Published in final edited form as:

J Clin Child Adolesc Psychol. 2017 ; 46(2): 247–257. doi:10.1080/15374416.2016.1188699.

Sleep in Adolescents with Bipolar I Disorder: Stability and Relation to Symptom Change

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Abstract

Objective—Sleep disturbances are common features of bipolar disorder (BD) yet little is known about trajectories of sleep disturbances in youth with BD. Using longitudinal data, this study assessed the stability of sleep disturbances and their ability to predict symptom progression in adolescents diagnosed with BD compared to controls.

Method—Thirteen to nineteen year olds meeting diagnostic criteria for BD I ($n = 19$, 16.2 ± 1.75 years, 57.9 % female, 68.4% Caucasian) and psychiatrically healthy age-comparable controls ($n = 21$, 15.7 ± 1.48 years, 52.4% female, 57.1% Caucasian) were assessed for sleep onset latency, number of awakenings, and wake time, separately for weekdays and weekends using a self-report questionnaire. Sleep indices and symptoms of mania (Young Mania Rating Scale) and depression (Children's Depression Rating Scale) were assessed at two time points, T1 and T2, approximately twelve months apart. Correlations were used to examine stability of sleep indices across time points and regression models to examine the effects of T1 sleep on T2 symptoms.

Results—Adolescents with BD showed low stability on most sleep indices, whereas controls showed high stability on all sleep indices. After controlling for T1 depression symptoms, more T1 weekend awakenings and weekend wake time predicted significantly greater T2 depression symptoms in youth with BD but not in controls. No significant associations were found between T1 sleep and T2 mania symptoms.

Conclusions—These findings suggest that increased awakenings and wakefulness on weekends may represent an important therapeutic target for reducing depression in adolescents with BD.

Keywords

Adolescents; bipolar disorder; sleep; depression; mania

Introduction

Sleep and circadian disturbances are central features of bipolar disorder (BD). Episodes of mania or hypomania are characterized either by a reduced need for sleep or an inability to get adequate sleep (insomnia) (American Psychiatric Association, 2013) and an *earlier* timing of the circadian sleep-wake cycle (phase advance) (Salvatore et al., 2008). Depressive

episodes, which are frequently present in the course of BD, are often characterized by insomnia or hypersomnia (American Psychiatric Association, 2013), a delay (latency) of circadian timing and a preference for “eveningness” (Robillard et al., 2013). Studies of individuals with BD who are currently between mood episodes demonstrate that sleep and circadian disturbances, including longer onset latencies and wake periods during the night, and a more fragmented sleep/wake rhythm and less day-to-day stability, persist even outside of acute mood episodes in BD (Brill, Penagaluri, Roberts, Gao, & El-Mallakh, 2011; Gershon et al., 2012; Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005; Jones, Hare, & Evershed, 2005; Millar, Espie, & Scott, 2004). Evidence that sleep and circadian disturbances persist outside of acute mood episodes in BD suggests that these may be trait-like features of the disorder.

Given their chronic and persistent nature, sleep and circadian disturbances may have value for understanding the course of BD. Few longitudinal studies have examined the relation between sleep/circadian disturbances and illness course in BD. In one study of 54 adults diagnosed with bipolar I disorder, shorter sleep duration predicted a worsening in depression symptoms, but not mania symptoms, across a 6-month follow-up period (Perlman, Johnson, & Mellman, 2006). Another study of adults with bipolar spectrum disorders (N=196), found that more variability in sleep duration was associated with increases in both mania and depression symptoms over a 12-month follow-up (Gruber et al., 2011). Less regularity in social rhythms, or daily routines that help entrain natural circadian rhythms, has been found to predict faster relapse among adults with bipolar spectrum disorders (Shen, Alloy, Abramson, & Sylvia, 2008). In a study in which eleven adults with rapid cycling BD provided daily self-ratings of mood and sleep over the course of 18 months, shorter sleep duration was found to be predictive next-day manic or hypomanic onset (Leibenluft, Albert, Rosenthal, & Wehr, 1996). Similarly, a prospective study in which 59 adults with BD provided daily reports of their mood and sleep over the course of 5 months found that shorter sleep duration predicted increased next-day mania and longer sleep duration predicted increased next-day depression (Bauer et al., 2006). Taken together, these findings suggest that sleep and circadian rhythms may be important short-term and long-term predictors of mood symptoms in BD.

