

# Longitudinal Course and Risk Factors for Fatigue in Adolescents: The Mediating Role of Sleep Disturbances

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**Objectives** This study (1) examines fatigue over 1 year in adolescents with chronic pain ( $n = 61$ ) and depressive disorders ( $n = 51$ ) compared with healthy adolescents ( $n = 60$ ), (2) identifies longitudinal risk factors, and (3) tests sleep disturbances as a mediator between depression and fatigue. **Methods** Adolescents completed questionnaires at baseline, 6, and 12 months. Mixed effects models examined associations between risk factors and fatigue; structural equation modeling assessed contemporaneous and longitudinal mediation. **Results** Results revealed fatigue persisted at 1 year follow-up, with adolescents in the clinical samples experiencing greater fatigue than healthy youth at all time points ( $ps < .001$ ). Age, baseline depression, and baseline sleep disturbances predicted longitudinal fatigue for the total sample ( $ps < .05$ ), with variation in predictors by subgroup. Sleep quality mediated the contemporaneous effects of depression on fatigue in the clinical samples ( $ps < .05$ ). **Conclusions** Findings underscore the longitudinal course of fatigue and suggest that improving sleep disturbances may reduce fatigue in clinical samples.

**Key words** adolescents; depression; fatigue; recurrent and chronic pain; sleep.

## Introduction

Fatigue is a common complaint in clinical samples of adolescents with chronic medical conditions. Children with juvenile rheumatoid arthritis, neurological disorders, and other chronic pain conditions report significantly higher fatigue levels compared with population norms (Berrin et al., 2007; Gold, Mahrer, Yee, & Palermo, 2009; Varni et al., 2002). Fatigue has also been identified as one of the most frequent and distressing symptoms during active treatment by pediatric oncology patients, and is a symptom that persists after completion of treatment (Collins et al., 2000; Hinds et al., 2000; Ream et al., 2006). Furthermore, with research emerging to support the associations among fatigue, poor quality of life, and impaired role functioning (Gold, Mahrer, Yee, & Palermo, 2009), persistent fatigue may be associated with particular difficulties for

adolescents as they mature into adulthood. Despite the clinical significance of fatigue and its impact on health outcomes, there has been little examination of the course of fatigue in pediatric clinical populations.

Fatigue has been defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases a person's ability to carry out daily activities and participate at the usual level in family, school, and social roles. For example, the Patient-Reported Outcome Measurement Information System (PROMIS), a National Institute of Health roadmap initiative ([www.nihpromis.org](http://www.nihpromis.org)), used this definition to construct patient report measures of fatigue. Conventional assessment of fatigue commonly associates these symptoms alongside physical complaints such as pain and weakness, or poor sleep quality or quantity. Contemporary conceptualization of fatigue incorporates domains of general health,

adequate sleep, and rest periods, as well as psychological and physical wellbeing (Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002). Interference or impairment in one or more of these domains can result in the development of a problematic or distressing level of fatigue. The systematic evaluation of each construct is critical to identify one or more areas for targeted intervention. There are currently limited data on which domains or fatigue symptoms are most impacted in clinical samples.

The experience of a chronic medical condition may contribute to the development of fatigue in children and adolescents in several ways. Fatigue may be associated with physical causes such as pain or muscle weakness, or psychological factors such as depressed mood. Fatigue may also be associated with the status of the chronic illness, such as during the active phase of disease (e.g. chemotherapy treatment during cancer treatment or a flare of juvenile arthritis). Several cross-sectional studies have demonstrated that fatigue was associated with poorer quality of life, physical and school functioning in children with chronic pain conditions, cerebral palsy, and rheumatoid diseases (Berrin et al., 2007; Butbul Aviel et al., 2011; Gold et al., 2009; Reid, Lang, & McGrath, 1997; Varni et al., 2006; Varni, Burwinkle, & Katz, 2004; Varni, Burwinkle, & Szer, 2004). Importantly, research indicates that fatigue symptoms may persist well after the resolution of active disease (Collins et al., 2000; Hinds et al., 2000; Peterson, Mason, Nelson, O'Fallon, & Gabriel, 1997; Ream et al., 2006). These findings highlight the importance of assessing fatigue as an indicator of health status and as an outcome measure. Moreover, the evaluation for fatigue as a symptom and outcome has been included in recommendations outlined by PROMIS, which emphasize the need to use validated measures to assess patient-reported outcomes in clinical practice and research.

Less is known about the risk factors that may contribute to the development of fatigue over time. For children with cancer and rheumatological conditions, poor sleep quality is moderately associated with increased fatigue levels (Butbul Aviel et al., 2011; Erickson et al., 2011). Other risk factors for fatigue that have been identified in otherwise healthy adolescents include female sex, older age, somatic symptoms of pain, and depressive symptoms (ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2006; Viner et al., 2008). Additional research is needed to elucidate how these risk factors may uniquely predict the trajectories of fatigue for clinical samples, including adolescents with chronic pain problems and youth with depressive disorders.

While research has shown that sleep disturbances or insufficient sleep may contribute to the development of and prolongation of fatigue (Oginska & Pokorski, 2006), we know little about the mechanism that accounts for this

association in children and adolescents. Karlson and colleagues recently examined the relationship between depression status, presleep arousal, and fatigue in a sample of healthy college students (Karlson, Natalie, Olson, & Hamilton, 2010). Results revealed presleep arousal mediated the relationship between depression status and fatigue. Sleep disturbances (e.g., presleep arousal; sleep quality) may also play an important role in the longitudinal course of fatigue in clinical pediatric samples, and might lead to the identification of specific targets for treatment or prevention. This research is particularly important in clinical samples of adolescents with chronic pain and depressive disorders as they are known to have elevated sleep disturbances and may be at risk for fatigue (Palermo, Law, Churchill, & Walker, 2012; Palermo, Wilson, Lewandowski, Toliver-Sokol, & Murray, 2011).

