

Gender Differences in Sleep, Fatigue, and Daytime Activity in a Pediatric Oncology Sample Receiving Dexamethasone

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Objective To examine gender differences in sleep, fatigue, and daytime activity in a sample of children with acute lymphoblastic leukemia (ALL). **Methods** Participants included 88 children in maintenance treatment for ALL (34 girls; 54 boys). Participants wore an actigraph for 10 consecutive days (5 days pre-dexamethasone and 5 days during dexamethasone administration). Fatigue instruments were also administered. **Results** Girls napped more and had less fragmented night sleep than boys did. Wake time after sleep onset was sensitive to dexamethasone administration, revealing a differential direction of response for girls and boys. No gender differences were observed for subjective fatigue or daytime activity in the total sample. **Conclusions** Our preliminary findings support gender differences in the sleep of children with cancer after controlling for differences in age, treatment, and risk group. Future research that focuses on the etiology of gender differences and developing interventions will help clarify the clinical application of our findings.

Key words actigraphy; acute lymphoblastic leukemia; dexamethasone; fatigue; gender differences; pediatric oncology; sleep.

Within the conceptual framework of the biopsychosocial model of illness, gender differences are important as they may permeate all three aspects of the model including biological sex differences, psychological gender identity, and societal gender expectations or stereotypes (Engel, 1977). Gender-specific medicine has gained relevance as the scientific community continues to recognize gender differences in normal human functioning, pathophysiology, treatment response, and disease manifestation. Consequently, it is important that pediatric medicine verify the existence of gender differences, ascertain the mechanisms underlying such differences, and facilitate the development of treatment modalities or adjustments tailored to patient gender. Accordingly, this study aimed to examine gender differences in sleep, fatigue, and daytime activity in children receiving maintenance treatment for acute lymphoblastic leukemia (ALL). These symptoms are of interest in this population as studies of persons with cancer suggest that they are prevalent (Theobald, 2004). Indeed, fatigue was rated the most

disturbing treatment-related symptom in children with cancer in two longitudinal studies (Hinds et al., 2000; Hinds, Scholes, Gattuso, Riggins, & Heffner, 1990). Activity levels are of interest as inactivity may represent a mechanism underlying fatigue in survivors of ALL (Meeske, Siegel, Globe, Mack, & Berstein, 2005). Finally, poor sleep may compromise immune functioning, endocrine functioning, and other health-related outcomes (Lee, Cho, Miaskowski, & Dodd, 2004; Spiegel, Leproult, & Van Cauter, 1999); therefore, assessment and treatment of disturbed sleep, fatigue, and inactivity are vital in populations with cancer. Moreover, within the context of gender-specific medicine, ascertaining the presence of gender differences in their behavioral manifestation is essential.

Previous studies have shown administration of prednisone, an anticancer steroidal medication, negatively affects sleep and daytime functioning in children with cancer (Drigan, Spirato, & Gelber, 1992; Harris, Carel, Rosenberg, Joshi, & Leventhal, 1986). Similarly, data

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presented here were collected as part of a larger study that aimed to establish the relations between systemic exposure to dexamethasone (also an anticancer steroidal medication) and adverse behavioral effects on sleep and fatigue in children receiving maintenance treatment for ALL (Hinds, 2007a). Dexamethasone was specifically targeted for this study because it is central to contemporary treatment of ALL, is more potent than prednisone when given at a conventional dosage, and is associated with serious adverse events including osteonecrosis and changes in sleep and fatigue (Bostrom et al., 2003; Drigan et al., 1992; Harris et al., 1986; Kaspers, Pieters, & Veerman, 1997). Results of the published primary analysis revealed a significant decrease in nocturnal awakening and increases in subjective fatigue, total sleep time, and duration of daytime naps after dexamethasone administration. Despite some variability with respect to age and ALL risk group, the authors concluded that dexamethasone treatment adversely altered sleep and fatigue in children and adolescents with ALL, the effect being cumulative over the 5-day drug study period. Our work is a secondary analysis that will not only clarify the relationship of gender with sleep, fatigue, and daytime activity in this sample but also determine whether dexamethasone administration influences any observed gender differences.

Gender differences in the physiology and behavioral manifestations of sleep have been previously documented (Manber & Armitage, 1999; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). There is evidence to support gender differences in sleep across the developmental lifespan, but few studies have focused on gender differences in children's sleep. Within existing studies, there are differences in the samples and methodology. Previous studies on healthy children from Israel and Japan have found gender differences in sleep by using an actigraph, a nonintrusive, wristwatch-style device that objectively records movement and is accompanied by software that produces a number of quantitative activity and sleep variables. One such study of 13- to 14-year-old Japanese school children (Gaina, Sekine, Hamanishi, Chen, & Kagamimori, 2005) indicated that girls performed better than boys on sleep indicators, with boys having more inefficient sleep and more awakenings. Sadeh, Raviv, and Gruber (2000) reported similar results in 140 healthy Israeli children (2nd, 4th, and 6th graders), with girls having longer and more motionless sleep than boys.

