Dexamethasone Alters Sleep and Fatigue in Pediatric Patients With Acute Lymphoblastic Leukemia

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BACKGROUND. Dexamethasone improves the cure rate of childhood acute lymphoblastic leukemia (ALL) but causes physical and behavioral adverse events. The objective of the current study was to determine the effect of dexamethasone exposure on sleep and fatigue in pediatric patients with ALL.

METHODS. One hundred pediatric patients with low-risk or standard-risk ALL were enrolled on 1 of 3 protocols (St. Jude Total XV, Children's Oncology Group [COG] 9904, or COG 9905) at 3 institutions. The mean age of the cohort was 9.24 ± 3.23 years (range, 5.03-18.14 years). The majority of patients were white (79%) males (62%) with standard-risk ALL (63%). The cohort was divided into 4 subgroups: St. Jude low-risk, St. Jude standard-risk, COG low-risk, and COG standard-risk. Patients wore a wrist actigraph to monitor sleep activity during 2 consecutive 5-day periods: During the first period, they did not receive dexamethasone; and, during the second period, they did. Patients and their parents completed fatigue instruments on Days 2 and 5 of each period, and parents completed sleep diaries.

RESULTS. Actual sleep minutes, sleep duration, total daily nap minutes, and fatigue increased significantly during the dexamethasone treatment for 3 to 4 of the subgroups. Total daily nap minutes increased significantly for both standard-risk groups during the dexamethasone treatment. Parents reported significant increases in their child's nighttime awakenings, restless sleep, and nap time during dexamethasone treatment.

CONCLUSIONS. Dexamethasone treatment during continuation therapy for childhood ALL significantly and adversely altered sleep and fatigue, confirming that sleep and fatigue are behavioral responses to dexamethasone. *Cancer* **2007; 110:2321–30.** © *2007 American Cancer Society.*

KEYWORDS: pediatric sleep, fatigue, acute lymphoblastic leukemia, dexamethasone, actigraphy, sleep diary.

Dexamethasone is central to contemporary treatment of acute lymphoblastic leukemia (ALL) because of the drug's marked antileukemic effects compared with other glucocorticoids, such as prednisone.[1–12] Although it is highly effective in the treatment of ALL, dexamethasone also is associated with adverse behavioral events, including mania, psychosis, and altered sleep and fatigue.[11–15] Because dexamethasone evokes variable patient responses,[16] it is possible that behavioral responses are related to interindividual variability in systemic exposure to dexamethasone. Before we can determine tailored dosing schedules, we must establish the correlation between dexamethasone and adverse behavioral effects, particularly sleep and fatigue.

The frequency of adverse events related to sleep and fatigue caused by dexamethasone in pediatric ALL therapy is unknown.

Earlier studies of the effects of short-term, high-dose prednisone therapy on behavior, mood, and sleep of pediatric oncology patients. as reported by their parents, indicated significant negative change in the child's attention/hyperactivity, emotional lability, sleep quality, and mood during the on-prednisone week compared with the off-prednisone week.[13,14] In 2 cases of mania or panic in adolescent girls who received dexamethasone as part of their treatment for ALL, the initial symptom was disrupted sleep.[15]

Sleep in well and chronically ill children and adolescents is a complex, vulnerable process involving multiple physiologic body systems that are influenced by certain dynamic biologic, social, cultural, and psychologic factors that simultaneously affect each other.[17,18] Sleep in children and adolescents evolves in somewhat predictable ways, with decreasing nighttime and daytime sleeping and nighttime awakenings occurring with age.[18–22] Reported outcomes of disrupted or poor-quality sleep are increased daytime sleepiness and inattentive behaviors,[23,24] irritability and altered mood,[25–27] reduced ability to learn and use executive functioning abilities,[28–32] lower perceived health-related quality of life and well being,[33,34] and adversely affected immune system indicators.[35] Sleep is sensitive to acute and chronic illnesses and related stressors, such as hospitalizations, and to medications, including glucocorticoids.[36] Disrupted sleep patterns, including those induced by illness and medications, can persist once they are established.[37,38] Sleep quality and fatigue of children and adolescents on and off dexamethasone for the treatment of ALL have not been reported previously.

