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Sleep Disturbance in Adolescent Survivors of Childhood Cancer

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Abstract

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Sleep disturbances are commonly experienced by pediatric cancer patients during treatment. These sleep disturbances are known to affect physical, cognitive/behavioral, and emotional health and impact overall quality of life of these patients. Less is known, however, of the sleep patterns in children and adolescents who have survived cancer or the effects of poor sleep on this population. Adolescents in particular may be at risk for poor sleep and its adverse affects due to their developmental age. Although some research on adolescent survivors of cancer and sleep has been published, thus far these studies use subjective measures of sleep, which may not fully capture the complexities of sleep disturbance in this population. A greater understanding of the nature of sleep and sleep impairments and their association with selected adverse outcomes in adolescent survivors of childhood cancers will provide a crucial foundation for the examination and identification of mechanisms underlying these problems and the development of population-specific interventions.

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BACKGROUND

Sleep disturbances are commonly experienced by pediatric cancer patients during treatment. These sleep disturbances are known to affect physical, cognitive/behavioral, and emotional health and impact overall quality of life of these patients. Less is known, however, of the sleep patterns in children and adolescents who have survived cancer or the effects of poor sleep on this population. Adolescents in particular may be at risk for poor sleep and its adverse affects due to their developmental age. Although some research on adolescent survivors of cancer and sleep has been published, thus far these studies use subjective measures of sleep, which may not fully capture the complexities of sleep disturbance in this population. These studies are also limited by homogenous populations of survivors, and generally lack an explicit guiding theoretical or conceptual framework. The proposed dissertation will serve to fill a gap in the current adolescent cancer survivorship literature. A greater understanding of the nature of sleep and sleep impairments and their association with selected adverse outcomes in adolescent survivors of childhood cancers will provide a crucial foundation for the examination and identification of mechanisms underlying these problems and the development of population-specific interventions.

Adolescent Sleep:

Sleep duration and timing of sleep are known to change over the course of childhood growth and development. Healthy adolescents need approximately nine hours of sleep per night (Carskadon & Acebo, 2002; Carskadon et al., 2002). During adolescence, sleep onset is biologically delayed due to an increased sensitivity to evening light (Carskadon, Acebo, Richardson, Tate, & Seifer, 1997; Carskadon, Labyak, Acebo, & Seifer, 1999; Carskadon, Vieira, & Acebo, 1993; Hagenauer, Perryman, Lee, & Carskadon, 2009; Shinkoda, Matsumoto,

Park, & Nagashima, 2000). This natural delay, compounded by early school start times, opportunities for after school and evening activities (i.e., texting, television, and computer games) (Carskadon, 1990; Wahistrom, 2002; Wolfson & Carskadon, 1998), and caffeine and alcohol use (Carskadon & Dement, 2005; Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002), places adolescents at risk for insufficient sleep duration. Less than 15% of adolescents in one study reported regularly sleeping eight or more hours on school nights and over one-fourth reported sleeping less than seven hours per night (Anderson, Storfer-Isser, Taylor, Rosen, & Redline, 2009; Wolfson & Carskadon, 1998). Additionally, as many as 25% of children and adolescents experience a sleep disorder, such as obstructive sleep apnea, insomnia, or movement disorders (Mindell, Owens, & Carskadon, 1999). However, impaired sleep is more commonly a result of poor sleep habits and shortened sleep duration resulting from the developmental, behavioral, and social factors above (Mindell et al., 1999).

Adolescent Health and Impaired Sleep:

Impaired sleep is a risk factor of cognitive/behavioral, emotional, and physiological consequences. In healthy adolescents, cognitive/behavioral issues include fatigue and daytime sleepiness, poor executive function, and poor academic performance (Anderson et al., 2009; Carskadon, 1990; Dewald, Meijer, Oort, Kerkhof, & Bogels, 2010; Morrison, McGee, & Stanton, 1992; Roberts, Roberts, & Duong, 2009). Adolescents reporting impaired sleep also experience greater anxiety and depressed mood, and more aggressive or withdrawn emotions than their normal sleeping peers (Alfano, Zakem, Costa, Taylor, & Weems, 2009; Coulombe, Reid, Boyle, & Racine, 2011; Moore et al., 2009; Morrison et al., 1992). Longer sleep duration in adolescents has been shown to be protective against depression and suicidal ideation (Gangwisch et al., 2010). Some studies, though not all (Calamaro et al., 2010), report an

association between impaired sleep and obesity in adolescents (Beebe et al., 2007; Gupta, Mueller, Chan, & Meininger, 2002; Noland, Price, Dake, & Telljohann, 2009), as well as pre-hypertension (Javaheri, Storfer-Isser, Rosen, & Redline, 2008).