With respect to fatigue, gender differences have been reported in children with cancer as well as cancer survivors. A study of 149 children receiving chemotherapy for cancer found girls to self-report more frequent

fatigue than boys (Hockenberry et al., 2003). Two studies of childhood cancer survivors found females to have higher self-reports of fatigue than males did (Meeske et al., 2005; Mulrooney et al., 2004;). Meeske et al. (2005) posited that inactivity represents a mechanism underlying fatigue in ALL survivors; thus this aspect of daytime functioning should be assessed.

Evidence supports gender differences in daytime activity levels of healthy children, but the extent to which age and maturity interact with these differences is clouded by the variability in methodology (e.g., subjective ratings of activity vs. objective measures such as actigraphy or assessment of biological vs. chronological age). A study that used accelerometers with healthy children found boys to be more active than girls across age groups, with overall activity levels decreasing for both genders as they approach adolescence (Riddoch et al., 2004). In contrast, a study using self-report measures of activity found gender differences in daytime activity to dissipate after controlling for biological versus chronological age (Thompson, Baxter-Jones, Mirwald, & Bailey, 2003).

Our aim was to examine gender differences in sleep, fatigue, and daytime activity in a sample of children with cancer that is homogenous in terms of diagnosis, time point in treatment, and receipt of dexamethasone. The following hypotheses were tested: (a) sleep variables differ by gender, with boys demonstrating more disturbed sleep (in terms of more nocturnal awakenings and wake time after sleep onset) and girls demonstrating longer duration of sleep (in terms of greater total sleep time); (b) fatigue scores differ by gender, with girls having higher levels of subjective fatigue than boys; (c) girls demonstrate greater daytime napping as additional support for gender differences in the fatigue experience; and (d) daytime activity level differs by gender, with boys demonstrating greater daytime activity than girls. Also, interactions between gender and dexamethasone administration on variables of sleep, fatigue, and activity were examined. Data were explored within and across risk groups as group differences on study variables were anticipated due to known differences in dosage and treatment (e.g., more aggressive treatment for standard-risk groups). To our knowledge, no studies have examined gender differences in sleep, fatigue, and daytime activity in populations with pediatric cancers.

Methods

Participants

To be eligible for participation, children (and parents) had to be English speaking, 5- to 17-years old, available

Table I. Demographic Characteristics of 88 Children with ALL

Characteristic	Protocol, ALL-risk group				Total (n = 88)
	Total XV low (n = 23)	Total XV standard (n = 27)	COG low (n = 13)	COG standard (n = 25)	
Age (years) [M(SD)]	7.37 (1.76)	10.56 (3.45)	6.76 (1.40)	10.50 (3.32)	9.15 (3.24)
Female	7.85 (1.83)	12.48 (3.49)	8.44 (1.06)	10.86 (3.64)	10.38 (3.47)
Male	7.17 (1.74)	9.59 (3.09)	6.01 (0.70)	10.03 (2.97)	8.37 (2.85)
Gender (n)					
Female	7	9	4	14	34
Male	16	18	9	11	54
Ethnicity (n)					
Caucasian	18	22	12	19	71
African American	4	6	0	2	12
Other	0	0	1	4	5

ALL, acute lymphoblastic leukemia.

to participate at the designated time point in treatment, and willing to give assent (children) and consent (parents). Participants initially included 100 children with low- or standard-risk ALL, all of which were in the same maintenance period of treatment, and receiving the same continuation therapy at one of three sites: St Jude Children's Research Hospital, Memphis, TN, USA; Texas Children's Cancer Center, Houston, TX, USA; or the Hospital for Sick Children, Toronto, Canada. The study was approved by the institutional review board at all three study sites. Because 12 of the 100 participants in the primary study lacked actigraphy data due to equipment failure or insufficient recordings, the sample size for the secondary analysis was reduced to 88. This 12% reduction is less than that reported in previous pediatric actigraphy studies (28%; Acebo et al., 1999). The distribution of participants by age, gender, ethnicity, and risk group is presented in Table I. The distribution of age was significantly different among the four risk groups (younger mean age in low-risk groups) and boys were significantly younger than girls. Both these differences were expected because of known differences in risk factors and prevalence rates of ALL by gender and age. However, gender did not differ by risk group.

