitating, or perpetuating factors (as cited in Savard and Morin, 2001). In this case, adolescence may be a predisposing factor involved in the development of insomnia; chemotherapy a precipitating factor; and sleep routines, low activity levels, and daytime sleep may perpetuate sleep disturbances (Savard & Morin, 2001).

Quality of Life

Quality of life (QL) of children/adolescents with chronic conditions is recognized increasingly as an important indicator of disease and treatment outcomes. Long-term survival has increased dramatically for many childhood chronic conditions including cancer. Traditional clinical outcomes assess the progress of disease and effectiveness of treatment but fail to assess the impact of disease on daily physical and social functioning, emotional well-being, and perceptions of illness (Thomas, Mitchell, O'Rourke, & Wainwright, 2006). Quality of life, often referred to as health-related quality of life (HRQOL) in the chronic illness literature, provides a broader measure of child/adolescent health status identifying disease factors impacting children/adolescents' lives (J. M.

Perrin et al., 2008). The classic definition of QL comes from the World Health Organization's (WHO) (1946) definition of health as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity" (p. 2). This definition proposed the minimum number of conceptual domains as three: physical, mental, and social. QL as it applies to children with chronic conditions (i.e. HRQOL), is usually defined by four dimensions, adding a separate dimension for symptoms (King et al., 1997).

Two general approaches are used to assess QL, categorical and non-categorical. Categorical approaches assess QL as it relates to specific diseases (e.g. cancer, asthma, diabetes) while non-categorical approaches are more generic and allow for comparisons between diagnostic groups. Categorical approaches, using disease-specific measures, have the advantage of focusing on issues of immediate relevance to children/adolescents with specific diseases, but do not allow for comparisons between children/adolescents with other diseases or healthy children. Non-categorical or generic approaches, that focus on issues common to all children, have the advantage of comparability but may not detect changes relevant to children with specific diseases (Sawyer et al., 2004).

Chronic illness puts children/adolescents at risk for psychosocial problems though few will actually evidence psychopathology (Eiser, 1994). The fact that illness puts children/adolescents at risk, in and of itself, is important. The specific disease, however, may not be the greatest risk, as children with similar risk profiles (e.g. disease, treatment, symptoms) display wide variations in adaptation, illustrating the complexity of risk as it relates to illness. In the Disability-Stress-Coping Conceptual Model (Wallander & Varni, 1992), risk-factors such as disease parameters (e.g. diagnosis, severity of disease, medical

problems, bowel/bladder control, visibility, cognitive functioning, and brain involvement), functional independence, and psychosocial stressors (i.e. disability-related problems, major life events, daily hassles) interact with resistance factors such as intrapersonal factors (e.g. temperament, competence, motivation, problem-solving ability), social-ecological factors (e.g. family environment, social support, family members' adaptation, utilitarian resources), and stress processing (i.e. cognitive appraisal, coping strategies) to determine adaptation (i.e. mental health, social functioning, and physical health). Conceptually then, similarities among children/adolescents with different chronic conditions may affect QL more than their specific conditions (Wallander & Varni, 1992).

Theoretically, there is an assumption that greater adaptation and the ability to achieve developmental landmarks leads to a higher QL. There is a strong link between quality of life and development in children/adolescents with chronic conditions. For many children/adolescents with chronic conditions, the illness is experienced in the context of normal development. Families and health care providers strive to normalize chronic conditions by balancing the tasks of illness management with the continuing development of the child (Stein, Westbrook, & Bauman, 1997). Even though cancer is a life-threatening event, the survival, long treatment, and follow-up are more characteristic of a chronic condition. Therefore, QL, from the perspective of adolescents with chronic conditions, is similar to that of healthy adolescents, and determined by the extent to which their illness interferes with their abilities to be independent, participate in school and activities, get along with others, and develop a positive self-concept and self-esteem.

Health-related QL (HRQOL) for children receiving treatment for cancer has been defined as a general sense of well-being derived from abilities to participate in normal activities, interact with others, feel cared about, cope with physical, emotional, and cognitive discomforts, and find meaning in the illness experience (Hinds et al., 2004). Symptoms clearly have an adverse effect on the QL of children/adolescents with cancer (Woodgate et al., 2003). Major stressors related to treatment reported by children/adolescents include procedures (e.g. needles, lumbar punctures, bone marrow tests), loss of control, hospitalizations, relapses, fear of dying, other children dying, check-up results, hair loss, infections, and not being able to be with friends. The effects of these major stressors on the well-being (i.e. QL) of children/adolescents include low self-esteem; feeling miserable, tired, sad, lethargic, and depressed; inability to attend school and participate in sports causing problems such as withdrawal, being different, feeling rejected, losing touch with peers, being behind in school; and overall feelings of isolation. Children/adolescents with cancer are also perceived to behave more maturely than their peers (McCaffrey, 2006) which may further differentiate them.

Sleep disturbance and other treatment-related symptoms have potentials to affect all three domains of QL. The primary tasks of adolescence, which are to increase independence from parents and mastery over the environment, are accomplished by participating in school and extracurricular activities. The physical domain is primarily concerned with function, and includes mobility, self-care, going to school, and participating in extracurricular activities. School is the primary social role for adolescents (Msall et al., 2003). “School” however can be defined differently (e.g. home schooling, tutoring) and many children/adolescents in acute phases of illness do not attend school.

Functional limitations for adolescents with cancer might include increased sick days, long absences from school during intense treatment or acute illness, inability to participate in contact sports due to low platelet counts, pain and fatigue interfering with normal activities, and the need for physical care from parents. The mental domain consists of feelings such as fear, sadness, anger, and anxiety, which are often exacerbated by the context of cancer. Indeed, older children and adolescents may have more difficulty than younger children with cancer and treatment because their advanced cognitive abilities make them more aware of the life-threatening context of their illness and the demands care has on their families.

The literature on quality of life in children with chronic conditions, and cancer specifically, is limited by the approaches (categorical and non-categorical), a plethora of instruments with limited reliability and validity, sample variability in illness severity, and vague understanding of “school” as it relates to acute and chronic illness.

Summary

The literature related to children/adolescents with cancer is limited by small sample sizes, inclusion of younger children with adolescents, time since diagnosis, and time when data were collected (i.e. prospective, retrospective). Clearly, adolescents with cancer experience multiple symptoms, differing in frequency, intensity, and distress that interfere with developmental goals and negatively affect quality of life. Cancer treatment presents much potential for disturbing sleep, including an inherent threat to safety. A description of sleep-wake patterns and sleep disturbances in adolescents receiving chemotherapy is warranted.

This study was proposed to examine sleep, symptoms, and quality of life in adolescents 10 to 19 years, to extend our understanding of the experiences of adolescents with cancer. Adolescents participating in this study varied in terms of adjuvant treatment modalities, chemotherapy protocols, treatment phases, and symptoms. All of the adolescents, however, were actively receiving chemotherapy and expected to experience symptoms varying in frequency, intensity and distress.

CHAPTER 3

Design and Methods

The purpose of this prospective, cross-sectional study was to describe nocturnal sleep-wake activity in adolescents receiving chemotherapy, and explore relationships between sleep, disease and treatment-related symptoms, and quality of life. This chapter describes the design and methods used for this study. Sections include sample and setting, measures, procedure, data management and analysis.

Sample and Setting

A sample of adolescents receiving chemotherapy was recruited from the two regional children's cancer centers in Portland, Oregon, that serve adolescents/children in Oregon and Southwest Washington. Adolescents were recruited irrespective of type of cancer, phase of treatment; and whether the cancer was primary, secondary, or a relapse. The recruitment goal was 50, a reasonable sample for establishing the magnitude of relationships between variables. A cross-sectional design was chosen to provide a broad description of adolescents with cancer that included variability in diagnosis and treatment phase (Miaskowski, Dodd, & Lee, 2004).

Adolescents were eligible to participate in the study if they were 10 to 19 years of age and actively receiving chemotherapy for a primary or secondary cancer, or relapse. Pubertal development also was assessed using the Self-Administered Rating Scale for Pubertal Development (SRPD) (Carskadon & Acebo, 1993) to further describe the sample. Pubertal status of females and males was categorized based on secondary sex characteristics, as pre-, early, middle, late or post-pubertal. Secondary sex characteristics related to puberty were assessed by presence of growth spurt, body hair growth, skin

changes (i.e. pimples); for boys, voice deepening and facial hair growth; and for girls, breast development and menarche.

Written assent and consent from a parent or legal guardian were obtained for participants 10 to 17 years of age. Written consent was obtained from 18 and 19 year old subjects. Participants were required to read, speak, and understand English. Adolescents were excluded if they had a diagnosis of mental illness prior to cancer or cognitive issues (e.g. developmental delay) that precluded participation. Decisions to exclude an adolescent were made by the investigator, an experienced pediatric nurse with nine years of experience, in conjunction with chart reviews, and informal discussions with physicians, parents, and adolescents. Hospitalized adolescents were included only if their treatment protocol required extended hospitalization or if the trajectory of their past treatment made seven days out of the hospital unlikely.

Table 1

Study Variables and Measures

Variable	Measure
Sleep-wake activity	Actigraphy 7-Day Diary
Baseline sleep patterns	Sleep Routines “Before you were Sick” (BYWS)
Sleep quality	Adolescent Sleep Wake Scale (ASWS)
Sleep hygiene	Adolescent Sleep Hygiene Scale (ASHS)
Symptoms	Memorial Symptom Assessment Scale (MSAS)
Quality of Life	Pediatric Quality of Life Inventory Version 4.0 Teen Report (PedsQL)
Descriptive data	Interview Guide

Measures

The following section describes the instruments used to measure the study variables. The study variables and measures are summarized in Table 1.

Sleep-Wake Activity

Nocturnal sleep-wake activity was assessed using objective (i.e. actigraphy) and subjective (i.e. 7- Day Sleep Diary, Adolescent Sleep Wake Scale, Adolescent Sleep Hygiene Scale) measures. Together these measures described the influences of behavior and biology on adolescent sleep patterns.

Actigraphy. Actigraphy estimated sleep-wake activity from gross motor activity while the diaries assessed sleep patterns from self-reports. While polysomnography (PSG) is the gold standard for measuring sleep-wake states, it requires a laboratory setting or monitoring equipment in the home. Wrist actigraphy was optimal for this study because it allowed for a non-invasive assessment of sleep/wake patterns at home (Sadeh, Hauri, Kripke, & Lavie, 1995). Validity of actigraphy data has been established in laboratories using PSG and actigraphy measures simultaneously. Agreement was relatively high (.85) for healthy individuals and clinical populations of various ages, regardless of the computer software used to score the actigraphy; correlations between whole night sleep measures and sleep efficiency were also acceptable at .80 (Sadeh & Acebo, 2002). Because validity testing was largely done in laboratories where the environment was controlled and data was collected by protocol, the likelihood of error was low compared to the home. Because of potentials for error in home settings, 5 days of measurement were recommended for reliable measures of sleep start, wake minutes,

and sleep efficiency, and 7 days for detecting individual differences in sleep periods (Acebo et al., 1999).

Each participant wore a model AW-64 Actiwatch® (Mini Mitter, Bend, OR) for seven consecutive days and nights. The Actiwatch is a small, rugged, watch-like device that logs gross motor activity using an accelerometer into a digitally integrated recording system. Prior to data collection, watches were programmed to record at 30-second epochs with a medium wake-threshold of 40. Actiware® 5.0 software scored each epoch as sleep or wake by comparing the activity counts for the epoch in question with those immediately surrounding it to the threshold value of 40 (Respironics Mini Mitter, 2006). If the value was calculated to be less than or equal to the wake threshold value, the epoch was scored as sleep.