The objective of the current study was to determine the correlation between systemic exposure to dexamethasone and sleep quality and fatigue levels in pediatric patients during continuation therapy for childhood ALL. Two hypotheses were tested: 1) Dexamethasone contributes to changes in sleep efficiency, actual sleep minutes, sleep duration, nocturnal awakenings, total daily sleep minutes, and daily nap minutes and increased fatigue in children and adolescents; and 2) patient demographic variables (ie, age, sex, and ALL risk category) influence the extent of change in sleep and fatigue observed during dexamethasone treatment.

MATERIALS AND METHODS
Eligibility Criteria
Eligible patients were ages 5 to 18 years and were receiving continuation therapy for ALL at St. Jude Children's Research Hospital (St. Jude), Texas Children's Cancer Center (TCCC), or the Hospital for Sick Children. Patients at St. Jude were treated on the Total XV protocol; patients at TCCC or at the Hospital for Sick Children were treated on Children's Oncology Group (COG) 9904 or COG 9905 studies. No data were collected until after Week 50. The timing of the 10-day data collection periods was selected for 1) similarity in treatment across risk groups within each ALL clinical trial, 2) less intense treatment demands on patients and families, 3) availability of patients and parents at the treatment settings for planned return visits, and 4) ability to maintain the same sleep environment (the patients' homes) for the 10-day study period. Only patients in the low- or standard-risk ALL categories participated in this study, because treatment for high-risk or very-high-risk ALL differs considerably from the treatment for low- and standard-risk ALL.

Patients needed to be English speaking, willing to provide consent according to institutional guidelines, and had parental consent to participate. There were no exclusions based on concurrent drugs. Eligible parents were English speaking, willing to participate in this study, and willing to allow their child to participate in the study. The study was approved by the institutional review boards at all 3 study sites.

The ALL Protocols
The objective of Total XV, COG 9904, and COG 9905 protocols is to increase the cure rate in children and adolescents with ALL with the use of risk-directed therapy. The criteria used in risk classification are summarized in Table 1. Dexamethasone dosing is substantially higher in the Total XV protocol than in the COG protocols (Table 2). Therefore, for our study, the St. Jude (Total XV) patients were analyzed separately from patients who were treated at the other sites on the 2 COG protocols.

Study Design
Patients served as their own control. The 10-day study included 2 treatment periods: During the first 5 days, patients did not receive dexamethasone (off-dex); and during the second consecutive 5 days, they did (on-dex). Patients wore an actigraph on their dominant wrist 24 hours a day for 10 days. Parents and patients who were age ≥7 years independently completed fatigue instruments on Days 2 and 5 of each treatment period, and parents completed a sleep diary on those same days. This 10-day design exceeded the criterion for number of nighttime recordings needed to obtain reliable actigraph assessments of sleep in children and adolescents.[39]

TABLE 1
Risk Criteria Used in 3 Pediatric Acute Lymphoblastic Leukemia Protocols

Low ALL risk category	Standard ALL risk category
St Jude Total XV protocol	
WBC <50×10⁹/L and ages 1–9.9 y, or DNA index ≥1.16, or *TEL-AML1* fusion	T-cell or B-lineage ALLs that do not meet the criteria for low-risk or high-risk ALL*
No CNS3 disease	
No overt testicular disease	
No adverse genetic features	
No poor early response	
COG 9904, 9905 protocol	
WBC <50×10⁹/L and ages 1-9.9 y	B-lineage ALLs that do not meet the criteria for low-risk, high-risk, or very-high-risk ALL†
No adverse genetic translocations	
No CNS3 status	
No overt testicular disease, and	
The presence of 1 of the following:	
TEL-AML1 fusion or trisomes	
of chromosomes 4 and 10	

ALL indicates acute lymphoblastic leukemia; WBC, white blood cells; *TEL-AML1*, the ets variant 6-acute myeloid leukemia 1 fusion gene; CNS3, central nervous system stage 3 disease.