Current evidence for sleep disturbances in BD comes primarily from studies of adults. Little research is available on the presentation or effects of sleep disturbances in youth with BD. Studies assessing the symptom presentation of BD in pediatric patients using medical record reviews, self-reports, and/or parent reports have documented that, as is found with adults, a reduced need for sleep typically occurs during manic periods in youth with bipolar symptomatology (Ballenger, Reus, & Post, 1982; Ferreira Maia, Boarati, Kleinman, & Fu, 2007; Findling et al., 2001; Geller et al., 2002; Holtmann et al., 2007; Jerrell & Shugart, 2004). Some studies have also documented that in comparison to age-matched controls, youth with symptoms of BD have more difficulty falling asleep, experience more awakenings throughout the night, and spend more time awake during these awakenings (Lofthouse, Fristad, Splaingard, & Kelleher, 2007; Mehl et al., 2006; Roybal et al., 2011), whereas other studies have not demonstrated such differences (Mullin, Harvey, & Hinshaw, 2011). Although there is some evidence that specific sleep disruptions, such as difficulty falling asleep, occur primarily during depressive phases (Lofthouse et al., 2007), information

on the correspondence of specific sleep disturbances to phases of illness is not yet available, possibly because youth with bipolar disorder tend to display a less episodic pattern of illness than do adults (Biederman et al., 2004).

Whereas studies conducted with adults with BD suggest that disturbances in sleep and circadian rhythms are reliable predictors of symptom change (Perlman et al., 2006; Shen et al., 2008) there has been limited investigation of the contribution of these disturbances to illness course in youth with BD. The few available studies have provided mixed findings. In one study, a clinical record review of 82 children diagnosed with BD (Mean age = 10.6 years, SD = 3.6 years) showed that insomnia and parasomnias, a category of sleep disorders that includes sleepwalking and nightmares, were frequently reported by parents as the initial symptoms they retrospectively observed in their children long before the initial onset of the disorder, usually prior to age 3, suggesting that sleep disturbances may precede first episode onset in BD (Faedda, Baldessarini, Glovinsky, & Austin, 2004).

Another study examined the longitudinal impact of self-reported sleep on mood symptoms in 12-17 year olds (N=53) diagnosed with bipolar spectrum disorders. This study found that sleep difficulties, and particularly irregular sleep rhythms and more awakenings, were significantly associated with symptoms over a two-year follow up period (Lunsford-Avery, Judd, Axelson, & Miklowitz, 2012). In a longitudinal study of 6-18 year old offspring of parents with bipolar disorder, subjective sleep difficulties such as frequent nighttime awakenings were associated with higher rates of development of the disorder in at-risk youth (Levenson et al., 2015). By contrast, a study of 13-19 year old youth offspring of parents with bipolar (n=25) found that although these youth had significantly shorter sleep onset latency and less variable sleep fragmentation by actigraphy than controls, symptomatic bipolar offspring reported more subjective sleep disturbances than asymptomatic bipolar offspring, suggesting that in these high-risk offspring, sleep disturbances co-occur with mood symptoms rather than precede them (Jones, Tai, Evershed, Knowles, & Bental, 2006).

There are several possible reasons why findings vary across studies. First, studies differ in sample selection (children with BD versus children of parents with BD) and the measures used to assess sleep disturbances (actigraphy vs. self-reported sleep vs. parent reported symptoms). Second, while measuring sleep in adolescents, it is important to account for the developmental stage of the adolescent and the day of the week sleep is assessed. Bed times become increasingly delayed over the course of development, coinciding with pubertal changes that occur across late childhood and adolescence (Carskadon, Vieira, & Acebo, 1993; Crowley, Acebo, & Carskadon, 2007; Russo, Bruni, Lucidi, Ferri, & Violani, 2007). A delayed bed time is likely to result in shorter sleep durations on weekday nights relative to weekend nights due to early rise time on school days (Carskadon, 1990). To our knowledge, only one study has separately measured weekday versus weekend sleep in post-pubertal youth with BD (Roybal et al., 2011). The findings of this study indicated that adolescents with BD sleep significantly longer on weekends relative to weekdays, and that the duration of their weekend sleep is comparable to that of healthy controls (Roybal et al., 2011).

In summary, there is preliminary evidence that sleep disturbances are common among youth with BD, characterized principally by more wake time during the night compared to

typically developing healthy controls, and may precede the onset of a mood episode. Few studies in BD have directly examined the persistence of sleep disturbances in youth with bipolar disorder, or the longitudinal impact of sleep disturbances on mood symptoms. Additional studies in this area are clearly needed to gain a better understanding of disturbed sleep in the development and progression of BD in youth.