Table 2

Definitions of Selected Actigraphy Variables (Acebo et al., 1999)

Variable	Definition
Rest Interval	Minutes between the time lights are turned off with the intention of sleep, end of sleep period, and getting out of bed
Sleep start time	First of at least 3 consecutive minutes scored as sleep
Sleep end time	Last of at least 5 consecutive minutes scored as sleep just prior to awakening
Sleep period (sleep duration)	Minutes from sleep start time to sleep end time
True sleep time (TST)	Minutes from sleep start to sleep end scored as sleep
Wake after sleep onset (WASO)	Minutes from sleep start to sleep end scored as wake
Sleep efficiency (SE)	Percentage of the sleep period scored as sleep

The Actiwatch has been used in a variety of pediatric populations to measure sleep-wake activity (Armitage et al., 2004; Gaina, Sekine, Chen, Hamanishi, & Kagamimori, 2004; Gaina, Sekine, Hamanishi, Chen, & Kagamimori, 2005; Hoffmann, Emslie, Thompson, Rintelmann, & Armitage, 2004), and has been validated in adult (Kushida et al., 2001) and pediatric (Hoffmann et al., 2004) populations with polysomnography.

Diary. An investigator-developed, one-page, 7-day sleep diary was used to assess subjective sleep-wake activity (See Appendix A). The diary had morning and evening questions. In the mornings, participants recorded their bedtime the night before, number of nighttime awakenings, sleep duration, and morning wake time. In the evenings, they recorded daytime naps and overall daytime sleepiness (1 not sleepy at all, 5 most sleepy). Throughout the day medications (drug, dosage, time taken), other than chemotherapy, were recorded in the diary. Content validity of the diary was supported by the literature and the content of other sleep diaries (Berger et al., 2005; K. Lee & Ward, 2005; Manber, Bootzin, Acebo, & Carskadon, 1996).

Baseline Sleep Patterns

Sleep Routines "Before You Were Sick" Questionnaire (BYWS). A brief investigator-developed "Before You Were Sick" questionnaire was used to assess baseline sleep routines prior to cancer diagnosis and allow comparisons with sleep routines in the context of chemotherapy, a need identified in a previous study (Gedaly-Duff et al., 2006b) (See Appendix B). The questionnaire assessed school-night and weekend bedtimes, wake-times, durations, and nighttime awakenings, referencing the "before they were sick" period.

Sleep Quality and Sleep Hygiene

Sleep quality and sleep hygiene (i.e. behaviors that inhibit or facilitate sleep) were measured by the Adolescent Sleep-Wake Scale (ASWS) and Adolescent Sleep Hygiene Scale (ASHS), which assess behaviors as they relate to the Five Behavioral Dimensions of Sleep (i.e. Going to Bed, Falling Asleep, Maintaining Sleep, Reinitiating Sleep, and Returning to Wakefulness). Behavioral dimensions of sleep are significant because they reflect the influences of both behavior and biology on sleep patterns.

Adolescent Sleep-Wake Scale (ASWS). The ASWS, a modified version of the Children's Sleep Wake Scale (LeBourgeois, Giannotti, Cortesi, Wolfson, & Harsh, 2005), is a 28-item scale which assesses sleep quality in adolescents ages 12 to18 years along 5 behavioral dimensions: Going to Bed (5 items), Falling Asleep (6 items), Maintaining Sleep (6 items), Reinitiating sleep (6 items), and Returning to Wakefulness (5 items) (See Appendix C). The behavioral dimensions are also subscales. The Going to Bed subscale assesses readiness for going to bed (e.g. "I want to stay up and do other things," "I enjoy bedtime"). The Falling Asleep subscale assesses settling down and going to sleep (e.g. "I have trouble settling down," "I fall asleep quickly"). The Maintaining Sleep subscale assesses activities occurring during sleep (e.g. restlessness, talking in sleep, awakening more than one time). The Reinitiating Sleep subscale assesses ability to go back to sleep when awakened (e.g. "I have trouble going back to sleep," After waking up at night, I wake up another family member"). The Returning to Wakefulness subscale assesses how they feel when they awaken, and how long it takes them "to feel completely awake." Respondents indicate how often these sleep behaviors have occurred during the past month on a 6-point scale (never, once in awhile,

sometimes, quite often, frequently if not always, always). The reference time was changed to the "last week" for this study. After reverse scoring appropriate items, mean scores are calculated for the total and subscales. All scores range from 1 to 6, with higher scores indicating better sleep quality. Reliability estimates of internal consistency have been reported for the full scale (Cronbach α = .80 to.86) and subscales (Cronbach = .60 to .82) (LeBourgeois, 2001; LeBourgeois et al., 2005).

T-tests revealed significantly better sleep quality, as measured by the ASWS total score, among a sample of healthy Italian adolescents (M = 4.41, SD = .53) than a sample of healthy American adolescents (M = 4.0, SD = .72) (t = -11.39, p < .001). Italian adolescents also had significantly higher scores on all behavioral dimensions (i.e. subscales) of the ASWS than American adolescents. For the Going to Bed subscale, Italian adolescents had a mean score of 4.16 (SD = .88) and American adolescents a mean score of 3.83 (SD = 1.05) (t = -6.16, p < .001). For the Falling Asleep subscale, Italian adolescents had a mean score of 4.60 (SD = .74) and American adolescents a mean score of 4.08 (SD = 1.0) (t = -10.64, p < .001). For the Maintaining Sleep subscale, Italian adolescents had a mean score of 4.88 (SD = .86) and American adolescents a mean score of 4.28 (SD = .96) (t = -11.92, p < .001). For the Reinitiating Sleep subscale, Italian adolescents had a mean score of 5.14 (SD = .70) and American adolescents a mean score of 4.77 (SD = .92) (t = -8.05, p < .001). For the Returning to Wakefulness subscale, Italian adolescents had a mean score of 3.26 (SD = 1.28) and American adolescents a mean score of 3.05 (SD = 1.25) (t = -3.00, p < .001) (LeBourgeois et al., 2005).

Adolescent Sleep Hygiene Scale (ASHS). The ASHS (LeBourgeois et al., 2005), a modified version of the Child Sleep Hygiene Scale, is a 28-item scale which assesses

sleep-facilitating and sleep-inhibiting behaviors in adolescents ages 12 to 18 along 6 conceptual domains: physiological (5 items), cognitive (6 items), emotional (3 items), sleep environment (4 items), substances (2 items), and sleep stability (4 items) (see Appendix D). The physiological subscale assesses physiological behaviors that might facilitate or inhibit sleep (e.g. drinking caffeine, physical activity, feeling hungry or having a stomachache before bed). The cognitive subscale assesses behaviors that might heighten or dull cognition prior to sleep (e.g. watching television, playing video games, talking on the telephone, replaying events of the day in their mind). The emotional subscale assesses emotions felt before going to bed or while trying to sleep (e.g. worry about things happening at home or school, feeling upset). The sleep environment subscale assesses the environment in which they try to sleep (e.g. loud music, watching television, room temperature). The substance subscale assesses for use of alcohol and/or tobacco. The sleep stability scale assesses for differences between bedtimes/wake-times on weekdays/weekends. Respondents indicate how often these sleep-inhibiting or facilitating behaviors have occurred over the past month on a 6-point scale (always, frequently-if not always, quite often, sometimes, once-in-awhile, and never). The reference time was changed to the “last week” for this study. Mean scores are calculated for the total and subscales. Item scores range from 1 to 6, with higher scores indicating better sleep hygiene. Reliability estimates of internal consistency have been reported for the full scale (Cronbach $\alpha = .80$) and subscales (Cronbach $\alpha = .46$ to $.74$).

T-tests revealed significantly better sleep hygiene scores among healthy Italian adolescents than healthy American adolescents on the total ASHS score, and the physiological, cognitive, emotional, sleep environment, daytime-sleep, sleep-stability

subscales. On the total ASHS score, Italian adolescents had a mean score of 4.5 (*SD* = .57) and in American adolescents a mean score of 4.0 (*SD* = .61) (*t* = -13.03, *p* < .001). On the physiological subscale, Italian adolescents had a mean score of 4.7 (*SD* = .86) and in American adolescents a mean score of 3.9 (*SD* = .92) (*t* = -17.4, *p* < .001). On the cognitive subscale, Italian adolescents had a mean score of 4.0 (*SD* = .90) and in American adolescents a mean score of 3.3 (*SD* = .96) (*t* = -13.5, *p* < .001). On the emotional subscale, Italian adolescents had a mean score of 4.7 (*SD* = .99) and in American adolescents a mean score of 4.2 (*SD* = 1.01) (*t* = -8.9, *p* < .001). On the sleep environment subscale, Italian adolescents had a mean score of 5.0 (*SD* = .79) and in American adolescents a mean score of 4.5 (*SD* = 1.00) (*t* = -10.4, *p* < .001). On the daytime-sleep subscale, Italian adolescents had a mean score of 5.1 (*SD* = 1.31) and in American adolescents a mean score of 3.9 (*SD* = 1.75) (*t* = -14.3, *p* < .001). On the sleep-stability subscale, Italian adolescents had a mean score of 3.8 (*SD* = 1.09) and in American adolescents a mean score of 3.3 (*SD* = 1.10) (*t* = -8.8, *p* < .001). Mann-Whitney *U* tests found higher scores on the substance-use and bed/bedroom-sharing domains among American adolescents (*M* = 23.3, *SD* = .67; *M* = 5.1, *SD* = 1.30) than Italian adolescents (*M* = 5.4, *SD* = 1.09; *M* = 4.5, 1.88) (*z* = -9.3, *p* <.001; *z* = -4.3; *p* < .001). There was no significant difference between groups on the bedtime routines subscale (LeBourgeois et al., 2005). The updated version of the ASHS did not include the daytime sleep, bedtime routine, and bed/bedroom sharing subscales.

Symptoms

Memorial Symptom Assessment Scale (MSAS 7-12). The MSAS 7-12 (Collins et al., 2002) assesses the prevalence, frequency, intensity, and distress of 8 symptoms:

tiredness, sadness, itching, pain, worry, appetite, nausea, and trouble going to sleep (See Appendix E). A blank item is provided at the end for an additional symptom, for a total of 9 potential symptoms. The symptoms are recorded as present or absent, and if present, are rated for frequency, intensity, and distress or "bother" on a 4-point scale (0 = not at all and 3 = almost all the time). Of note, intensity is not measured for changes in appetite and nausea; and prevalence and distress are the only dimensions measured for trouble sleeping. The total score is calculated by averaging the dimensions of each symptom and adding them together. The range of possible scores is 0 to 27. Convergent validity has been tested by comparing the individual symptom items on the MSAS (7-12) with corresponding visual analog scales (VAS) evaluating nausea, sadness, and pain. Correlations were .74, .70, and .76 respectively, all with p values < .01. Each MSAS symptom item was then correlated with an overall sense of well-being VAS; correlations ranged from .12 to .43, all except "itch" reached significance with p values < .01 (Collins et al., 2002). This instrument has been used exclusively with children and adolescents with cancer.

The symptom "numbness and tingling in hands and feet" was added to the MSAS (7-12) for this study, in the same format as the other 8 symptoms. Neuropathies, often described as "numbness and tingling in hands and feet," are common symptoms associated with the drug vincristine (Hamilton, 2005). This modification increased the number of symptoms to 10 and the possible range of scores from 0 to 30. The MSAS was administered twice, once on the first day of data collection referencing the week before treatment, and once at the completion of data collection, referencing the week following treatment.