To identify the individual contributions of physical and psychological functioning to fatigue levels over time, this study expands on previous research by examining fatigue symptoms in two clinical samples: Adolescents with chronic pain and adolescents with depressive disorders. Comparing these two groups to healthy adolescents may help identify the mechanisms that account for the development and persistence of fatigue. This study adds to the limited existing research by identifying the risk factors and mediators that contribute to fatigue. Specifically, the study aimed to (1) examine and compare the longitudinal trajectory of fatigue symptoms over the course of 1 year in three groups of adolescents, (2) identify baseline risk factors for fatigue over time, and (3) test sleep disturbances as a concurrent and longitudinal mediator of the association between depressive symptoms and fatigue over 12 months. We hypothesized that adolescents with chronic pain and adolescents with depressive disorders would experience greater fatigue symptoms compared with healthy youth, and that fatigue symptoms would persist over the course of 12 months. Furthermore, we hypothesized that female sex, older age, greater pain intensity, higher depressive symptoms, poorer sleep quality, and higher presleep arousal would predict greater problems with fatigue over time in all three cohorts. Finally, we hypothesized that greater sleep disturbances (poorer sleep quality and higher presleep arousal) would mediate the relationship between depressive symptoms and fatigue both concurrently and over 12 months in all three groups.

## Materials and Methods

This study was part of a larger longitudinal study investigating sleep-wake patterns in adolescents in the

northwestern region of the United States. The research protocol was approved by the Institutional Review Boards at the institutions where the study was conducted, and all participants provided informed consent/assent before data collection. Previous publications have focused on associations among pain and sleep-wake disturbances (Law, Dufton, & Palermo, 2012; Lewandowski, Palermo, Motte, & Fu, 2010; Murray, Murphy, Palermo, & Clarke, 2012). However, these reports did not examine fatigue or the trajectory of fatigue over time.

### **Participants**

Participants were adolescents, ages 12–18 years old, from three groups: Adolescents with chronic pain, adolescents diagnosed with a primary depressive disorder, and healthy adolescents. Adolescents with chronic pain were recruited from a multidisciplinary pediatric pain clinic. Eligible participants were approached either during their initial evaluation at the clinic or via a letter mailed to their home. Eligibility criteria included that the pain was unrelated to chronic disease and that pain was present for  $\geq 3$  days a week for 3 months or longer. Exclusion criteria included developmental delay, comorbid medical conditions (e.g., cancer, diabetes), presence of psychosis or active suicidal ideation, inability to ambulate independently, or that the participant was unable to speak or understand English.

The sample of adolescents diagnosed with depressive disorders were youth from two sources: (1) adolescents participating in a randomized controlled trial of depression in young people [brief cognitive-behavioral therapy (CBT) vs. usual care], or (2) adolescents identified from a health maintenance organization pharmacy database as being diagnosed with a depressive disorder. Eligibility criteria included (1) a diagnosis of major depression disorder, dysthymic disorder or depression based on the Schedule for Affective Disorders for School-Age children [K-SADS; (Kaufman et al., 1997)] and (2) a score of  $\geq 16$  for males and  $\geq 20$  for females on the Center for Epidemiological Studies Depression Scale [CES-D; (Radloff, 1977)]. Exclusion criteria were developmental delay, comorbid medical conditions, presence of psychosis or active suicidal ideation, inability to ambulate independently, and being unable to speak or understand English.

The third cohort (healthy adolescents) was recruited from the community through local advertisements. Interested adolescents were screened for eligibility via telephone or in person for the following criteria: (1) absence of current chronic pain, (2) absence of comorbid medical conditions, and (3) no known diagnosis of a developmental disability. Adolescents for this cohort were also

excluded if they met criteria for a depressive disorder on the K-SADS.

The total sample consisted of 172 participants from three cohorts: 61 adolescents with chronic pain, 51 adolescents with primary depression, and 60 healthy adolescents. For the cohort of adolescents with chronic pain, 61 of 97 potential participants were enrolled, 16 declined and 20 did not meet eligibility criteria. The most common reason for ineligibility for adolescents with chronic pain was pain related to presence of a comorbid chronic disease (e.g., arthritis). For the cohort with depression, 219 potential participants were identified from the two sources described above and 134 were excluded for not meeting eligibility criteria. The most common reason for ineligibility for the depressed sample was not meeting K-SADS criteria for a current diagnosis of a depressive disorder. There were 34 adolescents who declined and 51 were enrolled. For the cohort of healthy adolescents, 60 of 107 potential participants were enrolled, 6 declined, and 41 were not eligible. The most common reason for ineligibility for the healthy sample was presence of chronic pain or a current diagnosis of a depressive disorder. For participants in all groups, the primary reason for declining to participate was the time commitment involved in the 12-month study.

### **Procedure**

On enrollment, parents or guardians provided written informed consent and adolescents provided written assent. All adolescents and their parents participating in the study completed study questionnaires and separate K-SADS interviews at all three time points: Immediately after providing informed consent (baseline), 6-month follow-up, and 12-month follow-up. The first assessment was conducted during an in-home visit or at an agreed on public location (e.g., community center, library). The 6-month and 12-month assessments were completed via phone interviews and written questionnaires sent to participants' homes and returned via mail. Families were compensated with gift cards at each time point for their participation in the study.

### **Measures**

#### **Demographics**

Parents or guardians provided information on their child's age, sex, race, ethnicity, and body mass index exclusively at enrollment.