Eighty-four eligible participants declined to enroll in the study (refusal rate 45%), with more girls declining than boys (52 vs. 40%) and more adolescents declining than children (50 vs. 44.6%). Refusal rates were similar across ethnicities. The participant burden for the primary study was considerable, including blood sampling for assessing pharmacokinetics. The refusal rate for this study was not discrepant from other studies that have involved similar patients, methods (blood sampling), and burden (Gattuso, Hinds, Tong, & Srivastava, 2006).

Procedures

Participants were recruited from the three sites and from three large cancer treatment protocols. Participants at St Jude Children's Research Hospital were treated on the Total XV protocol; participants at the Texas Children's Cancer Center and the Hospital for Sick Children were treated on Children's Oncology Group (COG) 9904 and COG 9905 studies. COG is a multisite international pediatric cancer cooperative group. The Total XV and COG protocols aim to increase the cure rate in children and adolescents with ALL. The therapy used in these protocols is risk directed; that is, the appropriate intensity of treatment is matched to disease severity and patient characteristics. Disease characteristics were precisely determined and confirmed by early response to therapy. Dexamethasone dosing differed by risk group for the Total XV protocol and the COG protocols: Total XV participants [low risk: (8 mg/m²/day)/TID for 5 days (total pulse 40 mg/m²); standard risk: (12 mg/m²/day)/TID for 5 days (total pulse 60 mg/m²)] received higher doses than COG participants [low and standard risk: (6 mg/m²/day)/BID for 7 days (total pulse 42 mg/m²; 5-day pulse, 30 mg/m²)].

In the prospective repeated-measures study, participants served as their own control. Participation was voluntary and no compensation was provided. The timing of the 10-day period of data collection (after week 50 of treatment) was selected because of (a) similarity in treatment across risk groups by clinical trial, (b) low intensity of treatment demands on participants and families, (c) availability of participants and parents for scheduled follow-ups and assessments, and (d) ability to maintain the same sleep environment (the participants' home) for the two 5-day study periods.

Recruitment was based on planned follow-up visits; therefore, nurse coordinators for the protocols could notify study personnel when an eligible patient was scheduled to return during the data collection weeks. Research staff then contacted eligible patients and their parents. Enrolled patients had the actigraph applied in the outpatient clinic. During the first 5 days, participants did not receive dexamethasone (pre-dex), and during the second consecutive 5 days they received dexamethasone (on-dex) at the doses previously presented. Variables of activity/rest and sleep/wake were measured with a 24-hr wrist actigraph (dominant wrist), worn by participants for all 10 consecutive days. Participants at least 7-years old completed a self-report fatigue instrument on days 2 and 5 of each treatment week. A parent-report fatigue instrument was also administered on the same days for all ages.

Measures

Wrist actigraphy

The Mini Motionlogger AAM-32 (Ambulatory Monitoring Inc., Ardsley, NY, USA) is a noninvasive wristwatch-style device that objectively records movement or physical activity. It contains a biaxial piezoelectric sensor and a microprocessor with programmable epoch length. Data-storage capacity is determined by the epoch length; for this study, the epoch length was 1 min, as suggested by Littner et al. (2003). The system's accompanying software was used to extract several quantitative activity/rest and sleep/wake variables. Sleep was estimated by the algorithm reported by Sadeh, Sharkey, and Carskadon (1994), which has been validated within samples of children and adolescents; our 10-day study design exceeds the criterion for number of nighttime recordings necessary for reliable actigraph assessments (Acebo et al., 1999). For a detailed review of practice parameters and the role of actigraphy in the study of sleep, see Littner et al. (2003). Nocturnal variables extracted for this study were (a) number of awakenings (NWAK), (b) wake time after sleep onset (min) (WASO), and (c) total night sleep time (min). Daytime variables were (a) mean daytime activity (min), (b) total day sleep time (min), (c) number of naps, (d) mean nap duration (min), and (e) day sleep percent or percentage of the wake period spent sleeping. These key terms were recommended via Berger et al. (2007) via the National Cancer Institute State of the Science Conference on Sleep/Wake Disturbances in People with Cancer and Their Caregivers.