Sleep in Pediatric Cancer:

As many as 87% of childhood cancer patients experience sleep disturbances (Wright, 2011; Zupanec, Jones, & Stremler, 2010). Though some children experience trouble sleeping before being diagnosed with cancer, many report symptoms arise secondary to treatment (G. Rosen & Brand, 2011). Sleep disturbances can manifest as excessive daytime sleepiness, insomnia, hypersomnia, parasomnia (including conditions such as restless leg syndrome), sleep disordered breathing (such as central and obstructive sleep apneas), and circadian rhythm disorders (G. M. Rosen, Shor, & Geller, 2008; Walker, Johnson, Miaskowski, Lee, & Gedaly-Duff, 2010). Sleep disturbances can also occur together, for example, sleep disordered breathing and insomnia (G. Rosen & Brand, 2011; Walker et al., 2010; Zupanec et al., 2010). Sleep hygiene behaviors in adolescents receiving chemotherapy are similar to adolescents with chronic pain, who report significantly worse problems than healthy children with going to bed, falling asleep, and maintaining sleep (Walker et al., 2010).

The etiology of sleep problems in children with cancer is multifaceted. Especially in children with central nervous system (CNS) tumors, sleep problems often arise as a result of a direct neurological insult (Verberne, Maurice-Stam, Grootenhuis, Van Santen, & Schouten-Van Meeteren, 2012). The mechanism of insult can be the space-occupying tumor itself, or from treatment with cranial radiation, intrathecal chemotherapy, or surgery. Sleep disturbances can also result from neuroendocrine function secondary to insult to the HPA axis (Gordijn et al., 2012). Side effects of various medications used in cancer therapy, particularly dexamethasone

and other pain medications, have sedating effects and are associated with insomnia and resulting excessive daytime sleepiness (Vallance et al., 2010).

Health and Impaired Sleep in Pediatric Cancer Patients:

Similarly to healthy adolescents, pediatric cancer patients reporting impaired sleep are more likely to experience negative psychosocial, physiological, and cognitive/behavior sequelae that contribute to decreased health-related quality of life (Erickson et al., 2011). Pediatric cancer patients receiving chemotherapy who report sleep problems also report significantly worse pain than patients not reporting sleep problems (van Litsenburg et al., 2011). Patients with sleep impairment also report more worry (van Litsenburg et al., 2011), increased daytime sleepiness, and greater fatigue than patients without sleep impairment (Erickson et al., 2011). Emotional sequelae include greater depressive symptoms and behavior changes (Hockenberry et al., 2010). Obesity, anxiety, and seizures have also been related to sleep impairment in this population (G. Rosen & Brand, 2011).

Sleep in Pediatric Cancer Survivors:

While sleep disturbances are moderately well described in pediatric cancer patients in active treatment, less is known about how these children are affected by poor sleep in survivorship. Only two published studies investigate sleep duration in pediatric cancer survivors across different cancer diagnoses. These studies indicate that 55-68% do not meet the recommended sleep duration of nine hours (Mulhern et al., 1995; Tyc, Hadley, & Crockett, 2001). By comparison, prevalence of impaired sleep in young adult and adult survivors of childhood cancer (ages 18-50) varies between 13-50%, with differences between studies likely due to differences in measurement of sleep and statistical analyses (Meeske, Siegel, Globe, Mack, & Bernstein, 2005; Mulrooney et al., 2008). These studies together suggest that sleep

impairments that start in childhood during cancer treatment may persist into adolescence and adulthood. This finding is consistent with adult cancer survivorship literature, with sleep impairments often presenting during cancer treatment (Denlinger & Barsevick, 2009; Savard & Morin, 2001; Savard et al., 2005) and persisting as many as 10 years post-treatment (Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010).