#### **Pain Intensity**

Adolescents reported their usual pain intensity over the past 3 months using the 10-point Numerical Rating Scale (NRS), with 0 indicating "no pain" to 10 indicating

“the worst pain possible.” The NRS is a widely accepted measure of assessment of pain intensity in the pediatric population, and has demonstrated acceptable reliability and validity (von Baeyer, 2009).

### Fatigue Symptoms

The Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL-MFS) was completed by adolescents to assess fatigue symptoms over the past 4 weeks. This 18-item measure examines fatigue in three domains: General fatigue, sleep/rest fatigue, and cognitive fatigue. Sample items include “I feel too tired to do things that I like to do,” “I feel tired when I wake up in the morning,” and “It is hard for me to keep my attention on things.” The responses are scored on a 5-point scale ranging from “never” to “almost always.” Items are summed and scaled to compose a total fatigue score (0–100). Higher scores on the PedsQL-MFS indicate lower levels of fatigue. This measure has demonstrated excellent reliability and has been validated in healthy youth and pediatric medical populations (Gold et al., 2009; Varni, Burwinkle, Katz, Meeske, & Dickinson, 2002; Varni, Burwinkle, & Szer, 2004; Varni et al., 2002). For this study, we identified adolescents as having persistent fatigue if the PedsQL-MFS scores were  $\leq 65$  at all time points. This score has been suggested as an indication of severe fatigue comparable with that experienced by children undergoing active treatment for cancer (Meeske, Katz, Palmer, Burwinkle, & Varni, 2004).

### Sleep Quality

Adolescents rated their sleep quality over the past 4 weeks using the Adolescent Sleep Wake Scale (LeBourgeois, Giannotti, Cortesi, Wolfson, & Harsh, 2005). This 28-item measure examines subjective sleep quality at bedtime, throughout the night, and in the morning. Example items include “In general, I have trouble making myself go to bed at bedtime,” “during the night, I wake up more than once,” and “in the morning, I wake up feeling rested and alert.” There are five response options ranging from “never” to “always.” All items are summed for a total score, with higher scores indicating better quality sleep. This scale has been validated in the adolescent population (LeBourgeois, Giannotti, Cortesi, Wolfson, & Harsh, 2005; Palermo, Wilson, Lewandowski, Toliver-Sokol, & Murray, 2011).

### Presleep Arousal

The Presleep Arousal Scale is an 18-item questionnaire that assesses the frequency of cognitive and arousal symptoms before sleep onset (Nicassio, Mendlowitz, Fussell, &

Petras, 1985). Adolescents are asked to report presleep arousal symptoms over the past week with items assessing cognitive arousal (e.g., “I cannot shut off my thoughts and keep thinking about something”) and somatic arousal (e.g., “My mind is active and I do not feel sleepy”) symptoms. Response options are on a 5-point scale and range from “not at all” to “extremely.” Higher scores indicate greater levels of presleep arousal before falling asleep. This questionnaire has demonstrated acceptable internal consistency and test–retest reliability in healthy adolescents and adolescents with chronic pain (Gregory, Willis, Wiggs, & Harvey, 2008; Palermo, Toliver-Sokol, Fonareva, & Koh, 2007; Palermo, Wilson, Lewandowski, Toliver-Sokol, & Murray, 2011).

### Depressive Symptoms

Depressive symptoms were measured using the 20-item CES-D (Radloff, 1977). Adolescents report on depressive symptoms over the past week and items include “I felt depressed” and “I thought my life had been a failure.” The response options range from “rarely or none of the time” (less than 1 day) to “most or all of the time” (5–7 days). The total score is obtained from summing all items with the range of possible scores being 0–60. Higher scores indicate greater depressive symptoms. This measure has been validated and widely used in the adolescent population and has high internal consistency and adequate test–retest reliability in adolescent samples (Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000; Radloff, 1977; Wight, Sepulveda, & Aneshensel, 2004).

### Statistical Analyses

Baseline characteristics (demographics and clinical variables) were compared between the three groups using analysis of variance (ANOVA) for continuous variables and  $\chi^2$  test for categorical variables. For the first hypothesis, cross-sectional analyses of fatigue levels were compared between groups at each time point using ANOVA. The proportions of adolescents with persistent fatigue (defined as PedsQL-MFS  $\leq 65$  at all time points) were compared across groups using chi-squared test. Depressive symptoms, pain intensity, and sleep variables at baseline, 6 months, and 12 months were also compared between groups.

To test the second hypothesis, multivariable mixed effects models were used to examine the associations between fatigue and its risk factors over time (Pinheiro & Bates, 2009). Specifically age, sex, baseline sleep quality, baseline presleep arousal, baseline depressive symptoms, and baseline pain intensity were used as predictors of fatigue in the analyses. The use of mixed-effects models accounted for the correlation among outcomes within individuals due to

repeated assessments. Failure to adjust for such correlation may lead to a biased estimate of standard errors and inaccurate inference. Mixed effects models were conducted for the combined sample as well as individual groups.