The current study has two aims. First, in a sample of adolescents diagnosed with BD I, and age-matched adolescent controls, we examine the stability of sleep, as assessed across two time points, T1 and T2, approximately twelve months apart. Adolescence represents an important time period in which to examine sleep in relation to BD symptoms because it is a period both of high risk for the development of BD and of significant sleep changes. Given that sleep disruption has been identified as a reliable prodrome for mood onset in adults, better understanding of the contribution of sleep disruption to early development or progression of BD is needed. We assess sleep using a self-report measure administered separately for weekdays and weekends. A previous study examined T1 sleep in this sample and showed that adolescents with BD experienced longer sleep onset latency, more awakenings throughout the night, and more time spent awake during these awakenings, relative to age-matched controls (Roybal et al., 2011). We therefore focus on these specific sleep deficits, rather than a general sleep disturbance. We hypothesized that these sleep disturbances would persist at T2 for youth with BD relative to controls.

Second, we examine whether sleep indices assessed at T1 predict mood symptom severity at T2. Roybal et al. (2011) found cross-sectional associations at T1 between mood symptoms, assessed using structured diagnostic interview, and sleep indices. For example, at T1, a longer period of worsening of evening mood and higher levels of excessive guilt were found to be associated with longer sleep onset latency among youth with BD, and increased pacing, greater psychomotor retardation, and increased productivity were each associated with a greater number of awakenings and longer wake time during the night (Roybal et al., 2011). Based on these findings, we hypothesized that sleep disturbances at T1 would contribute to more severe symptoms of depression and mania at T2 for youth with BD but not in controls.

Method

Participants

Thirty-three post-pubertal adolescents diagnosed with bipolar I disorder (bipolar group, 16.2 ± 1.66 years old) and twenty-seven adolescents with no personal or family history of psychiatric disorders (control group, 15.5 ± 1.45 years old) were recruited from the Stanford University Pediatric Bipolar Disorders Program or the surrounding San Francisco Bay Area community. Participants in the bipolar group had experienced a single episode of mania within 6–12 months of research participation, based on DSM-IV-TR (American Psychiatric Association, 2000) diagnostic criteria. Mania in this group was not precipitated by exposure to recreational drugs, antidepressants, stimulants, or other medications or medical conditions. Given the potential risk for mood destabilization, youth in the bipolar group were not excluded on the basis of current psychotropic medication treatment. In addition, bipolar disorder commonly co-occurs with other psychiatric disorders (Kessler, Chiu,

Demler, & Walter, 2005) so participants in the bipolar group were not excluded on the basis of current comorbid psychiatric diagnoses other than alcohol or substance abuse or dependence in the previous six months.

Control group participants were required to have no lifetime history of psychiatric diagnoses, based on DSM-IV-TR diagnostic criteria, nor a family history of any mood or psychotic disorders. Control group participants were also excluded if they had been exposed to psychotropic medications. Participants were excluded if they had metal in their body or braces for a concurrent MRI study, head injury with loss of consciousness for over 5 minutes, IQ less than 80, seizures, or a developmental disorder.

Measures

Demographic information—Participants and their parents were asked to report on age, gender, and ethnicity. Socioeconomic status was assessed using the Hollingshead Four Factor Index (Hollingshead, 1975).

Psychiatric disorders—The Washington University in St. Louis Kiddie-Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS) (Geller, Williams, Zimmerman, & Frazier, 1996) was used to assess for the presence or absence of lifetime and current psychiatric disorders among all participants. The interview was administered separately to youth and their parents. The interview has demonstrated high inter-rater reliability for mania diagnosis and individual mania items (Geller et al., 2001), high 6-month stability for mania diagnoses and individual mania items (Geller et al., 2000) and high validity against parental and teacher reports (Geller, Warner, Williams, & Zimmerman, 1998). Diagnoses for the present study were determined by a consensus conference attended by a board certified child and adolescent psychiatrist (MKS) and at minimum masters-level researchers ($K > 0.90$ for all diagnoses). The Family History-Research Diagnostic Criteria (FH-RDC) (Andreasen, Endicott, Spitzer, & Winokur, 1977), was administered to parents of control group adolescents to confirm absence of mood and psychosis in first-degree relatives. The FH-RDC specifies criteria required for endorsing psychiatric disorders such as schizophrenia, depression, and bipolar disorder. The FH-RDC has demonstrated excellent inter-rater reliability and good reliability against a diagnostic standard (68-75%) (Andreasen et al., 1977).