Other studies of sleep in pediatric cancer survivors have focused exclusively on children with central nervous system tumors (Marcus, Trescher, Halbower, & Lutz, 2002). In one study, as many as 73% of children reported sleep disturbances, including excessive daytime sleepiness and sleep disordered breathing. Sleep disturbances were significantly associated with increased fatigue and poor psychosocial functioning (Mandrell et al., 2012). While these studies provide valuable information on the nature of sleep in this patient population, findings cannot be generalized to the broader population of survivors of childhood cancer, as the etiology of sleep disturbance in survivors of CNS tumors may differ greatly from that of other cancer survivors.

Health and Impaired Sleep in Adolescent Survivors of Childhood Cancer:

Apart from literature on pediatric CNS tumor survivors, only two studies to date examine the relationships between poor sleep and health outcomes in pediatric cancer survivors. A recent secondary analysis of data from an ongoing institutional cohort study of childhood cancer survivors in the Southeast revealed significant associations ($p<0.05$) between self-reported sleep problems and problems with depression, anxiety, memory, and academic difficulty. Additionally, participants with sleep problems were more likely to report a greater number of problems (i.e., anxiety, academic difficulty) than participants without sleep problems [OR=2.56, (1.75, 3.73)] (Desaulniers et al., 2012). In a study of acute lymphoblastic leukemia (ALL) survivors, increased sleep disturbance was significantly related to increased depressive symptoms and poor quality of

life per parents' report. However, ALL survivors reported better sleep quality and fewer depressive symptoms than their healthy peers (Gordijn et al., 2013). These conflicting subjective reports point to the need for further study in this population using validated, objective measures that fully capture the complexities of sleep disturbances and associations with other health outcomes.

Studies of older pediatric cancer survivors show similar patterns of negative sequelae associated with impaired sleep. One study found significant differences in subjectively reported sleep quality between young adult survivors of childhood cancer and their siblings (Mulrooney et al., 2008). Survivors with impaired sleep were more likely to have decreased physical functioning, fatigue, obesity, emotional instability (depressed mood/anxiety), and daytime sleepiness, and decreased neurocognitive functioning (including diminished organization, impaired task efficiency, and impaired memory) (Clanton et al., 2011; Meeske et al., 2005; Mulrooney et al., 2008). Compared to sleep-deprived siblings, sleep-deprived survivors also suffered greater decline in physical functioning and general health, suggesting impaired sleep may affect survivors differently than those without a history of cancer.

Methodological Issues:

Of the few studies done to date, the current literature describing impaired sleep in survivors of childhood cancer has several methodological limitations. Most studies use qualitative methods or subjective self-report to describe the prevalence and characteristics of impaired sleep (Meeske et al., 2005; Poretti, Grotzer, Ribi, Schonle, & Boltshauser, 2004). Though these measures provide valuable information on perception of sleep impairment, they may not fully capture the complexities of this late effect in cancer patients (Sateia & Lang, 2008). Studies using objective measures of sleep (i.e., actigraphy or polysomnography) are

limited by small sample sizes and homogenous populations of brain cancer survivors (Marcus et al., 2002; Van Someren et al., 2004). These studies suggest impaired sleep exists in cancer survivors; however, these findings cannot be generalized to the broader population of survivors of childhood cancer. Studies using both subjective and objective measures of sleep, larger sample sizes, and heterogeneous populations of survivors are needed to accurately describe sleep impairment and its effects on survivors of childhood cancer.

Many prior studies also lack a healthy comparison group(Desaulniers et al., 2012; Mulhern et al., 1995; Tyc et al., 2001). The addition of healthy controls in future studies would allow for between group comparisons of severity of sleep impairment. For example, Meeske illustrated that while self-reported sleep quality did not significantly differ between pediatric cancer survivors and their siblings, associated aspects of health were significantly worse in the cancer survivor group (Meeske et al., 2005). The addition of a healthy comparison group to future studies will further build a body of evidence in surrounding assessment of sleep and appropriate intervention for cancer survivors experiencing sleep impairments.