Fatigue Scale-Child (FS-C)

Fatigue was assessed by three respondent-specific scales (child, adolescent, and parent). While developing these scales, qualitative data from respondents indicated that the fatigue experience differs between children and adolescents; therefore, development of and assessment with differing instruments was warranted. For children, fatigue is defined as a profound sense of being weak or tired or of having difficulty with movement as measured by the FS-C. The FS-C was designed for children aged 7–12 years. This self-report instrument consists of 14 items that describe the intensity of the participant's fatigue on a 5-point Likert scale in the past 24 hr. Intensity ratings range from 0 (*no fatigue symptoms*) to 70 (*high fatigue*). The FS-C has been reviewed for face, content, and construct validity (Hinds & Hockenberry-Eaton, 2001; Hockenberry-Eaton & Hinds, 2000; Hockenberry et al., 2003). It has been completed by 150 children with cancer in the most recent testing and found to be internally consistent ($\alpha = .84$). Alpha coefficients ranged from .72 to .81 in our investigation.

Fatigue Scale-Adolescent (FS-A)

For adolescents, fatigue is defined as a complex changing state of exhaustion that may be a physical condition, a mental or emotional state, or a combination of physical, mental, and emotional tiredness as measured by the FS-A. This self-report instrument similar to the FS-C but designed for adolescents aged 13–18 years. It is composed of a 14-item scale in which the intensity of each fatigue item is rated on a 5-point Likert scale, with intensity ratings ranging from 14 (*no fatigue symptoms*) to 70 (*high fatigue*) in the past 24 hr. The FS-A has demonstrated good reliability ($\alpha = .67-.95$) as well as face, content, and construct validity (Hinds & Hockenberry-Eaton, 2001; Hinds et al., 2007b; Hockenberry-Eaton & Hinds, 2000; Hockenberry et al., 2003). Alpha coefficients ranged from .89 to .95 in our investigation.

Fatigue Scale-Parent (FS-P)

For parents, fatigue is defined as a state of diminished to complete loss of energy that is influenced by disease state, nutritional, emotional, environmental, personal/behavioral, family, and treatment-related factors as measured by the FS-P. The FS-P consists of 17 items that measure parents' perception of their child's fatigue in the past 24 hr on a 5-point Likert scale, with intensity scores ranging from 17 (*no fatigue*) to 85 (*high fatigue*). The FS-P has been completed by 150 parents with

Table II. Descriptive Statistics for Night Sleep/Wake, Day Rest/Activity, and Fatigue Variables

Variables	Boys (<i>n</i> = 54)		Girls (<i>n</i> = 34)	
	Pre-dex [<i>M</i> (<i>SD</i>)]	On-dex [<i>M</i> (<i>SD</i>)]	Pre-dex [<i>M</i> (<i>SD</i>)]	On-dex [<i>M</i> (<i>SD</i>)]
Night sleep/wake				
NWAK	17.21 (6.88)	15.82 (6.81)	12.56 (6.25)	11.79 (5.48)
WASO	85.74 (52.31)	95.74 (58.15)	70.07 (45.91)	59.16 (58.27)
Total sleep time	543.06 (62.47)	587.08 (100.27)	528.49 (55.09)	575.78 (83.88)
Day rest/activity				
Mean daytime activity	206.61 (44.14)	185.06 (46.31)	195.51 (34.23)	174.86 (34.97)
Total day sleep time	25.70 (35.90)	35.84 (40.19)	33.93 (38.80)	56.95 (38.31)
Number of daytime naps	0.29 (0.36)	0.43 (0.40)	0.32 (0.34)	0.64 (0.40)
Mean nap duration	21.76 (27.65)	31.91 (34.90)	28.02 (31.64)	47.60 (29.23)
Day sleep percent	2.84 (4.09)	4.11 (4.64)	3.51 (3.97)	6.59 (4.66)
Fatigue Scales				
Child (<i>n</i> = 32 boys; 21 girls)	9.78 (8.53)	16.40 (10.59)	8.24 (6.33)	17.50 (8.14)
Adolescent (<i>n</i> = 5 boys; 7 girls)	20.50 (5.74)	32.40 (12.90)	30.00 (9.07)	31.86 (12.20)
Parent (<i>n</i> = 53 boys; 31 girls)	32.24 (10.41)	43.97 (13.37)	34.52 (10.18)	45.03 (13.12)

n, number of participants; NWAK, number of awakenings; WASO, wake time after sleep onset; Pre-dex, week prior to administration of dexamethasone; On-dex, during administration of dexamethasone.

children of all ages and has acceptable internal consistency ($\alpha = .87$; Hinds & Hockenberry-Eaton, 2001; Hockenberry-Eaton & Hinds, 2000; Hockenberry et al., 2003). Alpha coefficients ranged from .91 to .92 in our investigation.