* Defined by the presence of the breakpoint cluster region-Abelson murine leukemia viral (*BCR-ABL*) fusion or by ≥1% leukemic blasts in bone marrow after 6 weeks of remission induction.

† High-risk ALL was defined by the presence of CNS3 status, testicular leukemia, or myeloid/lymphoid or mixed-lineage leukemia gene (*MLL*) rearrangement; and very-high-risk ALL was defined by the presence of *BCR-ABL* fusion, DNA index <0.81, or >25% leukemic blasts after 4 weeks or >5% leukemic blasts after 6 weeks of remission induction.

TABLE 2
Dexamethasone Dosages Used in 3 Pediatric Acute Lymphoblastic Leukemia Protocols

ALL risk group (No. of patients)	Dexamethasone dosage
St. Jude Total XV protocol	
Low risk(24)	8 mg/m² per d÷TID for 5 d (total pulse, 40 mg/m²)
Standard (33)	12 mg/m² per d÷TID for 5 d (total pulse, 60 mg/m²)
COG 9904, 9905 protocols	
Low risk (13)	6 mg/m² per d÷BID for 7 d (total pulse, 42 mg/m²; 5-day pulse, 30 mg/m²)
Standard risk (30)	6 mg/m² per d÷ BID for 7 d (total pulse, 42 mg/m²; 5-day pulse, 30 mg/m²)

ALL indicates acute lymphoblastic leukemia; TID, 3 times daily; COG, Children's Oncology Group; BID, 2 times daily.

Sleep Measures
Wrist actigraphy
The Micromini (Ambulatory Monitoring Inc., Ardsley, NY) is a wristwatch-style device that contains a biaxial piezoelectric sensor and a microprocessor with programmable epoch length. The system's accompanying software was used to compute the sleep characteristics (defined in Fig. 1). Sadeh's algorithm (previously validated against polysomnography in children[40]) is the basis of the sleep-wake scoring used in the software program.

Sleep Diary-Parent
The sleep diary is a 16-item report that was derived from work by Sadeh et al[41] that documents the parents' daily perceptions of their child's sleep and nap patterns during the previous 24-hour period and is completed in 6 to 8 minutes.

Fatigue Measures
Fatigue Scale-Child
The Fatigue Scale-Child (FS-C), which was designed for children ages 7 to 12 years, is a 14-item, self-report instrument that scores the intensity of the patient's fatigue on a 5-point Likert-type scale from 0

(no fatigue symptoms) to 70 (high fatigue) and requires from 6 to 8 minutes to complete.[42–44] In this study, the Cronbach α coefficients ranged from .72 to .81.

Fatigue Scale-Adolescent
The Fatigue Scale-Adolescent, which was designed for adolescents ages 13 to 18 years, is a 14-item, self-report instrument that measures adolescents' cancer-related fatigue on a 5-point Likert-type scale from 14 (no fatigue symptoms) to 70 (high fatigue) and requires from 3 to 4 minutes to complete.[42,43,45] In this study, the Cronbach α coefficients ranged from .89 to .95.

Fatigue Scale-Parent
The Fatigue Scale-Parent consists of 17 items that measure the parents' perception of their child's fatigue on a 5-point Likert-type scale from 17 (no fatigue) to 85 (high fatigue) and can be completed in 7 to 10 minutes.[44] In this study, the Cronbach α coefficients ranged from .91 to .92.

Concurrent Medications
A study team member completed concurrent medication data forms based on information from parents and a medical record review of medications the child received during the 2 5-day study periods. Forty-eight different medications were administered during the first 5-day period, and all but 7 were considered ongoing medications for the patient; 53 different medications were administered during the second 5-day period, and all but 18 were considered ongoing. Of the medications that were not considered ongoing