Finally, mediation models within the structural equation modeling (SEM) framework were constructed to test the third hypothesis that sleep quality and presleep arousal mediate the association between depressive symptoms and fatigue over 12 months. Specifically, two types of mediation effects were examined. The first model examined longitudinal mediation and the second model examined contemporaneous mediation. To test both types of mediation, the autoregressive model as described by Gollob and Reichardt (1991) and Cole and Maxwell (2003) was applied (Figure 1). Using this model, product  $a_1b_1$  is the estimator representing across time relations, and  $a_2b_2$  is the contemporaneous estimator reflecting relations of measures at the second time point. Sleep quality and presleep arousal were tested as mediators in separate autoregressive mediation models. Assessments of depressive symptoms and fatigue at baseline and at 12 months were included in the models to assess stability and account for covariance at baseline and at 12-month assessment. Both mediation effects were tested using the Sobel's test (Sobel, 1982) in the whole sample incorporating all three groups of adolescents, as well as in separate models by group.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.) and Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

## Results

### **Participant Characteristics at Enrollment**

The sample consisted of 172 adolescents [mean ( $M$ ) = 15.1 years, standard deviation ( $SD$ ) = 1.8], 61 adolescents had chronic pain, 51 adolescents were diagnosed with a depressive disorder, and 60 were healthy adolescents. The majority of participants were female (68%) and Caucasian (82.4%). There were no significant differences between groups on demographic characteristics, with the exception being ethnicity; there were fewer Caucasians in the healthy group compared with adolescents with chronic pain or primary depressive disorders. Table I presents demographics and clinical characteristics for the three study groups at enrollment.

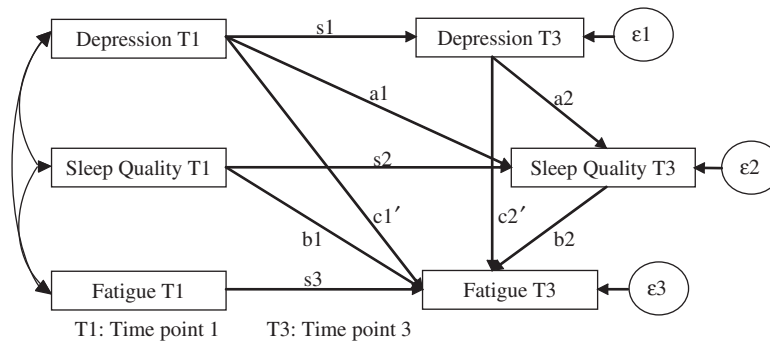
At enrollment, all of the adolescents with chronic pain reported having frequent pain. Over the previous 3 months, in the cohort of adolescents with chronic pain, 47(77%) experienced daily pain, 6 (9.8%) had pain three

to five times a week, and 8 (13.1%) had pain two to three times a week. Most commonly reported pain locations were headache ( $n = 30$ , 49.1%), abdominal pain ( $n = 20$ , 32.8%), lower back pain ( $n = 19$ , 31.1%), and limb pain ( $n = 17$ , 27.9%). For the cohort of adolescents with depression, 60.8% reported having pain at least two to three times per week in the preceding 3 months involving headaches ( $n = 26$ , 51%), limb pain ( $n = 24$ , 47.1%), upper back pain ( $n = 17$ , 33.3%), and lower back pain ( $n = 12$ , 23.5%). In comparison, less than a quarter of healthy participants (24.1%) reported frequent pain. For those healthy participants who did report experiencing pain two to three times/week, limb pain ( $n = 28$ , 46.7%), upper back pain ( $n = 18$ , 30%), and headaches ( $n = 13$ , 21.7%) were the most common pain locations.

All adolescents in the primary depression sample met criteria for a depressive disorder on the K-SADS at enrollment per our inclusion criterion. On average, adolescents with primary depression endorsed moderate depressive symptoms on the CES-D ( $M = 29.9$ ,  $SD = 6.2$ ), with depressive symptoms significantly higher compared with adolescents with chronic pain ( $M = 14.4$ ,  $SD = 9.8$ ) and healthy adolescents ( $M = 8.3$ ,  $SD = 6.1$ ,  $ps < .001$ ). The vast majority (97.9%) of youth with primary depression also met the CES-D cutoff for clinically significant depressive symptoms, compared with 29.5% of youth with chronic pain, and 15.3% of healthy adolescents. The cohort of adolescents with primary depression had the poorest sleep quality and highest levels of presleep arousal compared with adolescents with chronic pain and healthy adolescents ( $p < 0.001$ ). Table I details group comparisons on sleep variables.

### **Course of Fatigue Symptoms Over 12 Months by Study Group**

Results of ANOVAs examining group differences in fatigue at each time point revealed that, as hypothesized, adolescents with chronic pain and adolescents with primary depression displayed greater fatigue symptoms compared with healthy adolescents ( $p < 0.001$ ) at all three assessment periods (Table II). Specifically, adolescents with depression reported the greatest fatigue symptoms across groups, a pattern that remained consistent at enrollment, 6 and 12 months. Findings from analyses examining within-group changes in fatigue over time revealed that fatigue remained stable for healthy adolescents and adolescents with chronic pain, with neither group showing significant change over time. In contrast, the primary depression sample had significant changes in fatigue from enrollment to 6 months ( $\beta = 11.21$ ,  $p < 0.001$ ) and enrollment to 12 months ( $\beta = 10.89$ ,  $p < 0.001$ ), such that fatigue symptoms improved at 6 months and remained stable by the 12-month follow-up.