Planned Analyses

Independent longitudinal analyses using a Linear Mixed Effect model as described in Diggle, Heagerty, Liang, and Zeger (2005) were completed to assess the effects of gender on each night sleep/wake and day activity/rest variable. We used the PROC MIXED procedure from the statistical software package SAS 9.1 (SAS Institute Inc., 2000). Longitudinal analysis in which actigraphy data is examined for every 24-hr time period as opposed to averaging the variables across treatment weeks is considered superior for such data as it considers the correlation among the observations of the same patient over time. It is also relevant to our data because previous studies show that the effects of dexamethasone are cumulative (Hinds et al., 2007a). Longitudinal analyses were completed with each of the night sleep/wake and day activity/rest variables modeled as dependent variables. Week of treatment (pre-dex vs. on-dex) and gender (male vs. female) were entered into the model as were covariates of age (years) and risk group. We aimed to specifically evaluate gender differences for each sleep/fatigue variable after adjusting for these other covariates given known variations in risk group and age (Hinds et al., 2007a). We also performed an exploratory analysis on gender

differences within each risk group, since the four risk groups were not homogeneous with regard to treatment (including dexamethasone dose) and age. Such analyses were not conducted for the COG low-risk group because of its relatively small sample size ($n = 13$). Please note that the risk group analyses were exploratory as we lacked sufficient power to draw firm conclusions. Stratified two-sample Wilcoxon–Mann–Whitney tests were completed for each fatigue instrument to test for gender differences in fatigue.

Results

Sleep/Wake and Activity/Rest Results for Total Sample

Table II provides means and standard deviations for each night sleep/wake and day activity/rest variable. Generally speaking children had very disturbed sleep with an average of 12 awakenings or more per night and WASO of 1 hr or more. Even so, their total sleep time was not indicative of inadequate sleep duration as they slept as a group >8 hr per night on average. Table III summarizes the longitudinal regression analyses. The r^2 used here is the generalization of R^2 for linear regression framework to the linear mixed-effects model proposed by Xu (2003). This value represents the explained variation in the comprehensive model including covariates of age and risk group. Main effects for gender were found with boys having significantly more NWAK and WASO than girls did across treatment periods. For WASO, there was also

Table III. Longitudinal Regression Results for All Participants

Variables	Gender		Treatment		Treatment × Gender		<i>r</i> ²
	df	<i>F</i>	df	<i>F</i>	df	<i>F</i>	
Night sleep/wake							
NWAK	1, 80	9.08**	1, 758	4.79*	1, 757	0.05	.12
WASO	1, 80	5.56*	1, 767	3.75	1, 766	6.62*	.06
Total sleep time	1, 79	0.16	1, 766	3.11	1, 765	0.02	.12
Day rest/activity							
Mean daytime activity	1, 79	1.91	1, 759	15.63***	1, 759	0.10	.19
Total day sleep time	1, 80	10.00**	1, 767	0.00	1, 766	0.91	.06
Number of daytime naps	1, 80	9.47**	1, 767	0.15	1, 766	2.92	.10
Mean nap duration	1, 79	9.28**	1, 767	0.17	1, 766	0.35	.06
Day sleep percent	1, 80	9.61**	1, 769	0.00	1, 767	1.26	.07

*r*², the total variance explained by the comprehensive model that includes variables as seen above as well as covariates of risk group and age; NWAK, number of awakenings; WASO, wake time after sleep onset

Bold values signify statistical significance.

p* < .05, *p* < .01, ****p* < .001.

an interesting interaction between gender and week of treatment, with WASO decreasing in girls and increasing in boys during the on-dex treatment period. There was no gender difference in total night sleep time. Boys and girls did not differ in mean daytime activity level; however, girls had significantly higher total day sleep time, number of naps, mean nap duration, and day sleep percent than boys did across treatment weeks.

Sleep/Wake and Activity/Rest Results by Risk Group

The following is a summary of the results from the exploratory longitudinal regression analyses completed by risk group. Results for the COG standard-risk group were most similar to that of the total sample. Girls had significantly fewer NWAK than boys did [$F(1,22) = 10.43$, $p < .01$]. There was an interaction between gender and week of treatment [$F(1,215) = 6.10$, $p < .05$]. Specifically, girls had lesser WASO when on-dex ($M = 44.76$; $SD = 21.91$) than pre-dex ($M = 66.18$; $SD = 55.25$) and boys showed the opposite trend, with more WASO on-dex ($M = 90.73$; $SD = 63.17$) than pre-dex ($M = 76.24$; $SD = 43.81$). Girls had considerably more daytime sleep than boys did across treatment periods by way of total day sleep time [$F(1,22) = 11.04$, $p < .01$], number of daytime naps [$F(1,22) = 13.36$, $p < .01$], mean nap duration [$F(1,22) = 8.38$, $p < .01$], and day sleep percent [$F(1,22) = 14.07$, $p < .01$]. No gender differences were observed for the Total XV low- or standard-risk groups.