Key Term	Definition
Nocturnal awakenings	The wake episodes that occur between the onset and offset of each nighttime sleep interval, as measured by actigraphy
Sleep duration	The total number of minutes in bed and scored as nighttime sleep, as measured by actigraphy or parental sleep diary
Sleep efficiency	(time asleep: time in bed) $\times$ 100
Actual sleep minutes	Total number of minutes of nighttime sleep, as measured by actigraphy
Total daily sleep minutes	Total minutes of sleep and time in bed in a 24-hour period, as measured by actigraphy
Total daily nap minutes	Total number of minutes of daytime sleep, as measured by actigraphy
Fatigue – Child	A profound sense of being weak or tired or of having difficulty with movement, as measured by the Fatigue Scale–Child version (FS-C)
Fatigue – Adolescent	A complex, changing state of exhaustion that at times seems to be a physical condition, at other times a mental or emotional state, and still other times a combination of physical, mental, and emotional tiredness, as measured by the Fatigue Scale–Adolescent version (FS-A)
Fatigue – Parent	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 Fatigue Scale–Parent version (FS-P)

FIGURE 1. Definition of study variables.

during the on-dex week, the majority were related to procedures that were considered a single event. Transfusion status also was monitored, but no participant received a transfusion during the study period. Hemoglobin values ranged from 9.1 g/dL to 13.8 g/dL across both 5-day periods.

Sample Size Considerations

The sample-size justification was based initially on the only available sleep and steroid coefficients (sleep efficiency and prednisone) in children and adolescents with ALL; we then re-estimated sample size by using the data collected from the first 46 study participants (26 patients at St. Jude and 20 patients at TCCC). We used baseline values for sleep efficiency during the off-dex week to obtain an estimate of variability to be used in the sample-size calculation and completed 2 separate calculations: 1 for Total XV and 1 for COG 9904 and COG 9905. Similar to the effects of prednisone on sleep efficiency, we

anticipated that dexamethasone would have detrimental effects on sleep and, thus, based our sample estimates on a 1-sided hypothesis. We projected that a change of 10 U on dexamethasone would be important clinically. To detect this difference with 80% power at an level α of .05 and assuming a 1-sided test, approximately 27 evaluable patients were to be enrolled from each of 4 risk groups: St. Jude low risk, St. Jude standard risk, COG low risk, and COG standard risk. Given the lower enrollment in the COG low-risk group (n = 13 patients), findings from the off-dex versus the on-dex analyses for this risk group are considered exploratory.

Sample Characteristics

We enrolled 100 patients in the study. The majority were white boys between ages of 7 years and 12 years who met the criteria for either the St. Jude or COG standard-risk group. The distribution of patients by age, sex, race, and risk group is presented in Table 3.

TABLE 3
Demographic Characteristics of 100 Pediatric Patients With Acute Lymphoblastic Leukemia

Characteristic	No. of patients
Sex	
Girls	38
Boys	62
Age at enrollment, y	
<7	28
7-12	57
≥13	15
Race	
White	79
Black	14
Asian	1
Other	6
Protocol, ALL risk group	
St. Jude, low risk	24
St. Jude, standard risk	33
COG, low risk	13
COG, standard risk	30
Enrollment site	
The Hospital for Sick Children	12
St. Jude Children's Research Hospital	57
Texas Children's Cancer Center	31

ALL indicates acute lymphoblastic leukemia; COG, Children's Oncology Group.

Actigraph data are not available for 12 of the study participants because of actigraph failure or insufficient recordings, a rate that is less than half of the rate (28%) reported previously in pediatric studies.[19]

Statistical Analyses

To compare the average scores of study variables between the 2 5-day study periods, we used a 1-sample Student t test. Only those patients who had at least 3 of 5 days of actigraph data during each period were included in this analysis. Subsequently, longitudinal methods (PROC MIXED) that incorporated all observations were used to analyze the data, and the conclusions obtained from the 2 approaches were compared. Testing of the regression coefficient corresponding to risk group provided the evidence of difference in sleep and fatigue between the 2 study periods. We completed a similar analysis for all dependent measures based on actigraph measures and parent sleep diaries. After primary analyses were completed, we calculated observed power for each sleep variable (results not shown).