Depression and mania symptoms—Depression symptom severity was measured using the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski & Mokros, 1995), a widely used 17-item clinician-administered scale. Items assess core symptom domains including depressed mood, impairment in schoolwork, social withdrawal, anhedonia, irritability, sleep, appetite, suicidal ideation, and physical complaints and fatigue. In addition, the scale measures nonverbal expressions depression such as depressed appearance and slowed tempo of language. Items are scored on a 1-5 or 1-7 scale. Total scores range from 17 to 113, with higher scores indicating greater symptom severity. A score 28 or less indicates minimal or no symptoms and a score of 40 or above is indicative of depression. The scale has demonstrated good reliability and validity in adolescents 7–18 years old (Mayes, Bernstein, Haley, Kennard, & Emslie, 2010). Mania symptom severity was assessed

using the Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978), a widely-used 11 item clinician administered scale of mania symptom severity. Items assess core symptom domains including elevated mood, motor activity and energy, sexual interest, sleep, irritability, pressured speech, distractibility, racing thoughts, and disruptive or aggressive behavior. Scores range from 0 to 60, with higher scores indicating greater symptom severity. A score of less than 12 indicates asymptomatic to mild symptom severity (e.g., Suppes et al., 2005). The YMRS has demonstrated good psychometric properties (Young et al., 1978).

Pubertal development—The Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988) is a 5-item self-report scale that assessed pubertal status without using picture representations of developmental stages. Items assess for changes in body hair, changes in voice (for boys) or breast development (for girls), skin change, growth spurts, and facial hair (for boys) and menarche (for girls). In a large sample of sixth- and seventh-grade boys and girls (N=253), the measure was shown to have good reliability ($\alpha = 0.68$ to 0.87) and high correlations between a questionnaire version and physician ratings ($r = 0.61$ to 0.67) (Petersen et al., 1988).

Sleep—A self-report questionnaire was administered to youth to assess sleep onset latency, number of awakenings, and wake time during the night in the past week, separately for weekdays and weekends. Specifically, to assess for weekday sleep onset latency, adolescents were asked: “On school days in the past week, after you have gone to bed at night, about how long has it usually taken you to fall asleep?” To assess for weekday number of awakenings, adolescents were asked: “On school days in the past week, how many times have you usually woken up?” To assess for weekday wake time during the night, adolescents were asked: “How much time awake during a school night over past week?” These three questions were repeated to assess for weekend sleep.

Procedure

Stanford University's Institutional Review Board approved all study procedures. Potential participants for the bipolar group were recruited by referral to a Pediatric Bipolar Disorders Clinic and from the surrounding community. After parents and adolescents were explained the purpose and procedures of the study fully, written informed consent was obtained from the parents, and written assent was obtained from youth under the age of 18. Adolescents and their parents completed a demographic questionnaire, the PDS, and were interviewed using the KSADS, YMRS, and CDRS-R. A child and adolescent psychiatrist (MKS) or masters-level researchers administered all interviews. Names, dosages, frequency, and duration of use for each currently prescribed medication were recorded. Eligible participants were administered a sleep questionnaire. Participants returned for a second lab visit one year later. During this visit, the sleep questionnaire was re-administered. Participants were compensated \$125 for completing the study.

Analysis

We conducted preliminary analyses to verify that the BD group and the control group did not differ significantly in demographic composition, including age, gender, ethnicity, socioeconomic status, or pubertal development. Group differences in age, socioeconomic

status, and pubertal development score were evaluated using t-tests, and differences in gender and ethnicity were evaluated using chi square tests. We examined means, standard deviations, and range of each sleep index. Levene's test of heterogeneity was used to examine whether the variability of sleep indices was significantly different between the groups at either time point.

We tested hypotheses by conducting two sets of analyses. First, bivariate correlations were used to examine the stability in sleep indices between T1 and T2 within each group. Second, separate linear regression models were used to test the effects of each T1 sleep variable (sleep onset latency, number of awakenings, or wake time) on T2 symptom severity, while controlling for the effects of T1 symptom severity. That is, for each regression model, we entered T1 symptom severity, group, and T1 sleep (sleep onset latency, number of awakenings, or wake time) as predictors of T2 symptom severity. We separately considered depressive and manic symptom severity. All tests were completed using SPSS for Windows (version 22.0).

Results

Study Attrition and Sample Characteristics

Sixty participants (33 bipolar disorder group participants and 27 control group participants) completed T1 clinical and sleep assessments and were enrolled in the study. At T2, some people declined participation in T2 ($n=8$), moved ($n=5$), or were unable to complete the T2 assessment ($n=6$), yielding a final sample size of 19 bipolar group participants and 22 control group participants.