Fatigue for Total Sample

Table II gives means and standard deviations for each fatigue variable. There were no significant gender

differences on the parent, child, or adolescent fatigue scales after adjusting for risk group. However, these results must be interpreted with caution because after risk group adjustment, some of the comparisons were based on very few participants. Because of these concerns, we did not explore gender differences within risk groups or by age. Further, risk groups were significantly different by age and fatigue measures were also age dependent.

Discussion

The findings presented herein are supportive of gender differences in daytime and nocturnal sleep in children receiving treatment for ALL. The preliminary nature of this work prohibits us from drawing empirical conclusions about how best to apply this knowledge in the clinical setting; however, these findings are informative to future research. From the perspective of gender-specific medicine, because gender differences were found with some being sensitive to drug administration, researchers can develop and test new hypotheses regarding the mechanisms that underlie these differences, be they psychological (e.g., differential mood disturbance), social (e.g., differential expectations regarding sleep/activity behavior), and/or biological (e.g., differential drug metabolism) in nature. Establishment of mechanisms may contribute to development of gender-specific interventions for sleep and fatigue (e.g., gender-specific sleep hygiene practices) or gender-tailored treatment (e.g., differential drug dosing) to ultimately improve functioning and health-related quality of life in this population. Furthermore, the longitudinal effects of sleep disturbances and fatigue during treatment for ALL are

currently unknown, although there is evidence in the survivorship literature that sleep problems and fatigue are common in these individuals (Meeske et al., 2005; Mulrooney et al., 2004; Mulrooney et al., 2007). The degree to which their prevalence or severity are more manifest in survivors of cancer than in healthy sibling controls is unclear; however, this does raise questions for future research as to why these symptoms might persist including whether or not the etiology of these symptoms are the same from the point of treatment in childhood as they are as an adult survivor of cancer. The gender differences observed herein and within the survivorship literature further supports the inclusion of gender-specific investigations in this line of inquiry. Finally, the implications of prolonged sleep disturbance and/or fatigue for health-related outcomes in persons with cancer are a matter for future investigation.

The results of this preliminary work only partially supported our hypotheses. The r^2 -values (Table III) indicate that despite including many variables, relatively little variance was accounted for within our comprehensive models. This is surprising and further study is required to determine the reason for the larger proportion of observed variance especially given the magnitude of sleep disturbance experienced by the children. For example, our sample experienced on average 11–17 awakenings per night. In contrast, a study of healthy 2nd, 4th, and 6th grade children revealed only one or two awakenings per night, as assessed by actigraph recordings (Sadeh et al., 2000). Boys in our sample showed more disturbed sleep than girls did both before and during administration of dexamethasone; however, girls did not have more total nocturnal sleep time as expected. Observed differences in WASO were particularly sensitive to dexamethasone administration and revealed a differential response for girls and boys.

Despite having less disturbed nocturnal sleep, objectively girls demonstrated greater daytime napping in the total sample. This result suggests that gender differences may exist in the fatigue experience. Contrary to this finding, gender differences were not found in subjective fatigue. Gender differences in subjective fatigue may not exist in our sample because of the significant differences found in sleep disruption and daytime compensatory behavior (e.g., napping). Gender differences observed in other populations might be suppressed in our sample by the more disturbed nocturnal sleep in boys and higher rate or duration of napping in girls. In contrast, this null finding may have been due to limitations of our fatigue instrumentation. Analyses had

to be conducted separately for the three instruments (child, adolescent, and parent), thus resulting in small sample sizes for fatigue analyses (e.g., only 13 participants in adolescent analysis). Consequently, statistical power may have been insufficient. Often, much larger sample sizes are required to detect individual differences such as gender differences. Another limitation is that there is currently no well-established cut score for these instruments; therefore, it is unclear what score is indicative of clinically significant fatigue.

We further anticipated daytime activity levels to differ by gender, with boys having greater mean daytime activity than girls; however, this hypothesis did not hold true for the total sample. Although this result did not support our hypothesis, literature on this topic is conflicting (Riddoch et al., 2004; Thompson et al., 2003); therefore, our result is not entirely unexpected. However, chronobiology studies on the impact of pediatric cancer treatment on circadian rhythms in boys and girls may be more informative about and more sensitive to differences in daytime activity and sleep patterns than was the examination of distinct sleep and activity variables reported in this study.