For fatigue data, we calculated a summed score for each fatigue questionnaire at each time point. We computed the average fatigue score for each study period and tested whether the differences between those 2 scores were significantly different from zero by using the 1-sample Student t test. We also used the

mixed-effects models, which incorporated all observations, to assess the impact of time period (off-dex or on-dex) on fatigue. The criterion for significance for all analyses was a P value at the level of $\alpha = .05$. All analyses were performed with the SAS software package (Release 9.1; SAS Institute, Inc., Cary, NC).

RESULTS

Dexamethasone Alters Most Sleep Parameters in Pediatric Patients With ALL

According to the actigraphy measurements, dexamethasone treatment was associated significantly with increases in sleep duration, actual sleep minutes, total daily sleep minutes, and total daily nap minutes and with decreased nocturnal awakenings (Table 4). During the on-dex period, the average actual sleep minutes, average sleep duration, and average nap minutes increased significantly in 2 of the 4 risk groups, and average total daily sleep minutes increased significantly in 3 of the 4 risk groups (Table 5). Parents' responses in the sleep diary indicated significant increases in their child's nighttime awakenings, restless sleep, and nap time in 1 to 4 of the risk groups during the on-dex period and in tiredness and loss of energy during the on-dex period across all 4 risk groups (Table 4).

Dexamethasone Increases Fatigue
Patient self-reports of fatigue

Results of the PROC MIXED analysis indicated significant increases in FS-C scores between the 2 5-day periods within each risk group and across all 4 risk groups ($P < .0001$). Significant increases in fatigue also were evident in the COG standard-risk group ($P = .014$) and in the total patient group of patients ages 13 years to 18 years ($P = .007$) (Table 4). Significant increases in fatigue between the measurement days (Days 2 and 5) of each 5-day period also were observed (Table 6).

Parental reports of patient fatigue

Parents reported significant increases in their child's fatigue during the on-dex period for every risk group at both data comparison points (Table 4). The PROC MIXED analyses yielded results similar to those obtained using the t test.

Demographic Variables Influence Dexamethasone-induced Changes in Sleep
ALL risk group

Risk group was associated significantly with change in sleep efficiency ($P = .012$), actual sleep minutes ($P = .013$), and nocturnal awakenings ($P = .034$).

TABLE 4
PROC MIXED Analyses Comparing Sleep (as Measured by Wrist Actigraphy and Parental Sleep Diary) and Fatigue Scales During Periods Off and On Dexamethasone

Outcome variable	St. Jude low risk	St. Jude standard risk	COG low risk	COG standard risk	All patients*
Wrist actigraph data					
Sleep efficiency	.44	.068	.29	.39	.36
Actual sleep min	.002†	.54	.042†	.001†	<.001†
Sleep duration	.001†	.011†	.010†	.009†	<.001†
Total daily sleep min	<.001†	.001†	.046†	<.001†	<.001†
Nocturnal awakenings	.008†	.36	.11	.12	.043†
Total daily nap min	.13	.014†	.65	.012†	<.001†
Parental sleep diary data					
Sleep time, min	.16	.86	.33	.074	.047†
Difficulty falling asleep?	.061	.21	.94	.001†	<.001†
Enough sleep?	.020†	.010†	.15	.004†	<.001†
Wake up at night?	.001†	.053	.033†	.005†	<.001†
Sleep restlessly?	.001†	.16	.25	.004†	<.001†
Nap during the day?	.081	.076	.095	<.001†	<.001†
Tired during the day?	<.001†	<.001†	<.001†	<.001†	<.001†
Usual energy?	<.001†	<.001†	<.001†	<.001†	<.001†
Fatigue Scales					
FS-C	.019†	.031†	.048†	<.001†	<.001†
FS-A	—	.28	—	.014†	.007†
FS-P	<.001†	<.001†	<.001†	<.001†	<.001†

COG indicates Children's Oncology Group; FS-C, Fatigue Scale-Child; FS-A, Fatigue Scale-Adolescent; FS-P, Fatigue Scale-Parent.
* The estimates were adjusted by group (risk category).
† Significant difference.