CONCEPTUAL FRAMEWORK

Conceptualizing Impaired Sleep:

Lee's conceptual model of impaired sleep provides an excellent framework for describing sleep disturbance in this population. The model identifies three risk domains for impaired sleep: personal, developmental, and environmental (Lee, 2003; Lee et al., 2004). Personal risks encompass the individual's internal environment, both physiological and psychological. In cancer patients, personal risks would include aspects of cancer diagnosis, treatment, and time off therapy. Developmental risks refer to lifestyle and behaviors, such as a person's age, their sleep hygiene, and the amount of caffeine a person may drink in a day. Environmental risks refer to challenges in the sleep environment, including distractions such as noise, texting or television. Factors within these domains have the ability to influence the quality and quantity of sleep. According to Lee's model, any constellation of factors within these domains may precipitate sleep impairment. Lee's model defines impaired sleep as either sleep deprivation or sleep disruption. Sleep deprivation refers to insufficient amounts of sleep, while sleep disruption refers to frequent interruptions in nocturnal sleep (Lee, 2003). For children with cancer, both sleep deprivation and/or sleep disruption have a significant negative impact on a variety of health outcomes (Ayas, White, Al-Delaimy, & al., 2003; Kripke, Garfinkel, Wingard, Klauber, & Marier, 2002; Tamakoshi & Ohno, 2004). Adverse health outcomes are conceptualized into four domains: physiological, cognitive/behavioral, emotional, and social (Lee, 2003). These domains mirror categories of late effects experienced by survivors of childhood cancer.

Future Directions – A Dissertation Proposal on Sleep in ASCC:

The proposed dissertation will serve to fill the current gap in cancer survivorship literature. Several conceptual models were initially considered as a guiding framework for this

study. After careful review, Lee's conceptual model of impaired sleep was selected for its inclusion of both risk factors and adverse outcomes related to impaired sleep. The model is adapted for this dissertation proposal **(see appendix, Figure 1)** to reflect the direct negative impact of selected personal factors on adverse health outcomes supported by current pediatric cancer survivor literature(Armstrong, Stovall, & Robison, 2010; Boman, Lindblad, & Hjern, 2010; Casillas et al., 2010; Chen, Colan, & Diller, 2011; Costa, 2010; Grewal et al., 2010; Huang et al., 2011; Ishida et al., 2010; Jarvela et al., 2011; Kenney et al., 2011; Kolinsky, Hayashi, Karzon, Mao, & Hayashi, 2010). Furthermore, the adapted model presented here reflects evidence that certain health outcomes may negatively impact sleep (Carotenuto et al., 2006; Long, Krishnamurthy, & Palermo, 2008; Patten, Choi, Gillin, & Pierce, 2000).

Many previous studies of pediatric cancer survivors have focused on patients with a specific diagnosis, including patients surviving acute lymphoblastic leukemia or central nervous system tumors. This proposal will exclude only patients with a prior diagnosis of a central nervous system tumor, or CNS metastasis, as the growth and treatment of these tumors may directly insult areas of the brain known to affect sleep. This will allow for sleep to be compared across diagnoses to determine if a particular diagnosis or treatment (such as radiation or chemotherapy) affects sleep impairment in adolescent survivors of childhood cancer.

The proposed dissertation will also include a group of healthy adolescents to serve as a comparison group. Enrolled survivors will identify friends with no cancer history or history of other chronic illness to enroll in the study. Friend matches convey several advantages. Friends are more likely to be of the same age, race, education, socioeconomic status, and to share similar social habits (e.g. using social networking and emailing/texting at same time) (Grimes & Schulz, 2005; Wacholder, Silverman, McLaughlin, & Mandel, 1992). Friend recruitment has been

successfully implemented in previous studies, including a study of parents of children with cancer,(Bunin, Vardhanabhuti, Lin, Anschuetz, & Mitra, 2011) and a study of children age 5-16 with and without epilepsy,(Kirsch & Wirrell, 2001) Some studies of childhood cancer survivors have used sibling controls;(Mulrooney et al., 2008; Zeltzer et al., 2009) however siblings of childhood cancer survivors have significant posttraumatic issues compared to children who had no family members with major chronic or mental illness (Alderfer, 2003; Kamibeppu et al., 2010). Though the use of friend matches introduces the possibility of a bias sample from lack of random sampling, it is efficient and cost-effective control for confounding demographic and social variables. The inclusion of a suitable comparison group will enable the proposed dissertation to determine differences in severity of sleep impairment in the two adolescent groups – similar to the comparisons made by Mulrooney and Meeske between groups of survivors and their siblings. Impaired sleep may be identified in both groups, however the affects of impaired sleep on other aspects of health may vary.