Pediatric Quality of Life Inventory Version 4.0 Teen Report (PedsQL)

The PedsQL is a generic scale that assesses the quality of life of adolescents 13 to 18 years (See Appendix F). The scale contains 23 items that assess function in four domains: physical (8 items), emotional (5 items), social (5 items), and school (5 items). The response options are: never (0), almost never (1), sometimes (2), often (3), and always (4). The domains are also the subscales. The physical subscale assesses difficulties with activities such as walking, running, sports activities, exercise, lifting, and bathing; and symptoms of hurt and low energy. The emotional subscale assesses feelings of fear (i.e. afraid or scared), depression (i.e. sad or blue), anger, trouble sleeping, and worry about what will happen to them. The social subscale assesses issues related to getting along with other teens, having friends, being teased, and keeping up with peers. The school subscale assesses problems paying attention in class, forgetting things, keeping up with school work, and missing school due to illness, medical appointments, and hospitalization. Total and subscale scores are obtained by reverse-scoring and linearly transforming items to a 0 to 100 scale, with higher scores indicating better quality of life (Varni, 1998-2005). For this study the reference point was changed from the “last month” to the “last week”.

The PedsQL™ Measurement Model uses generic and disease-specific scales to measure health-related quality of life in healthy adolescents/children and those with acute and chronic conditions. The PedsQL Generic Core Scales were developed to measure health as defined by the World Health Organization (World Health Organization, 1946) with the addition of role (school) functioning (Varni, 1998-2005). PedsQL Condition-Specific Modules were designed to complement generic scales and provide measurement

sensitivity for clinical populations (Varni, 1998-2005). The cancer module assesses problems with pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, physical appearance, and communication. The cancer module was not used because it included several items related to symptoms (e.g. “I feel too sick to my stomach to eat,” “I worry that my cancer will come back or relapse,” “I hurt a lot”). The MSAS 7-12, a multidimensional symptom measure, instead was used to measure symptoms. The generic PedsQL was ideal because it had few symptom items with potentials to correlate with the MSAS 7-12 and overestimate the strength of the relationship between variables (Nail, 2002).

The PedsQL has been used extensively in diverse pediatric populations including healthy children/adolescents and children/adolescents with a variety of chronic conditions including cerebral palsy (Varni et al., 2005), inflammatory bowel disease (J. M. Perrin et al., 2008; Varni et al., 2006), cystic fibrosis (Thomas et al., 2006), diabetes (Varni, Limbers, Burwinkle, Bryant, & Wilson, 2008), end-stage renal disease (Goldstein et al., 2008), heart disease (Varni, Seid, Knight, Uzark, & Szer, 2002), asthma (Chan, Mangione-Smith, Burwinkle, Rosen, & Varni, 2005), and cancer (De Bolle, De Clercq, De Fruyt, & Benoit, 2008; Penn et al., 2007; Varni, Burwinkle, & Katz, 2004; Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002). Internal consistency reliability estimates range from Cronbach $\alpha = .83$ to .90, and validity has been supported by the instrument’s ability to distinguish between healthy children and those with acute and chronic health conditions (Varni, Seid, & Kurtin, 2001).

Descriptive Data and Interview Guide

The brief interview and interactions with participants and their parents provided insight into adolescents' experiences with sleep and symptoms. Brief interviews were conducted at the end of data collection using specific questions on the Adolescent Sleep Wake Scale (ASWS) and the Memorial Symptom Assessment Scale (7-12) as a guide (see Appendix G). Three items on the ASWS were used in the interview guide: 1) "In general, how long does it usually take you to fall asleep after 'lights out'?" 2) "In general, how often do you usually wake up during the night?" 3) "After waking up during the night, how long does it usually take you to go back to sleep?" If respondents reported it took them 15 minutes or longer to fall asleep, they were asked an open-ended question such as "Can you tell me what is going on during that time?" If they reported waking up three or more times during the night, they were asked, "What do you think wakes you up?" The purpose of these open-ended questions was to capture symptoms and information about sleep that were not identified by the standardized instruments. Interview and other descriptive data were recorded by hand during or immediately following interactions.

The majority of adolescents in this study were in acute treatment phases and in the clinic or hospital frequently for monitoring and treatment. Data collection was anchored to a chemotherapy treatment, and the timing of chemotherapy changed frequently due to low blood counts and/or toxicities. Several participants received their chemotherapy in the hospital and started data collection on the day of discharge. All hospitalizations and clinic visits provided opportunities for additional interactions between the investigator and participants.

Procedure

Recruitment began after IRB approval was received from Oregon Health & Science University and Legacy Health Systems. Adolescents fitting the study criteria were identified and introduced to the study by a physician, staff nurse, nurse practitioner, or medical assistant. With the adolescent's permission, the investigator approached them to explain the study, procedures, timing of data collection, and answer questions. After consent and/or assent were complete, medical records were reviewed to confirm diagnosis, date of birth, race/ethnicity, date of diagnosis, and treatment protocol.

Data collection began on a day intravenous chemotherapy was administered in the clinic, or the day of discharge when chemotherapy was administered in the hospital. Participants were given an assessment booklet which contained the following questionnaires: Sleep Routines Before you were Sick (BYWS), Adolescent Sleep Wake Scale (ASWS), Adolescent Sleep Hygiene Scale (ASHS), Memorial Symptom Assessment Scale (MSAS) (7-12), Pediatric Quality of Life Inventory Version 4.0 (PedsQL) Teen Report, and the Self-Reported Pubertal Development Scale (SRPD). The questionnaires referenced the week prior to the chemotherapy treatment, and participants were given the choice of completing the assessment book in clinic, hospital, or at home. The Actiwatch (Mini Mitter, Bend, OR) was explained and placed on the non-dominant wrist. Participants were instructed to keep the watch on unless swimming or bathing.[6] They were instructed to push the event marker on the face of the watch each night when they turned out the lights to go to sleep, and upon awakening each morning. Lastly, the sleep diary was explained. The study telephone number was provided in case of questions

[6] Watch can be worn during bathing but the wet band frequently causes skin irritation.

or problems, and a tentative plan was made for retrieving study materials (e.g. at the next appointment, or by Fedex). Participants wore the watches and filled out the diaries for seven consecutive days and nights. A brief interview, which included a second administration of the MSAS and questions from the ASWS, was given verbally in person or by telephone after the seven days of data collection. The study materials were reviewed and efforts made to clarify or complete missing data at this second visit. Participants received a cash incentive of $50 when data were completed.

Data Management and Analysis

This section describes how data were managed (entered, verified, and cleaned) and analyzed, and includes a section detailing how actigraphy was scored.

Actigraphy Scoring

After the data were collected, the Actiwatch was placed on a reader connected to the computer and the data were downloaded into the Actiware program (Respironics Mini Mitter, 2006). The investigator set the rest interval (i.e. time in bed) for each night before the software could score sleep-wake activity and compute selected statistics (see Table 2). Setting the rest interval required a reasonable correspondence between event markers on the actigraphy record and/or diaries to limit overestimation of sleep related to quiet activity, watch removal, or failure. In this study, event markers and/or diaries were used to set the rest intervals. If the event markers and/or diaries were missing or incongruent with the actigraphy record, but a clear sleep period was visible, the rest interval was set according to actigraphy. In the absence of event markers, diaries, or a clear visual sleep period on the actigraphy record, the night was not scored and the statistics were not used in analyses. Individual mean scores for true sleep time (TST), wake after sleep onset

(WASO), and sleep efficiency were calculated only for participants who had at least 5 nights of scored actigraphy during data collection. Time variables were reported according to a 24 hour clock, a time keeping convention in which the day runs from midnight to midnight and is divided into 24 hours, numbered from 0 to 23. Sleep variables were reported in minutes. As a reference, a 24 hour period has 1440 minutes, 8 hours equals 480 minutes, and 9.25 hours, the ideal sleep duration for adolescents (Carskadon, 2002b), equals 555 minutes.

Data were entered using a double-entry process in which two people entered all data into separate spreadsheets. To verify the data, the spreadsheets were compared, differences highlighted, and resolved with the raw data. The verified data were then imported into SPSS 15.0 (SPSS Inc., 2006). Descriptive statistics (range, mean, median) and histograms or scatter plots for each variable, item, and scale were used to clean the data prior to analyses.

Descriptive statistics were used to describe the sample, actigraphy variables, and measures of sleep quality, sleep hygiene, symptoms, and quality of life. Cronbach alpha, a measure of internal consistency reliability, was computed for measures of sleep quality and quality of life. Correlations between total sleep time (TST) and wake after sleep onset (WASO), symptoms, and quality of life were computed to explore relationships between variables and determine effect-size estimates for future studies. Regression models were not analyzed because correlations between variables were not significant.

CHAPTER 4

Results

The primary aim of this study was to describe nocturnal sleep-wake activity in adolescents receiving chemotherapy using objective (i.e. actigraphy) and subjective (i.e. diaries and other self-report instruments) measures. The secondary aims were to explore relationships between sleep variables (TST and WASO), treatment-related symptoms, and quality of life. The demographic and clinical characteristics of the sample and reliability statistics for the instruments will be reported first, followed by the results, which are reported according to the specific aims. An individual participant is described at the end of the findings related to sleep, symptom, and quality of life.[7]

Sample

Demographic Characteristics

The sample consisted of 51 adolescents with cancer. The majority were male and Caucasian with a mean age of 14 years, ranging from 10 to 18 years (see Table 3). In terms of pubertal status, most of the females were in later phases of pubertal development; while males were more evenly distributed between pubertal categories (see Figure 4). The most common cancers were leukemia, lymphoma, bone tumors, and brain tumors. Other diagnoses were testicular rhabdomyosarcoma, alveolar rhabdomyosarcoma, ovarian teratoma, germ cell tumor, synovial sarcoma, and renal neuroblastoma. The mean and median times since diagnosis were 6.25 and 4 months respectively, ranging from 0 to 37 months (see Table 4). This was a primary cancer for 47 (92%) of the participants, a relapse for 3 (6%), and a secondary cancer for 1 (2%). All

[7] Names have been changed to protect anonymity.

participants lived in Oregon or Southwest Washington and were treated at one of two pediatric cancer centers in Portland, OR. Recruitment and data collection occurred between August 2007 and January 2008.

Table 3

Participant Demographic and Clinical Characteristics (n = 51[8])

Variable	Number	%
Gender		
Female	22	43
Male	29	57
Race or ethnicity		
Caucasian	38	75
Hispanic	7	14
More than one race	5	10
African American	1	1
Age (years) Mean = 14 years, SD = 2.7		
10-13 years	21	41
14-16 years	16	31
17-19 years	14	28

[8] Includes 2 participants who started but did not complete the study.

Table 4

Participant Clinical Characteristics (n = 51[9])

Diagnosis	Number	%
Leukemia		
Acute Lymphocytic	21	41
Acute Myelogenous	2	4
Lymphoma (Hodgkin's or Non-Hodgkin's)	8	16
Bone tumors (Osteogenic or Ewing's)	8	16
Brain tumors	6	12
Other	6	12
Time since diagnosis (months)	**# of Months**	**%**
Mean	6.25 ($\pm$ 8)	
$\leq$ 4	26	51
5-12	19	37
$\geq$ 12	6	12

[9] Includes 2 participants who started but did not complete the study.