Patients in the St. Jude standard-risk group had significantly lower sleep efficiency than patients in the COG low-risk group (regression coefficient, −10.77; $P = .0035$) and the COG standard-risk group (regression coefficient, −7.06; $P = .011$). Compared with the actual sleep minutes experienced by the COG low-risk group, both St. Jude risk groups slept less: the COG versus St. Jude low-risk group (regression coefficient, −86.47; $P = .011$) and the COG versus St. Jude standard-risk group (regression coefficient, −111.75;

TABLE 5
Mean Values of Sleep Variables From Patients Who Had ≥3 of 5 Days of Actigraphy Data Available

	Mean (±SD)								
	Sleep efficiency			Actual sleep mn			Sleep duration		
Risk Group	Off Dex	On Dex	P	Off Dex	On Dex	P	Off Dex	On Dex	P
St. Jude low risk	82.96 (8.07)	83.66 (7.15)	.61	433.13 (55.61)	474.12 (88.39)	<.01*	543.84 (44.51)	590.49 (62.73)	.001*
St. Jude standard risk	80.09 (13.38)	77.54 (13.80)	.09	403.66 (109.27)	412.18 (146.74)	.61	519.46 (62.90)	552.34 (101.17)	.051
COG low risk	90.34 (6.69)	88.65 (7.87)	.23	520.89 (61.46)	566.49 (161.32)	.23	589.33 (42.05)	647.26 (134.14)	.12
COG standard risk	86.32 (9.67)	87.47 (10.26)	.50	437.88 (87.81)	487.67 (97.85)	.001*	527.16 (62.36)	569.60 (74.27)	.006*

	Mean (±SD)								
	Total Daily Sleep Min			Nocturnal Awakenings			Total Daily Nap Min		
Risk Group	Off Dex	On Dex	P	Off Dex	On Dex	P	Off Dex	On Dex	P
St. Jude low risk	567.42 (51.27)	624.91 (81.80)	.002*	18.74 (7.44)	16.52 (6.21)	.03*	23.58 (27.45)	34.43 (31.07)	.16
St. Jude standard risk	545.25 (73.64)	599.47 (107.24)	.002*	16.43 (6.16)	15.38 (7.19)	.32	25.79 (37.80)	47.13 (37.95)	.018*
COG low risk	631.51 (78.47)	681.53 (136.15)	.23	11.47 (6.05)	12.71 (7.58)	.16	42.18 (66.14)	34.28 (52.34)	.56
COG standard risk	558.83 (51.20)	625.62 (88.04)	.001*	13.07 (6.42)	11.80 (5.10)	.38	31.67 (32.15)	56.02 (43.47)	.014*

SD indicates standard deviation; Dex, dexamethasone; COG, Children's Oncology Group.
* Significant difference.

TABLE 6
Differences in Fatigue Scores Between the Periods Off Dexamethasone and On Dexamethasone for Patients by Risk Group

Risk group	No.	Mean	SD	Median	Minimum	Maximum	Student t test	P
Difference of average fatigue between Wk 2 and Wk 1 on D 2								
St. Jude low risk	21	8.29	12.11	6.000	−9.000	34.00	3.14	.005
St. Jude standard risk	30	7.93	10.77	7.50	−13.00	30.00	4.04	<.001
COG low risk	14	10.14	9.10	8.00	−1.00	28.00	4.17	.001
COG standard risk	30	8.07	13.26	6.50	−10.000	37.000	3.333	.002
Difference of average fatigue between Wk 2 and Wk 1 on D 5								
St. Jude low risk	21	12.524	14.62	12.00	−13.00	43.00	3.93	<.001
St. Jude standard risk	31	8.61	15.50	7.00	−33.00	49.00	3.10	.004
COG low risk	13	19.54	12.61	17.00	3.00	45.00	5.59	<.001
COG standard risk	30	11.13	12.22	9.50	−12.00	41.00	4.99	<.001
Difference of average fatigue between Wk 2 and Wk 1								
St. Jude low risk	21	10.41	10.95	9.50	−8.50	31.00	4.35	<.001
St. Jude standard risk	28	8.000	12.11	7.25	−19.00	38.00	3.50	.002
COG low risk	13	14.65	9.56	15.00	4.00	35.50	5.53	<.001
COG standard risk	30	9.60	11.05	8.75	−11.00	39.00	4.76	<.001

SD, standard deviation; COG, Children's Oncology Group.