Lastly, the proposed dissertation will utilize both subjective and objective measures of sleep to most fully describe sleep impairment in this population. Actigraphy watches and sleep diaries will be used to collected objective sleep data. Actigraphy provides a non-invasive, objective measure of sleep/wake patterns and sleep disturbance. Actigraphy has a 91%-96.5% agreement with polysomnography, considered the gold standard for sleep measurement, for differentiating between sleep and wake states in adolescents (Sadeh, Sharkey, & Carskadon, 1994). While sleep diary reports are well correlated with objective sleep measures (Chambers, 1994), sleep diaries will be used only to aid in scoring and analysis of actigraphy data. The use of actigraphy will provide insight into the timing and duration of sleep in this population. The inclusion of subjective measures of sleep will capture data on adolescents' perceptions of their

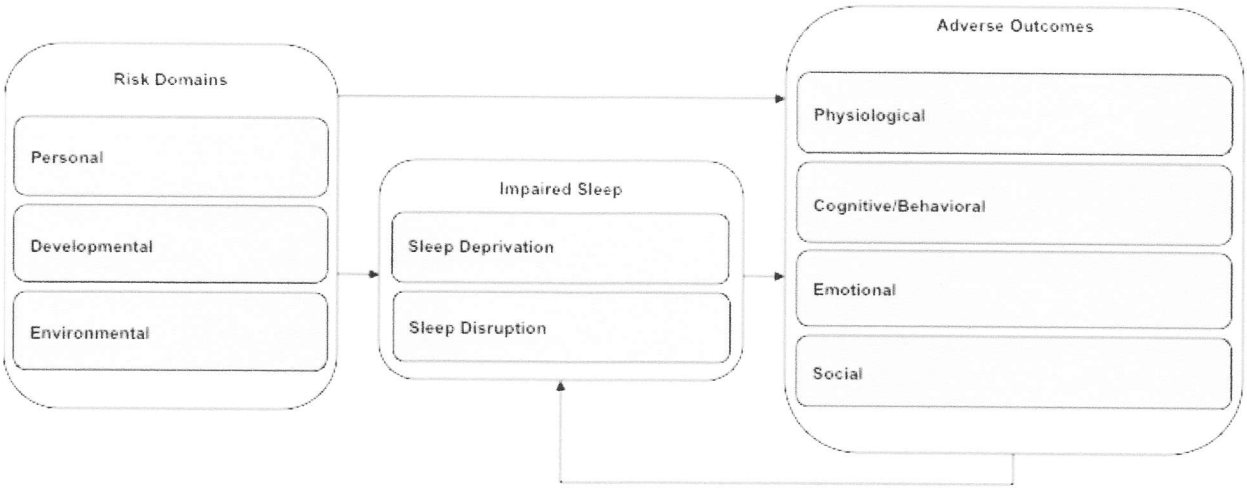
sleep, including information on sleep habits (i.e. if there is noise or light in the sleep environment, and if a regular sleep schedule is kept all week), and if adolescents feel they sleep well and sleep enough. These subjective and objective data together will provide a more complete picture of sleep in adolescent cancer survivors as compared to healthy adolescents.

Conclusions:

Currently, there is a significant gap in the pediatric cancer survivorship literature with regard to sleep. Prior studies of sleep duration indicate sleep may be insufficient in this population; however, only two studies of pediatric cancer survivors describe the prevalence of impaired sleep and associations between impaired sleep and other aspects of health. At present, no studies describe specific features of sleep in adolescent survivors of childhood cancer, such as the timing and duration. A large body of literature suggests that impaired sleep negatively affects aspects of cognitive, behavioral, emotional, and physiological health in healthy adolescents. Adolescent survivors of childhood cancer are already at risk for similar adverse health outcomes due to side effects of chemotherapy and radiation treatment, and may therefore be at even greater risk as a result of impaired sleep. However, there is currently insufficient knowledge of the impact of impaired sleep on the health, function, and quality of life in this population. This study aims to address these gaps in the literature. Findings from this dissertation will provide a greater understanding of sleep impairment and associations with various aspects of health in cancer survivorship, and further build upon the evidence required for the development of appropriate care and interventions for this population.

Appendix:

Figure 1: Lee's Conceptual Model of Impaired Sleep (Adapted)



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