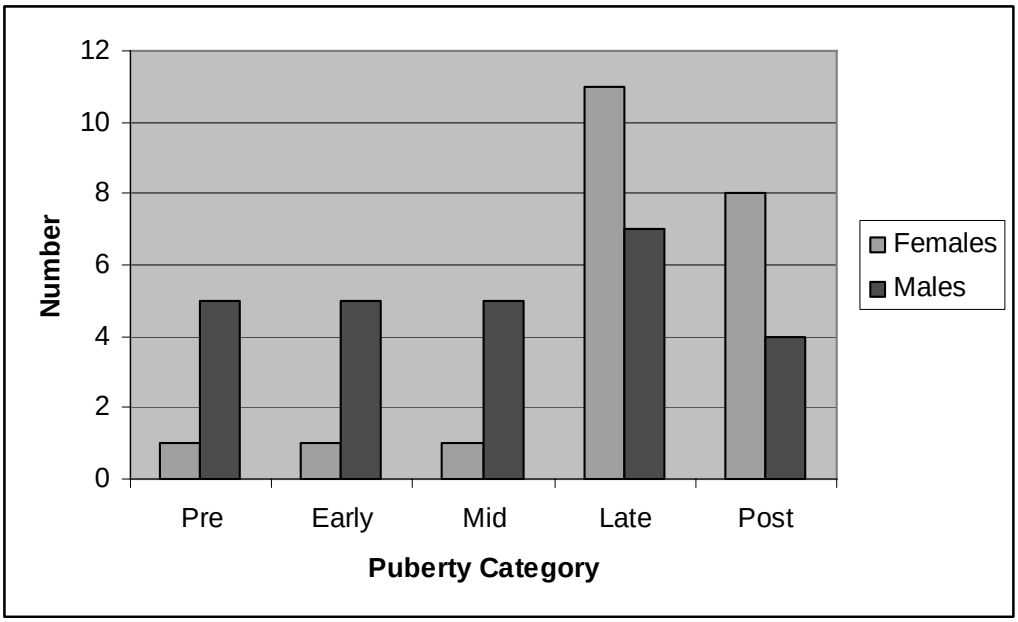

Figure 4. Number of Participants (Females and Males) in Pubertal Categories Based on Secondary Sex Characteristics (n = 51).

Participants received one or more of the following intravenous chemotherapeutic agents prior to data collection: vincristine, cyclophosphamide, cytarabine, methotrexate, procarbazine, ifofsomide, etoposide, carboplatin, daunarubicin, doxorubicin, cisplatinum, bleomycin, actinomycin, rituximab, mitoxantron, or gemtuzumab. The mean and median number of agents administered prior to data collection was 2. Fourteen (27%) of participants received a single agent (vincristine, methotrexate, or cyclophosphamide), 23 (45%) received 2 agents, 10 (20%) received 3 agents, and 4 (8%) received 4 or more agents. Eighteen (35%) participants received chemotherapy as in-patients and 33 (65%) as out-patients. Data were collected in the home setting for 48 (94%) participants and in the hospital for 3 (6%). Of those hospitalized at data collection, two had AML and were treated with protocols that required extended hospitalization after treatment; the third hospitalized participant had spent only two to three days per month out of the hospital since his diagnosis six months prior.

Although some of the participants were in maintenance chemotherapy for leukemia and feeling relatively well, most of them were in acute phases of treatment and experiencing multiple disease and treatment-related symptoms. As outpatients, three participants had enteral feeding tubes, two were receiving parenteral nutrition, two were on crutches from recent limb salvage surgery, and one was in a wheel chair due to neuropathic complications.

Setting

The setting of the pediatric oncology outpatient clinic was hectic. Depending on the reason for the clinic visit, activities included measurement height and weight measurements, vital signs, accessing of implanted central venous ports,[10] blood draws, and administration of medications including chemotherapy, blood transfusions, intravenous hydration; as well as visits from physicians, nurse practitioners, and social workers. Recruitment, data collection, data retrieval, and interactions occurred amidst this plethora of other activities.

Instrument Reliability

Broadly speaking, reliability is a measure of the degree to which test scores are free from systematic and unsystematic errors (Pedhazer & Schmelkin, 1991). Alpha coefficient (i.e. Cronbach alpha) is a commonly reported estimate of reliability based on internal consistency. This statistic is substantively meaningful when the instruments, or subscales of an instrument, are measuring the same phenomenon. The estimated reliability of an instrument refers to the percentage of the variance of the total score that

[10] A needle is inserted through the skin into the port (usually in the chest) and secured with a dressing; usually stays accessed for the duration of a clinic visit or hospitalization.

is reliable, or systematic, variance (Pedhazer & Schmelkin, 1991). Cronbach alphas were calculated for the ASWS and the PedsQL, which both showed good internal consistency reliability at .83 and .91 respectively (see Table 5). Cronbach alphas were not reported for the ASHS and MSAS (7-12). For the MSAS, symptoms are not expected to be internally consistent so the alpha coefficient is not substantively meaningful. For sleep hygiene, another type of reliability would be more meaningful due to the broad scope of sleep hygiene, behaviors which are not expected to be related to each other; other types of reliability testing have not been reported.

Table 5

Internal Consistency Reliability of Study Instruments

Instrument	Cronbach Alpha
Adolescent Sleep Wake Scale (ASWS)	.83
Pediatric Quality of Life Inventory (PedsQL)	.91

Aims

The purpose of this study was to describe nocturnal sleep-wake activity in adolescents receiving outpatient chemotherapy, and explore relationships between sleep, disease and treatment-related symptoms, and quality of life. All instruments were administered on the first day of data collection (i.e. a chemotherapy treatment date), referencing the week prior to chemotherapy treatment. The MSAS was administered verbally a second time, one week later, referencing the week since treatment at the end of data collection. Descriptive statistics (i.e. minimum, maximum, mean, and standard deviations) are reported for all measures.

Primary Aim

The primary aim of this study was to describe the nocturnal sleep-wake activity of adolescents receiving chemotherapy using objective and subjective measures. The objective measure was actigraphy and the subjective measures included two investigator-developed instruments: a one-page, 7-day sleep and medication diary and a "Before You Were Sick" questionnaire; two standardized instruments: the Adolescent Sleep Wake Scale (ASWS) and Adolescent Sleep Hygiene Scale (ASHS); and a brief interview.

Objective Measure of Sleep

Actigraphy. Means for actigraphy sleep variables (i.e. sleep duration, TST, WASO) were calculated for participants with at least five scorable nights[11] (see Table 6). Based on this criterion, 41 of the 51 study participants were included in these analyses. Of the 10 participants not included, two started but did not complete the study, two had watch failures, and one had lost data; five others had data that could not be scored reliably due to undefined sleep periods without event markers or diaries to substantiate the actigraphy data. Mean sleep start time was 23:11 (*SD* = 1:05) and sleep end time was 8:52 (*SD* = 1:10); the sleep end time indicated that most participants were not attending school. The mean sleep duration was 581 minutes (*SD* = 67), mean TST was 500 minutes (*SD* = 60), mean WASO was 80 minutes (*SD* = 29), and mean sleep efficiency was 82% (*SD* = 5%). Therefore, while the sleep duration was relatively high (9.7 hours), 80 minutes of that time was spent awake, leading to a low sleep efficiency.

[11] Measurements over at least five days are recommended for getting reliable measures of sleep start, wake minutes, and sleep efficiency, and seven nights for seeing individual differences (Acebo et al., 1999).

A one-way ANOVA revealed no significant statistical differences in actigraphy sleep variables by adolescent age group (i.e. early, middle, late). From early to late adolescence, however, mean sleep duration and TST were shorter, and sleep start time and end time advanced (see Table 7).

Table 6

Descriptive Statistics for Selected Actigraphy Variables

Variable	n	Min	Max	Mean	SD
Sleep duration (minutes)[12]	41	433	749	581	67
True Sleep Time[13] (TST)(minutes)	41	338	622	500	60
Wake After Sleep Onset [14] (WASO)(minutes)	41	28	139	80	29
Sleep efficiency (%)[15]	41	67	91	82	5
Sleep start time	45	21:22	2:00	23:11	1:05
Sleep end time	45	6:50	11:36	8:52	1:10

[12] Minutes from sleep start to sleep end including *both sleep and wake* (TST +WASO).

[13] Minutes of *sleep* from sleep start to sleep end (Sleep duration – WASO).

[14] Minutes of *wake* from sleep start to sleep end (Sleep duration – TST).

[15] *Percentage of sleep* from sleep start to sleep end (Sleep duration – WASO x 100).

Table 7
Means for Selected Actigraphy Variables for Adolescents in 3 age groups (n = 41): Early (10-13 yrs), Middle (14-16 yrs), and Late (17-19 yrs)

Variable	10-13 yrs N = 17	14-16 yrs N = 13	17-19 yrs N = 11
Sleep duration (minutes)	588	587	564
TST (minutes)	510	502	482
WASO (minutes)	78	84	76
Sleep efficiency (%)	83	81	83
Sleep start time	22:44	23:32	23:45
Sleep end time	8:32	9:10	9:11

Table 8

Descriptive Statistics for Sleep Routines Before Diagnosis (BYWS) and During Chemotherapy (DC)

Variable	N	Min	Max	Mean	SD
Bedtime weekdays					
BYWS	43	20:00	02:30	21:52	1:08
DC	43	18:30	02:00	22:28	1:26
Bedtime weekends					
BYWS	44	21:30	05:00	23:33	1:34
DC	43	20:30	02:00	23:15	1:11
Wake-time weekdays					
BYWS	43	05:30	08:00	06:36	0:34
DC	43	06:30	11:26	08:52	1:16
Wake time weekends					
BYWS	44	7:00	14:00	09:37	1:33
DC	43	4:30	12:15	09:02	1:36

Differences between sleep routines before diagnosis and during chemotherapy. A 2 x 2 within-subjects analysis of covariance was performed to compare differences

between weekday and weekend sleep schedules before diagnosis and during chemotherapy. The within-subjects factors were weekday versus weekend and before diagnosis versus during chemotherapy (see Figure 5). There was a significant within-subjects effect for weekday versus weekend ($F[1] = 22.2$; $p < .01$), but not for before versus during treatment. Post-hoc paired t-tests found significant differences between bedtimes on weekdays/weekends ($t[42] = -10.41$; $p < .01$) and wake-times on weekdays/weekends ($t[42] = -11.46$; $p < .01$) before chemotherapy. During chemotherapy, while there was a significant difference between bedtimes on weekdays/weekends ($t[42] = -0.16$, $p < .01$), there was no significant difference between wake-times on weekdays and weekends. The difference between bedtimes on weekdays and weekends was also shorter during chemotherapy (47 minutes) than before diagnosis

Table 9
ANOVA for Within-Subjects Effects of Sleep Routines on Weekdays/Weekends Before/During Chemotherapy (n = 38)

Source	df	F	p
Weekends/Weekdays	1	70.087	<.001
Before/During	1	1.094	.302
Weekend/Weekday* Before/During	1	9.454	.004
Subjects Within Weekends/Weekdays	38	-	-
Subjects Within Before/During	38	-	-
Subjects Within Weekend/Weekday* Before/During	38	-	-

(101 minutes). Therefore, sleep schedules during chemotherapy were consistent with weekend sleep schedules before diagnosis.

Diary data related to daytime naps, sleepiness, and medications. Participants also recorded naps, overall daytime sleepiness, and medications in their diaries. The diary question related to daytime naps was, "How much, if any, did you nap today?" Most participants responded with a single number, and it was unclear whether they responded with the number of naps or the number of hours they napped that day. Although actigraphs were worn continuously, naps were not evaluated by actigraphy. To do so, a more detailed diary of activities would have been necessary to limit overestimation of sleep caused by quiet activities such as watching television. Daytime sleep and/or low activity are likely important, however, and warrant further investigation. Daytime sleepiness was measured on a numeric scale from 1 (not sleepy at all) to 5 (most sleepy). The mean in this sample was 2.7 (*SD* = 0.8).