$P = .002$). Finally, the St. Jude low-risk group had more nocturnal awakenings per night than the COG low-risk group (regression coefficient, 5.23; $P = .011$) and the COG standard-risk group (regression coefficient, 3.83; $P = .038$).

Patient age
Age was associated with change in sleep duration (coefficient, −5.95; $P = .018$). Older patients were in bed less during the on-dex period. Older age also was associated with less total daily sleep minutes (coefficient, −8.39; $P = .002$).

Sex
Boys experienced significantly more nocturnal awakenings per night (coefficient, 3.19; $P = .020$) than girls. However, girls napped more (coefficient, 17.07; $P = .027$). More nocturnal awakenings were associated with lower sleep efficiency (coefficient, −0.6201; $P = .016$).

Parental Sleep Diary Findings
On Day 2 of the off-dex period, parental sleep diary data significantly exceeded actigraph data for 3 groups (St. Jude: low-risk group, $t = -2.51$; $P = .02$; standard-risk group, $t = -2.33$; $P = .027$; COG: low-risk group, $t = -3.74$; $P = .003$). These differences were limited to the first night of sleep diary monitoring and may reflect the parents' inexperience with estimating sleep indicators.

Fatigue Findings
Children experienced significantly more fatigue during the on-dex period than during the off-dex period

(regression coefficient, 6.70; $P < .0001$), and the fatigue findings were similar for adolescents (regression coefficient, 6.45; $P = .0074$). The extent of change in child fatigue was not associated with age ($P = .55$), sex ($P = .76$), or ALL risk group ($P = .66$); likewise, change in adolescent fatigue was not associated with age ($P = .45$), sex ($P = .75$), or ALL risk group ($P = .70$). Parents reported significant increases in their child's fatigue during the on-dex period (regression coefficient, 10.11; $P < .0001$), but their reports were not associated with patient age ($P = .86$), sex ($P = .65$), or ALL risk group ($P = .66$).

DISCUSSION
Actigraphic findings from this study indicate that dexamethasone treatment significantly alters sleep duration, actual sleep minutes, total daily sleep minutes, nocturnal awakenings, and total daily nap minutes in pediatric patients with ALL. Patient and parent fatigue reports both indicate that dexamethasone is associated with significantly increased fatigue. These findings confirm that altered sleep and fatigue are behavioral responses to dexamethasone.

The average sleep efficiency in the 4 risk groups for both 5-day study periods was lower than that of pediatric inpatients on a psychiatric unit (91.9%) and of healthy adolescents who were monitored for 1 week (87% and 89%)[46,47] and was lower than the sleep efficiency (90%) that is considered acceptable for children and adolescents. Only 1 of the 4 risk groups had an average sleep efficiency that met the acceptable level during the off-dex period, and none of the risk groups achieved that standard during the

on-dex period. This indicates that these patients had poor sleep quality even before they began the dexamethasone period. The poor sleep quality may be secondary to the treatment for ALL in terms of the chemotherapeutic agents or the systemic effects of the treatment.[48] but it is not secondary to hospitalization, because none of the patients had been hospitalized during the study period or during the previous several months. The actigraphy finding of low sleep efficiency is supported by parent reports of increased restless sleep of their ill child during the on-dex period. These combined objective and subjective reports indicate that dexamethasone interferes with sleep quality. The average actual sleep minutes in our cohort during both study periods was less than that reported for pediatric patients ages 7 to 14 years who were hospitalized on a psychiatric unit.[47] The average sleep duration for patients during both study periods exceeded that of pediatric outpatients with well-controlled asthma (8.2 hours) and that of age-matched, healthy children (8.3 hours).[49] The average sleep duration in our cohort on certain nights approached or exceeded the recommended sleep time of 10 to 11 hours for children and 9.2 hours for adolescents.[19,20] In addition, our pediatric cohort woke up, on average, 12 to 16 times each night (similar to the number of awakenings of 9 children with ALL who received vincristine during maintenance therapy but who slept in their home environment[50] and similar to the awakenings of 29 pediatric oncology patients who were hospitalized for scheduled chemotherapy for a solid tumor or acute myeloid leukemia[51]), whereas healthy children typically awaken 1 to 5 or 7 times each night.[18,19,52] These findings indicate that pediatric patients receiving dexamethasone for ALL have fewer actual sleep minutes, stay in bed longer, but have poorer sleep quality than well children, children with chronic illnesses, or hospitalized pediatric patients for illnesses other than cancer.