Our exploratory analyses by risk group revealed some gender differences on day and night sleep variables. There was variability among risk groups for several variables, including age, dexamethasone dosage, and disease characteristics. Sample characteristics for the COG and Total XV standard-risk groups were similar; however, the gender effects observed for the COG group do not hold true for the Total XV group. The Total XV risk group received a much higher dose of dexamethasone than the COG groups. The potent effects of higher doses of dexamethasone might overshadow gender differences observed in children receiving lower doses. Our future studies will focus on pharmacokinetics in this sample, which may help further elucidate the variance we observed. Another interesting characteristic of the COG standard-risk group is that this is the only risk group that had a nearly equal number of boys and girls; the other risk groups had considerably more boys than girls. Results for this group more closely matched those of the total sample than did the other risk groups and the difference in gender distribution may have contributed. A discrete treatment difference may have contributed to this discrepancy, or the discrepancy might simply be a statistical anomaly. We can only speculate why sleep, fatigue, and daytime activity variables differed among risk groups; however, these unique findings will guide future research on these observed differences.

Our data include a relatively large number of longitudinal measurements on a specific pediatric medical population and were collected from multiple sites, thus strengthening generalizability. Many methodological limitations to this work stem from it being a secondary analysis and not a prospective study. We lacked data regarding compliance with prescribed dexamethasone, the study was not powered to examine gender differences, we had a less than desirable refusal rate for participation, and risk groups were not stratified by gender. Future studies will prospectively study gender differences in variables before, during, and after drug administration so that gender-specific risk factors or drug sensitivity can be examined in detail. Examining such differences within large homogenous samples of children may benefit the study of interesting interactions observed in our retrospective analysis. Reliable and valid instruments for assessing subjective experiences such as fatigue in children need to be refined continuously. In this study, chronological age was related to differences on various sleep variables. Gender differences in children's sleep, fatigue, and daytime activity may be mediated by age or physiological maturity (Campbell, Darchia, Khaw, Higgins, & Feinberg, 2005; Knutson, 2005; Thompson et al., 2003). Hence, future studies should examine gender in the context of both physiological maturity (e.g., Tanner staging) and chronological age to elucidate differential treatment responses by gender and age or maturity.

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References

- Acebo, C., Sadeh, A., Seifer, R., Tzischinsky, O., Wolfson, A. R., Hafer, A., et al. (1999). Estimating sleep patterns with activity monitoring in children and adolescents: How many nights are necessary for reliable measures? *Sleep*, 22, 95–103.
- Berger, A. M., Wielgus, K. K., Young-McCaughan, S., Fischer, P., Farr, L., & Lee, K. A. (2007). Methodological challenges when using actigraphy in research: Cancer as a model. *Journal of Pain and Symptom Management*, *In press*.
- Bostrom, B. C., Sensel, M. R., Sather, H. N., Gaynon, P. S., La, M. K., Johnston, K., et al. (2003). Dexamethasone versus prednisone and daily oral weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: A report from the Children's Cancer Group. *Blood*, 101, 3809–3817.
- Campbell, I. G., Darchia, N., Khaw, W. Y., Higgins, L. M., & Feinberg, I. (2005). Sleep EEG evidence of sex differences in adolescent brain maturation. *Sleep*, 28, 637–643.
- Diggle, P. J., Heagerty, P., Liang, K. Y., & Zeger, S. L. (2005). Random effects models. *Analysis of longitudinal data*. New York: Oxford University Press.
- Drigan, R., Spirato, A., & Gelber, R. D. (1992). Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. *Medical and Pediatric Oncology*, 20, 13–21.
- Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, 196, 129–136.
- Gaina, A., Sekine, M., Hamanishi, S., Chen, X., & Kagamimori, S. (2005). Gender and temporal differences in sleep-wake patterns in Japanese schoolchildren. *Sleep*, 28, 337–342.
- Gattuso, J., Hinds, P., Tong, X., & Srivastava, K. (2006). Monitoring child and parent refusals to enrol in clinical research protocols. *Journal of Advanced Nursing*, 53, 319–326.
- Harris, J. C., Carel, C. A., Rosenberg, L. A., Joshi, P., & Leventhal, B. G. (1986). Intermittent high dose corticosteroid treatment in childhood cancer: Behavioral and emotional consequences. *Journal of American Academy of Child Psychiatry*, 25, 120–124.
- Hinds, P. S., & Hockenberry-Eaton, M. A. (2001). Developing a research program on fatigue in children and adolescents with cancer. *Journal of Pediatric Oncology Nursing*, 18(Suppl), 3–12.
- Hinds, P. S., Hockenberry, M., Gattuso, J., Srivastava, D. K., Tong, X., Jones, H., et al. (2007a). Dexamethasone alters sleep and induces fatigue in pediatric patients with acute lymphoblastic leukemia. *Cancer*, 110, 2321–30.
- Hinds, P. S., Hockenberry, M., Tong, X., Rai, S. N., Gattuso, J. S., McCarthy, K., et al. (2007b). Validity and reliability of a new instrument to measure