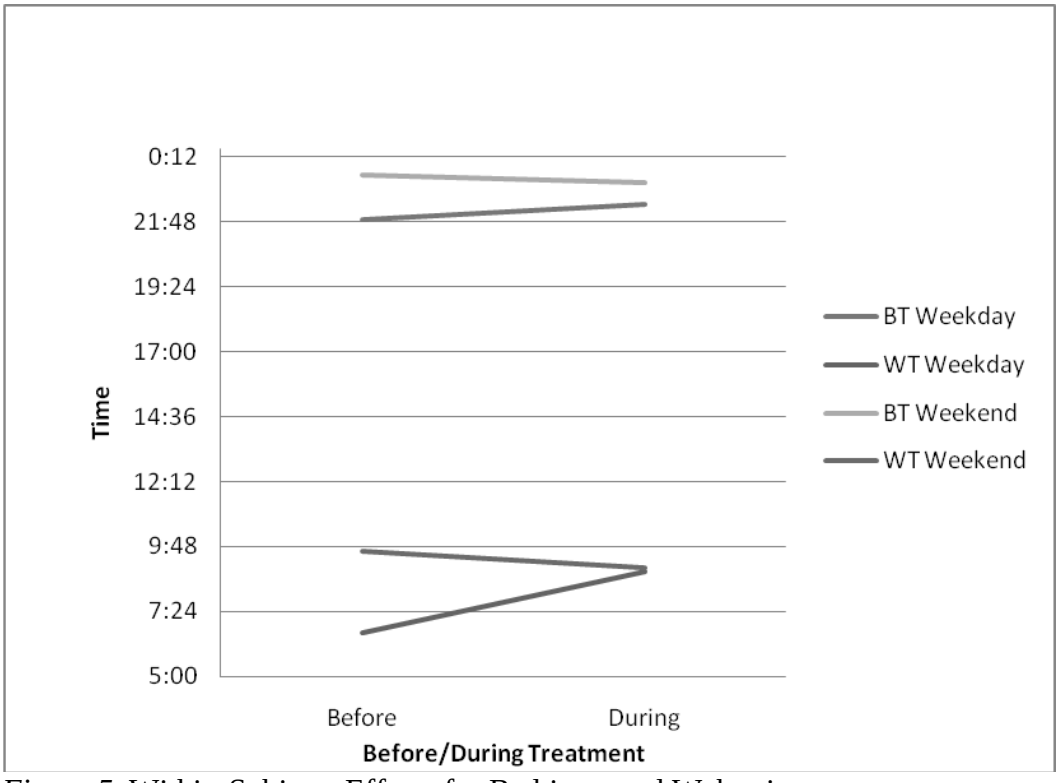

Figure 5. Within-Subjects Effects for Bedtimes and Wake-times on Weekdays/Weekends Before/During Chemotherapy.

Participants were asked to record medications (drug, dose, time) taken for symptom management, and medications that could affect sleep (i.e. prednisone, dexamethasone), in their diaries. The primary symptoms treated with medication were pain (i.e. nociceptive, neuropathic) and nausea. Symptom management medications were categorized by the investigator as analgesia using narcotic medications; analgesia for neuropathic pain; or antiemetic medications (see Table 9). Narcotic pain medications were oxycontin, oxycodone, MS Contin, morphine, vicodin, methadone, and dilaudid; neuropathic pain medications were gabapentin, pregabalin (Lyrica), clonazepam, and amitriptyline. Antiemetic medications were ondansetron, promethazine, dronabinol, granisetron, and aprepitant (Emend).

Half of the participants were taking corticosteroids (i.e. prednisone or dexamethasone), an integral part of ALL treatment, during data collection. Only one participant reported taking a medication prescribed specifically for sleep (i.e. zolpidem/Ambien). Certain medications (i.e. lorazepam, diphenhydramine, trazodone, amitriptyline) were used for various purposes. Lorazepam was used to treat anxiety, nausea, and sleep; diphenhydramine for allergic reactions and sleep. Trazodone and amitriptyline are antidepressants, but trazodone is used to treat sleep, and amitriptyline is used to treat sleep and neurpathic pain (American Society of Health-System Pharmacists Inc, 2007).

Table 10

Number of Doses of Analgesics and Antiemetic Medications Taken during 7-day Data Collection Period (n = 45, 6 missing)

Medications	n	Min	Max	Mean	SD
Analgesics (narcotic medications)	10	1	30	13	10
Analgesics (neuropathic pain medications)	5	7	21	15	6
Antiemetic	26	2	34	8	7
Total Doses	29	2	49	14	14

Of 51 participants, 6 had missing data for medication usage. Sixteen participants reported not taking any medications for symptom management; 7 of them were in maintenance chemotherapy for ALL. The other 9 participants, who did not take any symptom management medications, had various diagnoses (e.g. Ewing's, osteosarcoma, medulloblastoma) and were in earlier phases of treatment; these responses were not expected based on the treatment protocol.

Adolescent Sleep Wake Scale (ASWS) Adolescent Sleep Hygiene Scale (ASHS). Sleep quality was measured using the ASWS which assessed sleep quality along 5 Behavioral Sleep Dimensions: Going to Bed, Falling Asleep, Maintaining Sleep, Reinitiating Sleep, and Returning to Wakefulness. These behavioral dimensions were also subscales of the measure. Scores ranged from 1 to 6, with higher scores indicating better sleep quality (see Table 8).

The ASHS assessed sleep-facilitating and sleep-inhibiting behaviors along 6 conceptual domains: Physiological, Cognitive, Emotional, Sleep Environment, Substances, and Sleep Stability. Scores ranged from 1 to 6, with higher scores indicating better sleep hygiene (See Table 8). Sleep quality and sleep hygiene scores were 4.2 and 4.18 respectively.

Table 11

Descriptive Statistics for Adolescent Sleep Wake Scale (ASWS) and Adolescent Sleep Hygiene Scale (ASHS) Total and Subscale Scores

Scale	n	Min	Max	Mean	SD
ASWS					
Going to bed subscale	45	1.6	6	4.2	1
Falling asleep subscale	46	2	6	4.2	0.8
Maintaining sleep subscale	46	2	5.8	4.3	0.9
Reinitiating sleep subscale	46	3.5	6	4.8	0.7
Returning to wakefulness subscale	46	1.2	6	3.4	0.9
ASWS Total Score	46	2.8	5.4	4.2	0.6
ASHS					
Physical subscale	46	3	6	4.7	0.7
Cognitive subscale	46	2.3	5.5	3.9	0.8
Emotional subscale	46	2	6	4.7	1
Sleep environment subscale	46	2.5	6	5.0	0.9
Substances subscale	46	3.5	6	5.9	0.5
Sleep stability subscale	43	1.25	5.8	3.7	1.1
ASHS Total Score	46	3.7	5.6	4.2	0.5

Secondary Aims

The purpose of the secondary aims was to explore relationships between nocturnal sleep-wake activity (i.e. TST, WASO), treatment-related symptoms, and quality of life; and generate effect size estimates for future research. The relationship between nocturnal sleep-wake activity and treatment-related symptoms was explored using the Memorial Symptom Assessment Scale (MSAS 7-12), and the relationship between nocturnal sleep-wake activity and quality of life was explored using the Pediatric Quality of Life Inventory Version 4.0 Teen Report (PedsQL).

Memorial Symptom Assessment Scale (MSAS 7-12). The modified MSAS 7-12[16] assessed the presence, frequency, intensity, and distress of 10 symptoms the week before (T1) and the week after (T2) chemotherapy (see Table 11). Regardless of the agent itself, chemotherapy appears to cause a core set of symptoms, possibly because of proinflammatory cytokines (Wood, Nail, Gilster et al., 2006). Because the MSAS 7-12 focuses on the most prevalent symptoms, not surprisingly, all symptoms measured were prevalent (i.e. experienced by 10 [26%] to 34 [67%] participants). The mean total number of symptoms at T1 was 4 (*SD* = 2.1) and at T2 was 4 (*SD* = 1.8). Although paired t-tests revealed no statistical difference between the number of symptoms between T1 and T2, symptom characteristics (prevalence, intensity, and distress) did change (see Table 14 and 15). The investigator ranked the most prevalent symptoms as the three symptoms experienced by the highest percentage of participants; the most frequent symptoms as the three symptoms with frequencies rated as "a medium amount" or "almost all the time" by the highest percentage of participants who experienced them; the most intense symptoms as the three symptoms with intensities rated as "medium" or "a lot" by the highest percentage of participants who experienced them; and the most distressing symptoms as the three symptoms with distress ratings of "medium" or "very much" for the highest percentage of participants who experienced them.

[16] "Numbness and tingling of hand and feet" was added to the instrument.

Table 12
Mean, Standard Deviations, and Ranges for Individual Symptoms, Total Number of Symptoms, and MSAS Total Symptom Scores at T1 and T2

Variable	T1 Mean (SD) {Min/Max}	T2 Mean (SD) {Min/Max}
Tiredness	1.8 (0.6) {0.7-3.0)	2 (0.6) {0.7-3.0}
Pain	2.1 (.6) {1.0-3.0}	2.2 {1.0-3.0}
Appetite	1.7 (0.7) {1.0-3.0}	1.9 {0.5-3.0}
Nausea	1.5 (0.8) {0.5-3.0}	1.8 {0.5-3.0}
Numbness & Tingling	1.4 (0.7) {0.7-3}	1.7 {0.7-2.7}
Trouble going to sleep	1.7 (1.0) {0-3.0}	1.6 {0-3.0}
Sadness	1.8 (.6) {1.0-2.7}	1.9 {1.0-3.0}
Itch	1.5 (.6) {0.7-2.3}	1.7 {0.7-3.0}
Worry	1.8 (.6) {1.0-3.0}	2.1 (0.5) {1.0-3.0}
Other	NA[17]	NA
Total Number of Symptoms	4.0 (2.1) {1.0-9.0}	4 (1.8) {1.0-8.0}
Total Symptom Score	6.5 (5) {0-20.5}	7.9 (4.8) {0-18.5}

[17] NA = Not Applicable.

Before chemotherapy, the most prevalent symptoms were tiredness (54%), pain (52%), and changes in appetite (50%). The most frequent symptoms were tiredness (84%), pain (82%), and changes in appetite (80%). The most intense symptoms were pain (84%), tiredness (76%), and sadness (66%);[18] and the most distressing (i.e. troubling, bothersome) symptoms were sadness (73%), pain (71%), and trouble sleeping (56%). Responses to "other" symptoms were dry mouth, sore throat, low blood counts, muscle cramps, nerve pain in feet, smells, hot flashes, hypersensitivity, shakiness, worry about life, and thinking about and having treatments.

After chemotherapy, the most prevalent symptoms were. The most frequent symptoms were tiredness (90%), worry (83%), changes in appetite (83%), and pain (73%). The most intense symptoms were worry (92%), tiredness (87%), and pain (82%); [19] and the most distressing (i.e. troubling, bothersome) symptoms were worry (83%), pain (70%), and nausea (62%). Pain was the only symptom among the most prevalent, intense, and distressing at both time points.

[18] Changes in appetite, nausea and vomiting, and trouble going to sleep were not rated for intensity.

[19] Changes in appetite, nausea and vomiting, and trouble going to sleep were not rated for intensity.

Table 13

Prevalence and Characteristics of Symptoms on the Memorial Symptom Assessment Scale 7-12 before Chemotherapy (n= 46)

		Degree When Symptom Was Present									
Symptom	Prevalence[20] N (%)	Frequency N (%)			Intensity N (%)			Distress N(%)			
		Short	Med	Almost all	Little	Med	A lot	Not at all	Little	Med	Very much
Tiredness	25 (54)	4 (16)	13 (52)	8 (32)	6 (24)	16 (64)	3 (12)	4 (16)	12 (48)	7 (28)	2 (8)
Sadness	15 (33)	6 (40)	9 (60)	0	5 (33)	8 (54)	2 (13)	1 (7)	3 (20)	8 (53)	3 (20)
Itching	15 (33)	7 (47)	8 (53)	0	7 (47)	5 (33)	3 (20)	1 (7)	8 (57)	5 (36)	0
Pain	24 (52)	4 (17)	15 (66)	4 (17)	4 (17)	11 (46)	9 (37)	0	7 (29)	8 (33)	9 (38)
Worry	14 (30)	4 (29)	8 (57)	2 (14)	5 (36)	6 (43)	3 (21)	0	7 (50)	5 (36)	2 (14)
Appetite[21]	23 (50)	4 (20)	7 (35)	9 (45)	NE[22]	NE	NE	6 (30)	9 (45)	3 (15)	2 (10)
Nausea	22 (48)	14 (64)	4 (18)	4 (18)	NE	NE	NE	3 (14)	11 (53)	3 (14)	4 (19)
Trouble sleeping	17 (37)	NE	NE	NE	NE	NE	NE	2 (13)	5 (31)	5 (31)	4 (25)
Numbness & Tingling[23]	18 (39)	10 (55)	3 (17)	5 (28)	9 (50)	7 (39)	2 (11)	6 (33)	9 (50)	1 (6)	2 (11)
Other[24]	NA[25]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

[20] Number of participants who endorsed the symptom.