ALL risk group was associated significantly with only 3 sleep variables (sleep efficiency, actual sleep minutes, and nocturnal awakenings), as measured by actigraphy. Of the 4 risk groups, the St. Jude standard-risk group received the highest dose of dexamethasone, had significantly lower sleep efficiency than children in the COG risk groups, and had the lowest actual sleep minutes and sleep duration of all 4 groups. Dexamethasone treatment, rather than the ALL risk group, was the more consistent source of significant influence on sleep outcomes in our study.

Sex did not appear to influence fatigue, but it did influence 2 sleep variables. Boys experienced more nocturnal awakenings per night, and girls had more total daily nap minutes, suggesting that sleep may be sex-sensitive. In studies of healthy grade school children and high school youths, girls slept significantly longer than boys.[53,54] Age was not a consistent factor of influence on sleep or fatigue in our study. Only 2 sleep variables, sleep duration and total daily sleep minutes, were associated with age; the adolescents had less of both compared with the children.

Although the combined objective and patient and parent reports indicate that dexamethasone adversely affects multiple patient sleep-quality indicators and fatigue, the findings do not explicate the precise mechanism of influence. The significant increase in fatigue may have contributed to the extended sleep duration and increased total daily nap minutes. Together, these influences are known to interfere with sleep/wake cycles and sleep regulation.[48] Alternatively for the patients in the St. Jude standard-risk group, which experienced significantly more nocturnal awakenings than the other risk groups, the resulting sleep fragmentation may have contributed to these patient's increased time in bed as an attempt to recover sleep. Indirectly, the sleep fragmentation may have contributed to these patients' increased fatigue. Finally, individual differences in metabolism of dexamethasone may help to explain sleep and fatigue responses to dexamethasone. These possible explanations need to be examined in future studies.

The current study had several limitations. The small number of patients in the COG low-risk group means that findings specific to that risk group need to be considered "exploratory." In addition, our results primarily represent white boys ages 7 to 12 years with standard-risk ALL. We did not study daytime sleepiness, a variable that has been confused conceptually with or linked to fatigue,[22,23] nor did we study the functional outcomes of increased fatigue or altered sleep, such as cognitive or behavioral changes.[24,32,54] However, our study strengths include data collection at 3 pediatric cancer centers, which adds to the generalizability of study findings, the high number of fully evaluable patient responses for fatigue and sleep outcome indicators, the combination of patient, parent, and objective reports to study these variables, the ability to compare outcomes from consecutive periods when the patients did or did not receive dexamethasone, and the strength of the statistical findings. The clinical implications of this study include the need to prepare patients and families before the initiation of continuation therapy for ALL for a likely increase in sleep duration, actual sleep minutes, and total daily

sleep minutes and fatigue during dexamethasone treatment.

In conclusion, dexamethasone treatment alters sleep and fatigue in children and adolescents with ALL, and the degree of alteration differs by patient age, sex, and ALL risk category. Our future studies will examine the relation between these behavioral indicators and the biologic indicators of individual responsiveness to dexamethasone. These behavioral and biologic indicators have the potential to identify pediatric patients with ALL who will be the most sensitive to dexamethasone treatment, thereby allowing clinicians to design optimal dosing schedules for individual patients.

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