**Figure 1.** Autoregressive model examining sleep quality as a mediator between depressive symptoms and fatigue.

**Table 1.** Means and Standard Deviation for Variables at Wave 1

Variables	Healthy Means (SD); n (%)	Chronic pain Means (SD); n (%)	Depression Means (SD); n (%)	<i>p</i>
Age	14.8 (1.8)	15.1 (1.69)	15.4 (1.8)	.19
Gender female	43 (71.7%)	44 (72.1%)	30 (58.8%)	.24
Body mass index	22.4 (5.3)	23.3 (5.7)	24.2 (6.4)	.25
Race				.019
Caucasian	46 (76.7%)	57 (93.4%)	46 (90.2%)	
African American	7 (11.5%)	0 (0%)	7 (13.7%)	
Asian	1 (1.7%)	0 (0%)	1 (2.0%)	
American Indian	0 (0%)	2 (3.3%)	0 (0%)	
Other	6 (10%)	2 (3.3%)	6 (11.8%)	
Ethnicity				.472
Non Hispanic	52 (86.7%)	58 (95.1%)	40 (78.4%)	
Hispanic	3 (5%)	2 (3.3%)	7 (13.7%)	
Unknown	3 (5%)	0 (0%)	2 (3.3%)	
Pain intensity	3.1 (2.1)	6.4 (1.7)	4.8 (2.1)	<.001
Center for Epidemiological Studies Depression Scale	8.3 (6.1)	14.4 (9.8)	29.9 (6.2)	<.001
Sleep quality	4.36 (0.62)	3.83 (0.75)	3.30 (0.81)	<.001
Sleep hygiene	4.91 (0.44)	4.80 (0.56)	4.34 (0.56)	<.001
Presleep arousal	25.88 (6.60)	30.39 (9.67)	42.04 (10.78)	<.001

Note. SD = standard deviation.

Seeking to characterize the proportion of adolescents in each group with severe persistent fatigue symptoms, adolescents with a total fatigue score of  $\leq 65$  at all assessment periods were identified. Results revealed that 18 (29.5%) adolescents with chronic pain and 25 (49.0%) adolescents with primary depression reported persistently elevated levels of fatigue across 12 months compared with 6 (10.0%) healthy adolescents ( $p < 0.001$ ).

**Predictors of Fatigue Over 12 Months for the Total Sample and by Study Group**

Mixed linear models investigating the predictors of fatigue over 12 months were examined in the total sample and within each group of adolescents. For the total sample,

older age ( $\beta = 0.98, p = 0.04$ ), higher levels of baseline depressive symptoms ( $\beta = 0.48, p < 0.001$ ) and poorer baseline sleep quality ( $\beta = -7.6, p < 0.001$ ) emerged as significant predictors of greater fatigue over time. Contrary to hypotheses, sex, pain intensity, and presleep arousal at baseline were not associated with fatigue symptoms over time. To test the effect of study group, separate models were constructed for adolescents with chronic pain, adolescents with primary depression, and healthy adolescents. Results revealed that for the samples of adolescents with chronic pain and primary depressive disorders, only poorer sleep quality predicted greater fatigue levels ( $\beta = -6.6, p = 0.02$  and  $\beta = -9.8, p < 0.001$ , respectively). For healthy adolescents, greater depressive

Table II. Means and Standard Deviations of Clinical Variables Between Groups by Time Point

Clinical variables	T1	T2	T3	<i>p</i>
Fatigue <sup>a</sup>				<.001
Healthy	75.71 (13.34)	74.28 (12.25)	73.44 (13.18)	
Pain	60.38 (17.04)	63.16 (19.46)	62.75 (18.69)	
Depressed	46.65 (13.34)	57.68 (16.04)	58.83 (15.21)	
Sleep quality				<.001
Healthy	4.36 (0.62)	4.33 (0.69)	4.42 (0.69)	
Pain	3.83 (0.75)	3.87 (0.74)	3.98 (0.79)	
Depressed	3.30 (0.81)	3.95 (0.79)	3.90 (0.77)	
Presleep arousal				<.001
Healthy	25.88 (6.60)	27.93 (8.29)	27.86 (8.36)	
Pain	30.39 (9.66)	31.36 (9.57)	30.32 (9.12)	
Depressed	42.04 (10.78)	34.29 (11.03)	33.70 (10.40)	
Pain intensity				<.001
Healthy	3.1 (2.1)	3.7 (2.2)	3.8 (2.1)	
Pain	6.4 (1.7)	6.0 (2.0)	6.1 (2.2)	
Depressed	4.8 (2.1)	4.4 (1.9)	4.2 (2.0)	
Depressive symptoms				<.001
Healthy	8.34 (6.12)	10.68 (9.41)	11.29 (9.95)	
Pain	14.38 (9.78)	14.30 (9.78)	14.73 (10.28)	
Depressed	29.87 (6.22)	23.48 (8.03)	23.61 (8.16)	

Note. <sup>a</sup>Lower scores on the PedsQL Multidimensional Fatigue Scale indicate greater problems with fatigue.

symptoms ( $\beta = -0.76$ ,  $p = 0.003$ ) and poorer sleep quality ( $\beta = -5.7$ ,  $p = 0.006$ ) remained significant predictors of greater fatigue over time ( $ps < 0.01$ ).

### **Sleep Disturbances as a Mediator Between Depressive Symptoms and Fatigue**

Results of autoregressive mediation models that examined sleep quality and presleep arousal as mediators in the relationship between depressive symptoms and fatigue over time showed no significant longitudinal mediation between baseline depressive symptoms and fatigue symptoms at 12 months via sleep quality.

However, results were significant with contemporaneous mediation where sleep quality (at 12-month assessment) was a significant mediator between depressive symptoms and fatigue levels at 12 months ( $p < 0.001$ ). Subgroup analyses indicated that this contemporaneous mediation remained significant for the group with chronic pain and the group with primary depression ( $p = 0.05$ ); however, concurrent sleep quality did not mediate effects of depressive symptoms on fatigue in healthy adolescents. Similarly, presleep arousal was a significant contemporaneous mediator between depressive symptoms and fatigue ( $p < 0.001$ ) in the whole sample, in adolescents with chronic pain ( $p = 0.008$ ) and primary depression ( $p = 0.02$ ) but not in healthy adolescents.