[21] Instrument only measured prevalence, frequency, and distress.

[22] NE = MSAS 7-12 does not evaluate appetite or nausea for intensity, nor trouble sleeping for frequency and intensity.

[23] Item was added by author as it is a frequently reported side effect of vincristine.

[24] Other symptoms reported were dry mouth, sore throat, low blood counts, muscle cramps, nerve pain in feet, smells, thinking about and having treatments.

Table 14

Prevalence and Characteristics of Symptoms on the Memorial Symptom Assessment Scale 7-12 after Chemotherapy[26] *(n= 46)*

		Degree When Symptom Was Present									
Symptom	Prevalence N (%)	Frequency N (%)			Intensity N (%)			Distress N (%)			
		Short	Med	Almost all	Little	Med	A lot	Not at all	Little	Med	Very much
Tiredness	31 (67)	3 (10)	13 (42)	15 (48)	4 (13)	17 (55)	10 (32)	4 (13)	15 (48)	7 (23)	5 (16)
Sadness	15 (33)	8 (53)	4 (27)	3 (20)	4 (27)	5 (33)	6 (40)	0	6 (40)	6 (40)	3 (20)
Itching	12 (26)	9 (75)	1 (8)	2 (17)	4 (33)	3 (25)	5 (42)	2 (19)	3 (27)	3 (27)	3 (27)
Pain	22 (48)	6 (27)	4 (18)	12 (55)	4 (18)	11 (50)	7 (32)	0	6 (30)	8 (40)	6 (30)
Worry	12 (26)	2 (17)	7 (58)	3 (25)	1 (8)	9 (75)	2 (17)	0	2 (17)	7 (58)	3 (25)
Appetite[27]	22 (48)	4 (17)	11 (48)	8 (35)	NE	NE	NE	4 (20)	6 (30)	7 (35)	3 (15)
Nausea[28]	26 (51)	12 (46)	10 (39)	4 (15)	NE	NE	NE	1 (4)	9 (34)	6 (23)	10 (39)
Trouble sleeping[29]	21 (46)	NE	NE	NE	NE	NE	NE	3 (17)	5 (28)	6 (33)	4 (22)
Numbness & Tingling	18 (39)	5 (30)	6 (35)	6 (35)	6 (35)	8 (47)	3 (18)	3 (18)	9 (53)	4 (23)	1 (6)
Other	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

[25] NA = not applicable; see text for responses.

[26] Referenced the week after chemotherapy.

[27] Instrument measured only prevalence, frequency, and distress.

[28] Instrument measured only prevalence, frequency, and distress.

[29] Instrument measured only prevalence and distress.

Quality of Life

The Pediatric Quality of Life Inventory Version 4.0 Teen Report (PedsQL). The PedsQL contained 23 items assessing function in four domains: physical (8 items), emotional (5 items), social (5 items), and school functioning (5 items). The range of scores was 0 to 100, with higher scores indicating higher quality of life (Varni, 1998-2005) (see Table 13). The mean PedsQL total score was 60 (*SD* = 19). The lowest subscale score was on physical health (*M* = 48, *SD* = 29), reflecting the impact of symptoms on quality of life. The mean school functioning subscale was also low at (*M* =57, *SD* = 24). More than half of the sample (27) answered the questions related to school functioning, but fewer than 27 participants actually were attending school. Likely some participants answered the questions "as if they were going to school" or referencing a home tutor.

The domain of "school" had great variability in this sample. Data about school was collected by interview and medical record review. Several adolescents were too sick to attend school or were not allowed to attend because of neutropenia. One participant dropped out of high school prior to diagnosis and planned to earn a GED and attend technical college. One was diagnosed during her college orientation and took a leave of absence. One had enough credits to graduate from high school a year early. One had planned on "taking a year off" between high school and college before being diagnosed. Otherwise adolescents had home tutors and attended school when their blood counts were high enough and they felt "well enough." Adolescents in maintenance chemotherapy generally attended school, scheduling monthly clinic visits after school.

Table 15

Mean, Standard Deviations, and Ranges for PedsQL Total and Subscale Scores

Scale	n	Min	Max	Mean	SD
Physical health subscale	46	0	100	48	29
Psychosocial health subscale	45	39	100	69	16
Emotional functioning subscale	46	25	100	70	20
Social functioning subscale	45	20	100	70	20
School functioning subscale	27	0	100	57	24
Peds QL Total Score	46	29	93.1	60	19

Relationships between Variables

Correlations measure the size and direction of the linear relationship between two variables; the Pearson product-moment correlation coefficient, *r*, is independent of measurement scale and sample size (Tabachnick & Fidell, 2001). There were no significant correlations between sleep measures (i.e. TST, WASO) and symptoms or sleep measures and quality of life, and so regression analyses were not performed (see Table 14). There was, however, a significant relationship between symptoms after treatment and quality of life (r = -.375, p = .019), indicating quality of life was negatively affected by increased symptoms.

Table 16

Bivariate Correlations between True Sleep Time (TST), Wake After Sleep Onset (WASO), PedsQL total score[30], and MSAS2 Total Score[31]

Variable	1	2	3	4
1. PedsQL (n = 45)	--	-.375*	-.290	-.136
2. MSAS2 (n = 39)		--	.035	.170
3. TST (n = 36)			--	.192
4. WASO (n = 36)				--

*Correlation is significant at the 0.05 level (2-tailed).

A sub-analysis was done to determine if there were relationships between sleep variables (TST, WASO), symptoms, and quality of life for participants who reported trouble going to sleep on the MSAS. T-tests revealed no significant differences in sleep variables, symptoms, or quality of life between participants who reported and did not report trouble going to sleep on the MSAS.

Summary of Findings

The adolescents in this sample had fragmented sleep, but kept consistent sleep schedules on weekdays and weekends during chemotherapy. They experienced multiple symptoms with various frequencies, intensities, and distress, which negatively affected

[30] The items "I hurt or ache," "I have low energy," and "I have trouble sleeping" were removed from the PedsQL and "Did you feel sad yesterday or today" was removed from the MSAS so the strength of the relationship between symptoms and QL was not overestimated.

[31] The item "Did you have trouble going to sleep the last 2 nights?" was removed because it will correlate highly with the sleep measures and overestimate the strength of the relationship between sleep and symptoms (Nail, 2002).

the quality of their lives. Relationships between variables were not significant although the sample size was small. A larger sample size will be required to further explore relationships between sleep symptoms, and quality of life.

CHAPTER 5

Discussion

This study explored nocturnal sleep-wake activity and relationships between sleep, symptoms, and quality of life in adolescents receiving chemotherapy. This chapter will interpret the findings of the study in the broader context of the literature; identify strengths, limitations, and implications; and provide future directions for research. The findings are discussed as they relate to the Modified Model for the Study of Sleep in Adolescents with Cancer (see Figure 6). The model illustrates the broad approach taken in this study with respect to adolescent development and cancer, and the focus on behavioral dimensions of sleep that affect and are affected by quality of life, adolescence, cancer, treatment, symptoms, and sleep hygiene behaviors.

Figure 6. Modified Model for the Study of Sleep in Adolescents with Cancer.

Sample

The findings of the study were influenced by the acuity of the sample, with most of the adolescents in acute phases of chemotherapy. For these adolescents and their families, cancer was not experienced as a chronic illness, but rather as an acute life-threatening illness. Consistent with Rolland's (2005) Family Systems-Illness Model, the majority of these families were in the crisis phase of illness, undergoing crisis

reorganization, learning about the illness, treatment, and symptoms. The setting for cancer treatment is distinctly different for adolescents in acute versus chronic phases of treatment. During acute treatment phases, adolescents received maximal doses of chemotherapy with short intervals between doses. These adolescents were sick, experiencing intense symptoms with little respite. Because of the intensity of chemotherapy, adolescents were monitored closely for side effects and toxicities, and seen in the clinic one to three times per week. For adolescents with bone and brain tumors, chemotherapy was administered in the hospital over two to five days. Sometimes they were readmitted for side effects (e.g. fever and neutropenia, pain and dehydration related to mucositis). While setting of acute treatment provided more opportunities for interaction, the investigator's developmental and clinical expertise was required to collect data from acutely ill adolescents. In accordance with the findings of other studies, disease and treatment-related symptoms were a prominent, distressing aspect of their experiences (Docherty et al., 2006; Enskar et al., 1997; Hinds et al., 1992; Woodgate & Degner, 2004).

The setting of the chronic treatment referred to adolescents with acute lymphocytic leukemia in the maintenance phases of chemotherapy. While their immune systems were still suppressed, and complications requiring hospitalization did occur, maintenance chemotherapy generally was tolerated well. Adolescents were seen in clinic once a month for chemotherapy and blood counts. These families were finding "new normal" lives with cancer and treatment in the background. Interactions with these adolescents were much briefer, and usually included one face-to-face visit and a phone call for the interview.

Sleep

Sleep fragmentation. The adolescents in this study experienced fragmented sleep evidenced by a mean of 80 minutes of wake time after sleep onset (WASO) and a mean sleep efficiency of 82%. Sadeh (2000) defined poor sleep as a sleep percentage (i.e. sleep efficiency) lower than 90% or waking three times and/or more per night for 5 minutes or longer. According to this definition, the adolescents in this study had poor sleep. Other actigraphy findings that have been reported as fragmented or poor sleep include WASO, sleep efficiency, and nocturnal awakenings as determined by device-specific software or the investigator (V. Gedaly-Duff, K. Lee, L. Nail, H. S. Nicholson, & K. P. Johnson, 2006a; Hinds, Hockenberry, Rai et al., 2007; Sadeh, Raviv, & Gruber, 2000). The finding of fragmented sleep in this sample was consistent with Hinds et al. (2007) who reported mean sleep duration of 582 minutes and mean of 15 nocturnal awakenings in a sample of hospitalized children with cancer; and Gedaly-Duff et al. (2006) who reported a mean sleep duration of 482 minutes and a mean of 20 nocturnal awakenings in a sample of non-hospitalized children with leukemia.

The consistency of these findings in hospitalized and non-hospitalized patients suggests that hospitalization may not be the primary reason for fragmented sleep in adolescents/children with cancer. Hospitalized adolescents are assumed more likely to experience fragmented sleep because of sleep environment disruptions; and decreased quality of sleep related to disease and treatment-related factors and changes in usual activity levels (Hinds, Hockenberry, Rai et al., 2007) . Conversely sleep at home is assumed to be more consolidated. However, the findings of this study with those of Gedaly-Duff (2006) suggest sleep may be disturbed at home as well. Further

investigation into the nature of sleep fragmentation in hospitalized and non-hospitalized adolescents is necessary.

Sleep schedules. In this study, there were significant differences between bedtimes and wake-times on weekends and weekdays before treatment, but not during treatment. During treatment there was little difference between bedtimes and wake-times on weekends and weekdays. The majority of adolescents in this study were not attending school and therefore had sleep schedules not restricted by early school start times. Sleep routines during chemotherapy have a potential to perpetuate sleep disturbances precipitated by cancer treatment (Savard & Morin, 2001). Efforts should be made to transition adolescents back to sleep schedules before school re-entry.