Given the rate of attrition in the BD group, we conducted within-group comparisons of those who did and did not complete the study on demographic, clinical, and sleep characteristics. Within the BD group, those who did not complete T2 assessment did not differ significantly from BD sample in age, $t(31) = -.397, p = .694$, gender, $\chi^2(1) = .203, p = .653$, ethnicity, $\chi^2(4) = 2.162, p = .706$, socioeconomic status, $t(31) = -.552, p = .585$, pubertal development score, $t(31) = 1.139, p = .263$, YMRS score, $t(31) = .004, p = .997$, or CDRS-R score, $t(31) = .187, p = .853$. Those who did not complete T2 had *near* significantly greater sleep onset latency on weekdays, $t(31) = 1.966, p = .06$. No other sleep-related differences were found between BD group participants who completed T2 and those who did not. For control group participants, no significant differences were found between those who did not complete the T2 assessment and study participants in age, $t(25) = 1.574, p = .128$, gender, $\chi^2(1) = .386, p = .535$, socioeconomic status, $t(25) = .609, p = .549$, pubertal development score, $t(25) = -.209, p = .836$, YMRS score, $t(25) = .387, p = .702$, and CDRS-R score, $t(25) = .526, p = .604$. On the other hand, control group participants who did not complete T2 showed a trend level difference in ethnicity from control group study participants, $\chi^2(4) = 9.257, p = .055$. No sleep-related differences were found between control group participants who completed T2 and those who did not.

The demographic and clinical characteristics of the 41 study participants who completed both T1 and T2 time points are presented in Table 1. There were no significant differences between BD and control groups in age at T1 ($p = .075$) or T2 ($p = .411$), gender ($p = .839$),

ethnicity ($p = .126$), socioeconomic status ($p = 1.0$), or pubertal development at T1 ($p = .168$) or T2 ($p = .356$). Ten of 19 bipolar participants (52.6%) had at least one comorbid psychiatric diagnosis. These diagnoses included attention deficit and hyperactivity disorder ($n = 6$), anxiety disorders ($n = 4$), substance abuse or dependence (past only) ($n = 4$), oppositional defiant disorder ($n = 3$), dysthymia ($n = 2$), conduct disorder ($n = 1$), and bulimia nervosa ($n = 1$).

Group Differences in Means and Variances of Sleep Characteristics Over Time

Table 2 presents the means, standard deviations, and ranges of values for sleep indices at T1 and T2 for study participants. At T2, group comparisons showed no significant differences in sleep onset latency, number of awakenings, or wake time on weekdays or weekends (all $ps > .30$)¹. Levene's test of equality of variances indicated that the groups differed significantly at T1 in the variance of wake time on weekdays ($F = 13.595$, $p = .001$, $n = 38$) and on weekends ($F = 8.555$, $p = .006$, $n = 39$), with the BD group showing significantly higher variance on both these indices than controls. At T2, Levene's test of equality of variances indicated that the groups differed significantly in the variance of sleep onset latency on weekdays ($F = 5.523$, $p = .024$, $n = 39$) but not on weekends ($F = 0.545$, $p = .47$, $n = 39$) and the variance of wake time on weekdays ($F = 4.229$, $p = .048$, $n = 39$) but not weekends ($F = 0.028$, $p = .87$, $n = 39$). The BD group, again, showed significantly higher variance on both these indices than controls. The variance in number of awakenings at T2 did not differ significantly between groups for either weekday or weekend measures (both $ps > .96$).

Stability of Sleep in Adolescents with BD compared to Age-Matched Controls

The within group bivariate correlations of sleep across T1 and T2 time points are presented in Table 3. Within the BD group, the number of weekday awakenings reported at T1 was significantly correlated with number of weekday awakenings reported at T2 ($r = 0.46$, $p = 0.048$) but no other index of sleep disturbance was significantly correlated between T1 and T2 time points ($ps = 0.074$ to 0.92). By contrast, within the age-matched control group, each sleep variable was significantly correlated between the T1 and T2 time points, suggesting high stability in sleep measures over time for the control group: Sleep onset latency on weekdays ($r = 0.56$, $p = 0.013$) and on weekends ($r = 0.61$, $p = 0.004$), the number of awakenings on weekdays ($r = 0.54$, $p = 0.017$) and weekends ($r = 0.69$, $p = 0.001$), and the duration of wake time on weekdays ($r = 0.74$, $p = 0.001$) and weekends ($r = 0.53$, $p = 0.041$).