- cancer-related fatigue in adolescents. *Journal of Pain and Symptom Management*, *In press*.
- Hinds, P. S., Scholes, S., Gattuso, J., Riggins, M., & Heffner, B. (1990). Adaptation to illness in adolescents with cancer. *Journal of Pediatric Oncology Nursing*, *7*, 54–55.
- Hinds, P. S., Quargnenti, A., Bush, A., Pratt, C., Fairclough, D., Rissmiller, G., et al. (2000). An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with new diagnosed cancer. *European Journal of Oncology Nursing*, *4*, 6–17.
- Hockenberry-Eaton, M., & Hinds, P. (2000). Fatigue in children and adolescents with cancer: Evolution of a program study. *Seminars in Oncology Nursing*, *16*, 261–272.
- Hockenberry, M. J., Hinds, P. S., Barrera, P., Bryant, R., Adams-McNeil, J., Hooke, C., et al. (2003). Three instruments to assess fatigue in children with cancer: The child, parent, and staff perspectives. *Journal of Pain and Symptom Management*, *25*, 319–328.
- Kaspers, G. J., Pieters, R., & Veerman, A. P. (1997). Glucocorticoid sensitivity and resistance in childhood leukemia. *Drug resistance in leukemia and lymphoma II*. Netherlands: Harwood Academic Publishers.
- Knutson, K. L. (2005). The association between pubertal status and sleep duration and quality among a nationally representative sample of U.S. adolescents. *American Journal of Human Biology*, *17*, 418–424.
- Lee, K., Cho, M., Miaskowski, C., & Dodd, M. (2004). Impaired sleep and rhythms in persons with cancer. *Sleep Medicine Reviews*, *8*, 199–212.
- Littner, M., Kushida, C. A., Anderson, W. M., Bailey, D., Berry, R. B., Davila, D. G., et al. (2003). Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: An update for 2002. *Sleep*, *26*, 337–341.
- Manber, R., & Armitage, R. (1999). Sex, steroids, and sleep: A review. *Sleep*, *22*, 540–555.
- Meeske, K. A., Siegel, S. E., Globe, D. R., Mack, W. J., & Berstein, L. (2005). Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. *Journal of Clinical Oncology*, *23*, 5501–5510.
- Mulrooney, D. A., Mertens, A. C., Neglia, J. P., Green, D. M., Zeltzer, L., & Robison, L. L. (2004). Fatigue and sleep in survivors of childhood cancer: A report from the childhood cancer survivor study (CCSS). *Journal of Clinical Oncology*, *22*(Suppl 14), 8129.
- Mulrooney, D. A., Ness, K. K., Neglia, J. P., Whitton, J. A., Green, D. M., Zeltzer, L. K., et al. (2007). Fatigue and sleep disturbance in adult survivors of childhood cancer: A report from the childhood cancer survivor study (CCSS). *Sleep*, *In press*.
- Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, *27*, 1255–1273.
- Riddoch, C. J., Andersen, L. B., Wedderkopp, N., Harro, M., Klasson-Heggebo, L., Sardinha, L. B., et al. (2004). Physical activity levels and patterns of 9- and 15-yr-old European children. *Medicine & Science in Sports & Exercise*, *36*, 86–92.
- Sadeh, A., Raviv, A., & Gruber, R. (2000). Sleep patterns and sleep disruptions in school-age children. *Developmental Psychology*, *36*, 291–301.
- Sadeh, A., Sharkey, K., & Carskadon, M. (1994). Activity-based sleep-wake identification: An empirical test of methodological issues. *Sleep*, *17*, 201–207.
- SAS Institute Inc. (2000). SAS (version 9.1) [Computer software]. Cary, NC: SAS Institute, Inc., 2000–2004.
- Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *The Lancet*, *354*, 1435–1439.
- Theobald, D. E. (2004). Cancer pain, fatigue, distress, and insomnia in cancer patients. *Clinical Cornerstone*, *6*(Suppl 1D), s15–s21.
- Thompson, A. M., Baxter-Jones, A. D. G., Mirwald, R. L., & Bailey, D. A. (2003). Comparison of physical activity in male and female children: Does maturation matter? *Medicine and Science in Sports & Exercise*, *35*, 1684–1690.
- Xu, R. (2003). Measuring explained variation in linear mixed effects models. *Statistics in Medicine*, *22*, 3527–3541.