### **Discussion**

Our findings revealed that both clinical samples of adolescents, those with chronic pain and primary depressive disorders, experienced significantly greater fatigue symptoms when compared with healthy adolescents. Most notably, youth with primary depression reported the most severe symptoms of fatigue. The severity of fatigue experienced by adolescents with chronic pain and adolescents with primary depression in our sample are comparable with fatigue levels reported by children undergoing active treatment and chemotherapy for cancer (Erickson et al., 2011; Varni et al., 2002). Thus, our findings suggest that fatigue is an important clinical problem and may be a symptom that requires separate assessment and management, particularly in pediatric clinical samples such as youth with chronic pain and depressive disorders.

An important finding that emerged in our study was that the severity of fatigue remained relatively stable over the course of 12 months for adolescents with chronic pain and healthy adolescents. Although there was some improvement in fatigue levels in adolescents with depression at the 6- and 12-months follow-up, their PedsQL-MFS scores remained well below normative samples in the literature (Meeske, Katz, Palmer, Burwinkle, & Varni, 2004; Varni, Burwinkle, & Szer, 2004). It is not unexpected that clinical symptoms remained stable in this observational

cohort study; however, the variability of fatigue symptoms or lack thereof highlighted that fatigue may be an area of symptomatology that requires evaluation and targeted intervention to minimize the negative impact on other areas of functioning.

Results of subgroup analyses examining different predictors of longitudinal fatigue symptoms revealed some variation by study group, which suggests that there may be factors unique to the maintenance of fatigue within each sample. For example, while greater depressive symptoms predicted fatigue over 12 months in healthy youth, depressive symptoms did not emerge as a significant predictor for the sample of youth with primary depression or youth with chronic pain. This is consistent with the literature showing higher fatigue levels in healthy adolescents who suffer from subclinical depressive symptoms (Williamson et al., 2005). However, at greater levels of depressive symptoms such as in the cohort of adolescents with depressive disorders, depressive symptoms were not a significant predictor of fatigue. This finding may be a function of participants having both high levels of depressive symptoms and fatigue, such that the correlation was curtailed by limited variability. Nonetheless, it will be important to examine the relationship between clinical improvement in depressive symptoms and associated changes in fatigue level given the high levels of general, sleep/rest, and cognitive fatigue experienced by depressed youth in our sample.

Although clinical wisdom may implicate poor sleep as a factor in determining level of fatigue in youth, there has been a surprising lack of research on this relationship. Our findings add to this limited literature in demonstrating that poorer sleep quality was consistently associated with greater fatigue over time across all three groups of adolescents. Sleep quality may represent a modifiable risk factor that could be targeted in interventions designed to address adolescent fatigue symptoms. Finally, contrary to hypotheses, there was no association of pain intensity with fatigue (even in youth with chronic pain), suggesting fatigue is more strongly impacted by other factors.

Results of analyses examining mediation effects further underscore the clinical significance of sleep disturbances (poor sleep quality and high levels of presleep arousal) and their role in determining fatigue. In our sample of healthy adolescents and adolescents with physical and psychological conditions, sleep quality mediated the relationship between concurrent depressive symptoms and fatigue levels. These findings extend those reported by Karlson and colleagues in college students to the pediatric population (Karlson, Natalie, Olson, & Hamilton, 2010). However, the longitudinal mediation effect was not significant in the current study, indicating that symptoms at concurrent

time points are more powerful predictors. The clinical implication of these findings is that interventions focused on improving sleep quality may have an immediate impact on improving fatigue, and thus intervention early in the course of these symptoms would be recommended to interrupt and prevent longer term problems with fatigue.

Our findings should be interpreted in light of several limitations. The assessments in this study were based on subjective evaluations by the adolescents. Assessment of fatigue may be strengthened through physical examination and proxy-report of participation in activities by a parent, teacher, or medical provider. In particular, additional data could include the impact of fatigue on physical activity and role functioning (e.g., school, participation in family activities). In addition, the measures used had differing recall periods (e.g., one month, three months), which may have impacted on our results. However, the opportunity to collect data over 1 year may have minimized this potential impact. Another limitation was that we were not able to capture potential medication side effects that may have been experienced in our cohorts of adolescents diagnosed with depression and adolescents with chronic pain conditions, some of whom were on medications to treat these conditions. Future studies should specifically investigate the role of medications and their impact on short-term and long-term fatigue.

A final limitation is that the assessment of sleep for this study was based exclusively on adolescent self-report. Evaluation of sleep patterns and behaviors can be enhanced by the use of both subjective and non-self report measures (e.g., actigraphy, polysomnography). Additional assessment tools may provide more comprehensive information on sleep patterns and behaviors and help to identify specific etiologies of sleep disturbances to tailor future treatment plans. For this study, we focused on self-report because we were most interested in perceptions of sleep quality that could potentially be targeted in psychological treatment. Assessment of sleep duration, however, will be important to incorporate into future study methods because sleep restriction may contribute to fatigue symptoms. Future research can examine associations among fatigue and sleep duration both concurrently and over time, with a focus on how associations may differ among healthy youth and clinical samples.

In regards to clinical implications, our findings suggest that assessment of sleep and fatigue should be a routine component of the clinical evaluation of children with medical and psychiatric conditions. Assessment includes a comprehensive description of sleep patterns and behaviors (e.g., sleep schedule, routines, habits, thoughts, and behaviors at bedtime) and consequences (e.g., impact on



function, negative mood, fatigue, excessive daytime sleepiness) (Lewandowski, Ward, & Palermo, 2011). Both clinical interview and self-report questionnaires can be an important way to gather a thorough sleep history (see Lewandowski, Ward, & Palermo, 2011 for a review of self-report sleep questionnaires). For certain sleep complaints (e.g., symptoms of sleep disordered breathing), specialized sleep testing in a sleep laboratory setting may be recommended.