Sleep quality and sleep hygiene. The Adolescent Sleep Wake Scale (ASWS) and the Adolescent Sleep Hygiene Scale (ASHS), developed for healthy adolescents, provided important insights into sleep quality and sleep hygiene behaviors in adolescents receiving chemotherapy and also raised questions about the influences of cancer and chemotherapy. Adolescents in this sample had a higher mean ASWS total score (M = 4.2, SD = .6) than a healthy American adolescent sample (M = 4.0, SD = .71) (LeBourgeois et al., 2004). Explored further, mean scores were higher only on the “Going to Bed” (M = 4.2, SD = 1) and “Returning to Wakefulness” (M = 3.40, SD = .9) subscales than healthy adolescents (M = 3.83, SD = 1.05) and (M = 3.05, SD = 2 .25) respectively. In healthy adolescents these two variables reflect the effects of early school start times and discrepancies between school-nights and weekends. The majority of this sample was not attending school, and thus displayed less variability between weekdays and weekends.

The ASHS total score for this sample was not compared to the healthy American sample because three subscales had been removed in the updated version of the instrument. The subscales, however, were compared, and this sample had higher scores on physical, cognitive, emotional, sleep environment and sleep stability subscales were higher than those of healthy American adolescents (LeBourgeois et al., 2005).

The ASWS and ASHS were developed for healthy adolescents, and therefore, have limitations when used in adolescents with cancer. While healthy adolescents and adolescents with cancer engage in similar activities that affect sleep quality and sleep hygiene, such as watching television and playing video games before bedtime, cancer and chemotherapy present additional challenges for adolescents with cancer. Factors likely to affect sleep quality and hygiene in adolescents with cancer include symptoms, medications, low activity levels, and daytime sleep. These factors are not relevant to healthy adolescents, and so are not assessed. Further research is needed to identify how cancer and chemotherapy affect sleep quality and sleep hygiene in adolescents.

Symptoms

This sample experienced more symptoms the week before (M = 3.96, SD = 2.1) and after treatment (M = 3.98, SD = 1.8) than a previously reported sample of children/adolescents with cancer (M = 1.9, SD = 1.6) (Collins et al., 2002). This difference was likely because all of the adolescents in this study were receiving chemotherapy whereas other samples were mixed. At least half of the participants in this study reported tiredness, pain, changes in appetite, and nausea. In accordance with previous findings, the prevalence of symptoms was not necessarily related to their frequency, intensity, or distress (Collins et al., 2000; Collins et al., 2002; Hedstrom et al.,

2005). Pain was a significant symptom in this sample; the only symptom identified as frequent, intense, and distressing. Health care providers may be unaware of the pain experienced at home after treatment from procedures and treatment, and this should be investigated further. The MSAS 7-12 was limited in its assessment of sleep disturbance (i.e. trouble going to sleep) measuring it only in terms of prevalence and distress. Actigraphy however strengthened the assessment of sleep and identified fragmented sleep as a key issue.

Quality of Life

The mean total (M = 60, SD = 19) and physical health subscale scores (M = 47.8, SD = 29) were lower in this sample than another sample of children with cancer (M = 72, SD = 16) and (M =72, SD = 21) respectively, previously reported in the literature (Varni, Limbers, & Burwinkle, 2007). Quality of life scores were lower in this sample likely because all of the participants were receiving chemotherapy.

Quality of life was moderate to low in this sample of adolescents receiving chemotherapy, most of who were in acute phases of treatment. The lowest subscale score was on physical health which is not surprising, because symptoms limited their abilities to participate in normal activities. This finding provides further evidence for the impact of symptoms on quality of life in adolescents with cancer. The school subscale did not apply to many of the adolescents in the study because they were not attending school at the time. A better understanding of "school" in this population is necessary.

Relationships between Variables

This study did not find significant correlations between sleep measures (i.e. TST, WASO) and symptoms or sleep measures and quality of life. There was, however, a

significant relationship between symptoms after treatment (i.e. MSAS2) and quality of life, indicating quality of life was negatively affected by symptoms. The correlation between symptoms and quality of life coupled and the small to medium effect size between true sleep time (TST) and quality of life suggests that sleep may moderate the relationship between symptoms and quality of life, a hypothesis that will be explored in future studies.

Implications

A primary sleep disturbance in this population may be fragmented sleep rather than the usual truncated sleep period seen in healthy adolescents. Actigraphy was able to identify this problem whereas the usual clinical assessment of sleep duration using self-report would not have. Evaluations by sleep specialists should be considered for adolescents/children with cancer complaining of sleep disturbances. Most pediatric cancer centers are part of large tertiary hospital centers and therefore have access to sleep specialists. Pediatric oncologists and nurse practitioners would benefit from education on when to refer patients for sleep evaluations.

Etiologic factors involved in the development of insomnia in cancer patients can be characterized as predisposing, precipitating, or perpetuating factors (Spielman and Glovinsky in Savard and Morin, 2001). Adolescence may be a predisposing factor while chemotherapy may precipitate sleep disturbances. Sleep routines, low activity levels, and daytime sleep may perpetuate sleep disturbances (Savard & Morin, 2001). Careful consideration will need to be given to ways of improving sleep quality and sleep hygiene, recognizing that sleep need likely is greater for these adolescents.

Teaching adolescents with cancer healthy sleep hygiene behaviors such as avoiding late-afternoon naps, tobacco, alcohol, and caffeine prior to bedtime; following a bedtime routine; avoiding physiologically, cognitively, and emotionally stimulating activities before bedtime; sleeping alone, sleeping in a comfortable, quiet, toxin-free environment; maintaining a regular sleep schedule (LeBourgeois et al., 2004); and regular exercise (Wolfson, 2002) is important and likely should be a part of an intervention to improve sleep. Countermeasures developed to help healthy adolescents deal with daytime sleepiness caused by sleep phase delays and early school start times (e.g. planned 25 to 45 minute naps, reducing light exposure at night) may also help adolescents receiving chemotherapy manage disturbed sleep caused by chemotherapy, clinic visits, and hospitalizations. Additionally, non-pharmacological interventions (e.g. relaxation, biofeedback) may be helpful in improving sleep during treatment and beyond.

This study highlighted the need for multidimensional symptom assessment. More attention should be given to symptoms of sadness and worry because of the distress they cause. Most importantly perhaps, providers should ask about the presence of symptoms, including sleep disturbance, rather than wait for adolescents or parents to report them. In assessing quality of life, attention to “school” as a primary role is necessary.

Directions for Future Research

Directions for future research related to sleep, symptoms and quality of life in adolescents receiving chemotherapy include the following:

1. Further explore the nature of fragmented sleep in adolescents receiving chemotherapy.
2. Assessment of 24-hour sleep to address daytime and nocturnal sleep.

3. Develop an instrument to assess the influences of cancer and treatment on sleep quality and hygiene in adolescents.
4. Explore sleep as a moderating variable between symptoms and quality of life.
5. Develop an instrument to measure sleep disturbances in adolescents with cancer.
6. Describe the concept of "school" in adolescents in various phases of treatment.

Limitations

This study had several limitations. First it was limited by the cross-sectional design. It could not be determined whether individual or treatment factors were responsible for sleep and symptoms. A response-shift effect is another potential limitation of a cross-sectional approach. The response-shift effect refers to an adaptation to increased symptoms and decreased quality of life that occurs during treatment and essentially changes a patient's internal standard of measure. Essentially their internal scale changes and responses to the same instrument are incompatible (Sprangers, 1996). Therefore, adolescents in earlier phases of treatment will likely report differently than they would later in their treatment trajectory, or after a relapse.

Strengths

This study also had several strengths. It was prospective and the first study to examine sleep in adolescents receiving chemotherapy in outpatient settings. The study had a high consent rate and little missing data, indicating adolescents with cancer were willing to participate in research and able to complete daily diaries even during acute treatment. The non-categorical approach provided a broad description of adolescents

receiving chemotherapy and illustrated the tremendous impact of cancer and treatment on their lives.

CONCLUSION

This study examined sleep, symptoms, and quality of life in adolescents receiving chemotherapy. The sample reflected the expected age and cancer distributions, but most participants were in the first four to six months of treatment. Despite acute illness, adolescents were willing and able to participate in the study.

The Modified Model for the Study of Sleep in Adolescents with Cancer was an effective framework for examining the complex relationships between sleep, sleep hygiene behaviors, symptoms, cancer, chemotherapy, adolescence, and quality of life. This study found that adolescents receiving chemotherapy had fragmented sleep, and kept sleep schedules consistent with weekend schedules prior to diagnosis, indicating that most of the adolescents were not attending school during data collection. Adolescents receiving chemotherapy experienced multiple symptoms that were frequent, intense, and distressing; and these symptoms had a tremendous impact on their abilities to participate in normal activities, and their quality of life.

There was a significant relationship between symptoms and quality of life, but not between sleep and symptoms or sleep and quality of life. Future research will explore whether sleep might moderate the relationship between symptoms and quality of life. The long-term goal of this research will be to develop interventions to improve sleep and symptom management, and ultimately quality of life, in adolescents with cancer.

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APPENDICES

7-Day Sleep Diary

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Morning Questions							
What time did you turn out the lights to go to sleep last night?							
About how long did it take you to fall asleep?							
About how many times did you wake up during the night?							
About how many hours did you sleep last night?							
What time did you wake up this morning?							
Evening Questions							
How much, if any, did you nap during the day today?							
On a scale of 1 to 5, how sleepy did you feel during the day today (1 not sleepy at all, 5 most sleep)							

Medication Record

Please record any medicines you take during the day other than your chemotherapy (e.g. Benadryl, Zofran, phenergan, oxycodone, Tylenol, Lunesta)

DAY 1		
Medicine	Amount	Time Taken
DAY 2		
Medicine	Amount	Time Taken
DAY 3		
Medicine	Amount	Time Taken
DAY 4		
Medicine	Amount	Time Taken
DAY 5		
Medicine	Amount	Time Taken
DAY 6		
Medicine	Amount	Time Taken
DAY 7		
Medicine	Amount	Time Taken

Sleep Routines "Before You Were Sick" Questionnaire

We want to know what your sleep routines were like before you were sick.

Before you were sick…

1. What time did you go to bed on school nights?

    On weekends?

2. What time did you get up in the morning on school days?

    On weekends?

3. About how many hours did you sleep on school nights?

    On weekends?

4. How long did it take you to fall asleep on school nights?

    On weekends?

5. About how many times did you wake up during the night on school nights?

    On weekends?

Adolescent Sleep Wake Scale

The University of Southern Mississippi • Sleep Research Laboratory
self-report form for 12- to 18-year-old children

Directions

Using the choices below, circle ***how often*** the following things have happened ***during the past week*.**

Never – *has not happened*
Once in Awhile – *happened 20% of the time*
Sometimes – *happened 40% of the time*
Quite Often – *happened 60% of the time*
Frequently, if not always – *happened 80% of the time*
Always – *happened 100% of the time*

Questions 1 – 6 are ***only*** about you ***Going to Bed*** at bedtime		**Never 0%**	**Once in Awhile 20%**	**Sometimes 40%**	**Quite Often 60%**	**Frequently, if not Always 80%**	**Always 100%**
When it's time to go to bed...							
1.	…I want to stay up and do other things (for example: watch TV, play video games, or talk on the phone).	N	O	S	Q	F	A
In general...							
2.	…I have trouble making myself go to bed at bedtime.	N	O	S	Q	F	A
3.	…I am ready to go to bed at bedtime.	N	O	S	Q	F	A
4.	…I enjoy bedtime.	N	O	S	Q	F	A
5.	…I try to "put off" or delay going to bed.	N	O	S	Q	F	A
6.	How long do you ***usually*** "put off" or delay going to bed? (a) Less than 30 minutes (b) 30 to 60 minutes (c) More than 60 minutes						

Questions 7 – 13 are ***only*** about you ***Falling Asleep*** after "lights-out"		**Never 0%**	**Once in Awhile 20%**	**Sometimes 40%**	**Quite Often 60%**	**Frequently, if not Always 80%**	**Always 100%**
When it's time to go to sleep (lights-out)…							
7.	…I have trouble settling down.	N	O	S	Q	F	A
8.	…I feel sleepy.	N	O	S	Q	F	A
9.	…I lie down, <u>but</u> then get up and come out of the bedroom.	N	O	S	Q	F	A
In general...							
10.	…I have trouble going to sleep.	N	O	S	Q	F	A
11.	…I ***need help*** getting to sleep (for example: I need to listen to music, watch TV, take medication, or have someone else in the bed with me).	N	O	S	Q	F	A
12.	…I fall asleep quickly.	N	O	S	Q	F	A
13.	How long does it ***usually*** take you to fall asleep after "lights out"? (a) Less than 15 minutes (b) 15 to 30 minutes (c) More than 30 minutes						
Questions 14 – 20 are ***only*** about how you ***Sleep*** during the night (someone else could have told you these things)							

	During the night…						
14.	…I toss and turn in my bed.	N	O	S	Q	F	A
15.	…I am ***very*** restless.	N	O	S	Q	F	A
16.	…I moan, groan, or talk in my sleep.	N	O	S	Q	F	A
17.	…my legs kick or jerk.	N	O	S	Q	F	A
18.	…I wake up more than once.	N	O	S	Q	F	A
In general...							
19.	…I sleep soundly through the night.	N	O	S	Q	F	A
20.	How often do you ***usually*** wake up during the night? (a) Never (b) 1 to 2 times (c) More than 3 times						

Questions 21 – 27 are ***only*** about you ***Going back to sleep*** after waking during the night	**Always 100%** **Frequently, if not Always 80%** **Quite Often 60%** **Sometimes 40%** **Once in Awhile 20%** **Never 0%**					
After waking up during the night…						
21. … I have trouble going back to sleep.	N	O	S	Q	F	A
22. …I have trouble getting comfortable.	N	O	S	Q	F	A
23. …I wake up another family member.	N	O	S	Q	F	A
24. … I ***need help*** to go back to sleep (for example: I need to watch TV, read, or sleep with another person).	N	O	S	Q	F	A
25. …I feel scared.	N	O	S	Q	F	A

26.	…I roll over and go right back to sleep.	N	O	S	Q	F	A
27.	How long does it ***usually*** take you to go back to sleep after waking during the night? (a) Less than 15 minutes (b) 15 to 30 minutes (c) More than 30 minutes						
	Questions 28 – 33 are ***only*** about you ***Waking*** in the morning						
	In the morning, I wake up…						
28.	…and feel ready to get up for the day.	N	O	S	Q	F	A
29.	…feeling rested and alert.	N	O	S	Q	F	A
30.	…and just can't get going.	N	O	S	Q	F	A
In general…							
31.	…I ***need help*** waking up in the morning (for example: from an alarm clock or another person).	N	O	S	Q	F	A
32.	…I have trouble getting out of the bed in the morning.	N	O	S	Q	F	A
33.	How long does it take you to feel ***completely awake*** in the morning (circle one)? (a) Less than 5 minutes (b) 5 to 15 minutes (c) 15 to 30 minutes (d) More than 30 minutes						

Adolescent Sleep Hygiene Scale

The University of Southern Mississippi • Sleep Research Laboratory
self-report form for 12- to 18-year-olds

Directions

Using the choices below, circle ***how often*** the following things have happened ***during the past week***.

Never – *has not happened*
Once in Awhile – *happened 20% of the time*
Sometimes – *happened 40% of the time*
Quite Often – *happened 60% of the time*
Frequently, if not always – *happened 80% of the time*
Always – *happened 100% of the time*

		Never 0%	Once in Awhile 20%	Sometimes 40%	Quite Often 60%	Frequently, if not Always 80%	Always 100%
After 6:00 in the evening…							
34.	…I have drinks with caffeine (for example: cola, root beer, iced tea, coffee).	N	O	S	Q	F	A
35.	…I smoke or chew tobacco.	N	O	S	Q	F	A
36.	…I drink beer (or other drinks with alcohol).	N	O	S	Q	F	A
During the 1 hour before bedtime…							
37.	…things happen that make me feel ***strong emotions*** (sadness, anger, excitement).	N	O	S	Q	F	A
38.	…I am ***very active*** (for example: playing outside,	N	O	S	Q	F	A

	running, wrestling).						
39.	…I do things that make me feel ***very awake*** (for example: playing video games, watching TV, talking on the telephone).	N	O	S	Q	F	A
40.	…I drink ***more than*** 4 glasses of water (or some other liquid).	N	O	S	Q	F	A
	Always 100%						
	Frequently, if not Always 80%						
	Quite Often 60%						
	Sometimes 40%						
	Once in Awhile 20%						
	Never 0%						
I go to bed…							
41.	…and do things in my bed that keep me awake (for example: watching TV, reading).	N	O	S	Q	F	A
42.	…and think about things I ***need*** to do.	N	O	S	Q	F	A
43.	…feeling upset.	N	O	S	Q	F	A
44.	…and replay the day's events over and over in my mind.	N	O	S	Q	F	A
45.	…and worry about things happening at home or at school.	N	O	S	Q	F	A
46.	…with a stomachache.	N	O	S	Q	F	A
47.	…feeling hungry.	N	O	S	Q	F	A
I fall asleep…							
48.	…while listening to loud music.	N	O	S	Q	F	A
49.	…while watching TV.	N	O	S	Q	F	A
50.	…in a ***brightly*** lit room (for example: the overhead light is on).	N	O	S	Q	F	A

51.	…in a room that feels ***too hot*** or ***too cold***.	N	O	S	Q	F	A
I…							
52.	…use my bed for things ***other than sleep*** (for example: talking on the telephone, watching TV, playing video games, doing homework).	N	O	S	Q	F	A
53.	…check my clock several times during the night.	N	O	S	Q	F	A
	During the school week, I…						
54.	…stay up ***more than 1 hour*** past my ***usual*** bedtime.	N	O	S	Q	F	A
55.	…"sleep in" ***more than 1 hour*** past my ***usual*** wake time.	N	O	S	Q	F	A
On weekends, I…							
56.	…stay up ***more than 1 hour*** past my ***usual*** bedtime.	N	O	S	Q	F	A
57.	…"sleep in" ***more than 1 hour*** past my ***usual*** wake time.	N	O	S	Q	F	A

Memorial Symptom Assessment Scale

Instructions: We want to find out how you have been feeling in the last week.

1. Did you feel more tired than you usually do during the last week?

Yes or No

If Yes:

- How long did it last?
  1-A very short time 2-A medium amount 3-Almost all the time

- How tired did you feel?
  1-A little 2-A medium amount 3-Very tired

- How much did being tired bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

2. Did you feel sad during the last week?

Yes or No

If Yes:

- How long did you feel sad?
  1-A very short time 2-A medium amount 3-Almost all the time

- How sad did you feel?
  1-A little 2-A medium amount 3-Very sad

- How much did feeling sad bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

3. Were you itchy during the last week?

Yes or No

If Yes:

- How much of the time were you itchy?
  1-A very short time 2-A medium amount 3-Almost all the time

- How itchy were you?
  1-A little 2-A medium amount 3-Very itchy

- How much did the itching bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

4. Did you have pain during the last week?

Yes or No

If Yes:

- How much of the time did you have pain?
  1-A very short time 2-A medium amount 3-Almost all the time

- How much pain did you feel?
  1-A little 2-A medium amount 3-A lot

- How much did the pain bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

5. Did you feel worried during the last week?

Yes or No

If Yes:

- How much of the time did you feel worried?
  1-A very short time 2-A medium amount 3-Almost all the time

- How much worry did you feel?
  1-A little 2-A medium amount 3-Very worried

- How much did feeling worried bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

6. Did you feel like eating as you normally do during the last week?

Yes or No

If No:

- How long did this last?
  1-A very short time 2-A medium amount 3-Almost all the time

- How much did this bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

7. Did you feel like you were going to vomit (or throw up) during the last week?

Yes or No

If Yes:

- How much of the time did you feel like you could vomit?
  1-A very short time 2-A medium amount 3-Almost all the time

- How much did this feeling bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

8. Did you have trouble going to sleep during the last week?

Yes or No

If Yes:

- How much did not being able to go to sleep bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

9. Did you have numbness or tingling in your hands or feet during the last week?

Yes or No

If Yes:

- How much of the time did you feel numbness and tingling?
  1-A very short time 2-A medium amount 3-Almost all the time

- How much numbness and tingling did you feel?
  1-A little 2-A medium amount 3-A lot

- How much did the numbness and tingling bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

10. Was there anything else that made you feel bad or sick during the last week? If so, please write it here.

- How much of the time did you feel this?
  1-A very short time 2-A medium amount 3-Almost all the time

- How much of this did you feel?
  1-A little 2-A medium amount 3-A lot

- How much did this bother you or trouble you?
  0-Not at all 1-A little 2-A medium amount 3-Very much

Pediatric Quality of Life Inventory Version 4.0 Teen Report

In the past **ONE week**, how much of a **problem** has it been for you?

ABOUT MY HEALTH AND ACTIVITIES (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard for me to walk more than one block					
2. It is hard for me to run					
3. It is hard for me to do sports activity or exercise					
4. It is hard for me to lift something heavy					
5. It is hard for me to take a bath or shower by myself					
6. It is hard for me to do chores around the house					
7. I hurt or ache					
8. I have low energy					
ABOUT MY FEELINGS (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I feel afraid or scared					
2. I feel sad or blue					
3. I feel angry					
4. I have trouble sleeping					
5. I worry about what will happen to me					
HOW I GET ALONG WITH OTHERS (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. I have trouble getting along with other teens					
2. Other teens do not want to be my friend					

3. Other teens tease me					
4. I cannot do things that other teens my age can do					
5. It is hard to keep up with my peers					
ABOUT SCHOOL (problems with…)	**Never**	**Almost Never**	**Some-times**	**Often**	**Almost Always**
1. It is hard to pay attention in class					
2. I forget things					
3. I have trouble keeping up with my schoolwork					
4. I miss school because of not feeling well					
5. I miss school to go to the doctor or hospital					

Rating Scale for Pubertal Development

Introduction: The next questions are about changes that may be happening to your body. These changes normally happen to different young people at different ages. Since they may have something to do with your sleep patterns, do your best to answer carefully. If you do not understand a question or do not know the answer, just mark "I don't know."

Question	Response Options	Point Value
1. Would you say that your growth in height:	has not yet begun to spurt has barely started is definitely underway seems completed I don't know	1 2 3 4
2. And how about the growth of your body hair? ("Body hair" means hair any place other than your head, such as under your arms.) Would you say that your body hair growth:	has not yet begun to grow has barely started to grow is definitely underway seems completed I don't know	1 2 3 4
3. Have you noticed any skin changes, especially pimples?	skin has not yet started changing skin has barely started changing skin changes are definitely underway skin changes seem complete I don't know	1 2 3 4
FOR BOYS ONLY: 4. Have you noticed a deepening of your voice?	voice has not yet started changing voice has barely started changing	1 2

	voice changes are definitely underway voice changes seem complete I don't know	3 4
5. Have you begun to grow hair on your face?	facial hair has not yet started growing facial hair has barely started growing facial hair growth has definitely started facial hair growth seems complete I don't know	1 2 3 4
FOR GIRLS ONLY: 4. Have you noticed that your breasts have begun to grow?	have not yet started growing have barely started growing breast growth is definitely underway breast growth seems complete I don't know	1 2 3 4
5a. Have you begun to menstruate (started to have your period)?	yes no	4 1
5b. If yes, how old were you when you started to menstruate? Age in years		