Pediatric psychologists can play an important role in delivering treatment to promote healthy sleep habits and to treat diagnosed behavioral sleep disorders. In particular, behavioral sleep interventions may be helpful for addressing inadequate sleep duration, insomnia, and delayed sleep phase. Prevention strategies might include healthy sleep routines such as restricting caffeine intake in the evening, creating a regular sleep routine and schedule, and limiting the use of electronic devices during the evening. CBT for insomnia has been recommended by the American Academy of Sleep Medicine (AASM, 2005) for the treatment of adult insomnia and has been shown to be effective in diverse adult medical and psychiatric populations (Perlis, Junquist, Smith, & Posner, 2005). A similar evidence base is not yet available in pediatric populations. However, findings from the few available studies of behavioral treatments for sleep problems in pediatric medical populations are promising showing improvements in sleep quality and reductions in pain and fatigue in children and adolescents with fibromyalgia and cancer (Degotardi et al., 2006; Rosen, Shor, & Geller, 2008). Moreover, interventions used in pediatric chronic fatigue syndrome may be relevant for management of fatigue in other pediatric medical populations (Mackenzie & Wray, 2013).

Our findings suggest that fatigue is a significant problem for adolescents, particularly in clinical samples. Therefore, identifying the presence of fatigue and treating fatigue symptoms is critical to addressing broader health concerns and the functional outcomes in these populations. Further research is needed to determine how to best intervene to reduce fatigue symptoms and their impact, possibly improving functional outcomes. The consistent association between sleep quality and fatigue in this study also highlights the importance of developing effective treatments for sleep disturbances in pediatric clinical populations.

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## References

- AASM. (2005). *The International Classification of Sleep Disorders* (2nd ed.). Westchester, IL: American Academy of Sleep Medicine.
- Berrin, S. J., Malcarne, V. L., Varni, J. W., Burwinkle, T. M., Sherman, S. A., Artavia, K., & Chambers, H. G. (2007). Pain, fatigue, and school functioning in children with cerebral palsy: A path-analytic model. *Journal of Pediatric Psychology, 32*, 330–337.
- Butbul Aviel, Y., Stremmler, R., Benseler, S. M., Cameron, B., Laxer, R. M., Ota, S., . . . Feldman, B. M. (2011). Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. *Rheumatology (Oxford), 50*, 2051–2060.
- Chorpita, B. F., Yim, L., Moffitt, C., Umemoto, L. A., & Francis, S. E. (2000). Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. *Behaviour Research and Therapy, 38*, 835–855.
- Cole, D. A., & Maxwell, S. E. (2003). Testing mediational models with longitudinal data: Questions and tips in the use of structural equation modeling. *Journal of Abnormal Psychology, 112*, 558–577.
- Collins, J. J., Byrnes, M. E., Dunkel, I. J., Lapin, J., Nadel, T., Thaler, H. T., . . . Portenoy, R. K. (2000). The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management, 19*, 363–377.
- Degotardi, P. J., Klass, E. S., Rosenberg, B. S., Fox, D. G., Gallelli, K. A., & Gottlieb, B. S. (2006). Development and evaluation of a cognitive-behavioral intervention for juvenile fibromyalgia. *Journal of Pediatric Psychology, 31*, 714–723.
- Erickson, J. M., Beck, S. L., Christian, B. R., Dudley, W., Hollen, P. J., Albritton, K. A., . . . Godder, K. (2011). Fatigue, sleep-wake disturbances, and quality of life in adolescents receiving chemotherapy. *Journal of Pediatric Hematology/Oncology, 33*, e17–e25.
- Gold, J. I., Mahrer, N. E., Yee, J., & Palermo, T. M. (2009). Pain, fatigue, and health-related quality of

- life in children and adolescents with chronic pain. *Clinical Journal of Pain*, 25, 407–412.
- Gollob, H. F., & Reichardt, C. S. (1991). Interpreting and estimating in-direct effects assuming time lags really matter. In L. M. Collins, & J. L. Horn (Eds.), *Best methods for the analysis of change: Recent advances, unanswered questions, future directions* (pp. 243–259). Washington, D.C.: American Psychological Association.
- Gregory, A. M., Willis, T. A., Wiggs, L., & Harvey, A. G. (2008). Presleep arousal and sleep disturbances in children. *Sleep*, 31, 1745–1747.
- Hinds, P. S., Quargnenti, A., Bush, A. J., Pratt, C., Fairclough, D., Rissmiller, G., . . . Gilchrist, G. S. (2000). An evaluation of the impact of a self-care coping intervention on psychological and clinical outcomes in adolescents with newly diagnosed cancer. *European Journal of Oncology Nursing*, 4, 6–17, discussion 18–19.
- Karlson, C. W., Natalie, R. S., Olson, C. A., & Hamilton, N. A. (2010). Depression, Fatigue and Pre-Sleep Arousal: A mediation model. *Journal of College Student Psychotherapy*, 24, 307–327.
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, 36, 980–988.
- Law, E. F., Dufton, L., & Palermo, T. M. (2012). Daytime and nighttime sleep patterns in adolescents with and without chronic pain. *Health Psychology*, 31, 830–833.
- LeBourgeois, M. K., Giannotti, F., Cortesi, F., Wolfson, A. R., & Harsh, J. (2005). The relationship between reported sleep quality and sleep hygiene in Italian and American adolescents. *Pediatrics*, 115, 257–265.
- Lewandowski, A. S., Palermo, T. M., Motte, S. D. I., & Fu, R. (2010). Temporal daily associations between pain and sleep in adolescents with chronic pain versus healthy adolescents. *Pain*, 151, 220–225.
- Lewandowski, A. S., Ward, T. M., & Palermo, T. M. (2011). Sleep problems in children and adolescents with common medical conditions. *Pediatric Clinics of North America*, 58(3), 699–713.
- Mackenzie, C., & Wray, A. (2013). Chronic Fatigue Syndrome in children and young people. *Paediatrics and Child Health*, 23, 35–39.
- Meeske, K., Katz, E. R., Palmer, S. N., Burwinkle, T., & Varni, J. W. (2004). Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer*, 101, 2116–2125.
- Murray, C. B., Murphy, L. K., Palermo, T. M., & Clarke, G. M. (2012). Brief report: Pain and sleep-wake disturbances in adolescents with depressive disorders. *Journal of Clinical Child and Adolescent Psychology*, 41, 482–490.
- Nicassio, P. M., Mendlowitz, D. R., Fussell, J. J., & Petras, L. (1985). The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. *Behaviour Research and Therapy*, 23, 263–271.
- Oginska, H., & Pokorski, J. (2006). Fatigue and mood correlates of sleep length in three age-social groups: School children, students, and employees. *Chronobiology International*, 23, 1317–1328.
- Palermo, T. M., Law, E., Churchill, S. S., & Walker, A. (2012). Longitudinal course and impact of insomnia symptoms in adolescents with and without chronic pain. *Journal of Pain*, 13, 1099–1106.
- Palermo, T. M., Toliver-Sokol, M., Fonareva, I., & Koh, J. L. (2007). Objective and subjective assessment of sleep in adolescents with chronic pain compared to healthy adolescents. *Clinical Journal of Pain*, 23, 812–820.
- Palermo, T. M., Wilson, A. C., Lewandowski, A. S., Toliver-Sokol, M., & Murray, C. B. (2011). Behavioral and psychosocial factors associated with insomnia in adolescents with chronic pain. *Pain*, 152, 89–94.
- Perlis, M. L., Junquist, C., Smith, M. T., & Posner, D. (2005). *Cognitive Behavioral Treatment of Insomnia*. New York: Springer.
- Peterson, L. S., Mason, T., Nelson, A. M., O'Fallon, W. M., & Gabriel, S. E. (1997). Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: A controlled, population-based study. *Arthritis & Rheumatism*, 40, 2235–2240.
- Pinheiro, J. C., & Bates, D. M. (2009). *Mixed-Effects Models in S and S-PLUS*. New York: Springer Verlag.
- Radloff, L. S. (1977). The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*, 1, 385–401.
- Ream, E., Gibson, F., Edwards, J., Seption, B., Mulhall, A., & Richardson, A. (2006). Experience of fatigue in adolescents living with cancer. *Cancer Nursing*, 29, 317–326.

- Reid, G. J., Lang, B. A., & McGrath, P. J. (1997). Primary juvenile fibromyalgia: Psychological adjustment, family functioning, coping, and functional disability. *Arthritis & Rheumatism*, *40*, 752–760.
- Rosen, G. M., Shor, A. C., & Geller, T. J. (2008). Sleep in children with cancer. *Current Opinion in Pediatrics*, *20*, 676–681.
- Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. In S. Leinhardt (Ed.), *Sociological methodology* (pp. 290–312). San Francisco: Jossey-Bass.
- ter Wolbeek, M., van Doornen, L. J. P., Kavelaars, A., & Heijnen, C. J. (2006). Severe fatigue in adolescents: A common phenomenon? *Pediatrics*, *117*, e1078–e1086.
- Varni, J. W., Burwinkle, T. M., Berrin, S. J., Sherman, S. A., Artavia, K., Malcarne, V. L., & Chambers, H.G. (2006). The PedsQL in pediatric cerebral palsy: Reliability, validity, and sensitivity of the Generic Core Scales and Cerebral Palsy Module. *Developmental Medicine and Child Neurology*, *48*, 442–449.
- Varni, J. W., Burwinkle, T. M., & Katz, E. R. (2004). The PedsQL in pediatric cancer pain: A prospective longitudinal analysis of pain and emotional distress. *Journal of Developmental & Behavioral Pediatrics*, *25*, 239–246.
- Varni, J. W., Burwinkle, T. M., Katz, E. R., Meeske, K., & Dickinson, P. (2002). The PedsQL in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*, *94*, 2090–2106.
- Varni, J. W., Burwinkle, T. M., & Szer, I. S. (2004). The PedsQL Multidimensional Fatigue Scale in pediatric rheumatology: Reliability and validity. *Journal of Rheumatology*, *31*, 2494–2500.
- Varni, J. W., Seid, M., Smith Knight, T., Burwinkle, T., Brown, J., & Szer, I. S. (2002). The PedsQL in pediatric rheumatology: Reliability, validity, and responsiveness of the Pediatric Quality of Life Inventory Generic Core Scales and Rheumatology Module. *Arthritis & Rheumatism*, *46*, 714–725.
- Viner, R. M., Clark, C., Taylor, S. J., Bhui, K., Klineberg, E., Head, J., . . . Stansfeld, S. A. (2008). Longitudinal risk factors for persistent fatigue in adolescents. *Archives of Pediatrics & Adolescent Medicine*, *162*, 469–475.
- von Baeyer, C. L. (2009). Numerical rating scale for self-report of pain intensity in children and adolescents: Recent progress and further questions. *European Journal of Pain*, *13*, 1005–1007.
- Wight, R. G., Sepulveda, J. E., & Aneshensel, C. S. (2004). Depressive symptoms: How do adolescents compare with adults? *Journal of Adolescent Health*, *34*, 314–323.
- Williamson, R. J., Purcell, S., Sterne, A., Wessely, S., Hotopf, M., Farmer, A., & Sham, P.C. (2005). The relationship of fatigue to mental and physical health in a community sample. *Social Psychiatry and Psychiatric Epidemiology*, *40*, 126–132.