Long-Term Effects of Sleep on Symptoms in Adolescents with BD compared to Age-Matched Controls

After controlling for depressive symptom severity at T1, the number of awakenings on weekends at T1 related to depressive symptom severity at T2 ($\beta = .297$, $t = 2.897$, $p = .006$, CI for $\beta = 1.158$, 6.564). The final model accounted for 66.1% of explained variance (Table 4). Follow-up correlations indicated that, after controlling for depressive symptom severity at T1, the number of awakenings on weekends at T1 was significantly related to depressive

¹As reported in Roybal et al. 2011, at T1, youth with BD-I experienced significantly longer wake time on weekdays than did controls, $t(39) = 2.292$, $p = .034$.

symptom severity at T2 in the BD group ($r = .475$, $p = .040$, $n = 16$) but not in the control group ($r = .283$, $p = .241$, $n = 19$).

After controlling for depressive symptom severity at T1, wake time on *weekends* at T1 related to depressive symptom severity at T2 ($\beta = .310$, $t = 2.941$, $p = .006$, CI for $\beta = .047$, .255). The final model accounted for 63.2% of explained variance (Table 5). Follow-up correlations indicated that, after controlling for depressive symptom severity at T1, wake time on weekends at T1 was significantly related to depressive symptom severity at T2 in the bipolar group ($r = .462$, $p = .047$, $n = 16$) but not in the control group ($r = -.185$, $p = .462$, $n = 19$).^{2,3}

No significant effects were found for sleep onset latency on depressive symptom severity at T2, nor for sleep onset latency, number of awakenings, or wake time at T1 on mania symptom severity at T2.

Discussion

Despite evidence for sleep disturbances in youth with BD, few longitudinal studies have examined the stability or long-term effects of these disturbances on symptom progression in youth with BD. Our findings indicate that whereas control adolescents exhibit stability in all sleep variables measured across the T1 and T2 time points, adolescents with BD exhibit stability solely in the number of weekday awakenings. Despite this unstable presentation of sleep among BD youth, we found that sleep disturbances at T1 have long-term implications for symptom progression among adolescents with BD. Specifically, a greater number of awakenings and longer wake time on weekend nights predicted depression symptom severity one year later for adolescents diagnosed with BD. Effects were retained after controlling for T1 depression symptom severity. These results mirror findings in the adult BD literature showing that sleep disturbances are capable of predicting symptom change over time, representing important treatment targets.

We hypothesized that group differences in sleep disturbances identified at T1 would persist at T2. However, our findings revealed no significant group differences in sleep indices at T2. Although at T2 group comparisons did not reach significance, it is interesting to note that the BD group had significantly greater variability in weekday sleep onset latency and weekday wake time than controls, suggesting that youth with BD may experience a more variable sleep presentation on weekdays relative to control adolescents.

Furthermore, our findings show that whereas control adolescents display stability in sleep indices across study time points, adolescents with BD did not. Poor stability and increased variability in sleep measures has been previously reported with samples of adults diagnosed with BD. Relative to controls, adults with BD have been found to exhibit more variability

²Results were retained after removal of the sleep items from the CDRS-R for both weekend number of awakenings (Overall model $F(3,37) = 19.384$, $p < .001$, β for weekend awakenings = .277, $t = 2.551$, $p = .016$, CI for $\beta = .769$, 6.828) and weekend wake time (Overall model $F(3,37) = 16.280$, $p < .001$, β for weekend wake time = .276, $t = 2.378$, $p = .024$, CI for $\beta = .031$, .401).

³Given a trend-level difference between BD and control groups in age at T1 ($p = .075$), regression models were re-run with age included in the model. Results were retained for both weekend number of awakenings (Overall model $F(4,36) = 21.816$, $p < .001$, β for weekend awakenings = .307, $t = 3.076$, $p = .004$, CI for $\beta = 1.361$, 6.628) and weekend wake time (Overall model $F(4,36) = 17.647$, $p < .001$, β for weekend wake time = .299, $t = 2.797$, $p = .008$, CI for $\beta = .040$, .253).

and less day-to-day stability in both self-reported and actigraphy-assessed sleep, including wake time during the night (Eidelman, Talbot, Gruber, & Harvey, 2010; Jones et al., 2005; Millar et al., 2004). In adults, more variable sleep, and particularly more variable wake time during the night, has been found to relate to greater number of lifetime depressive episodes and more depressive symptoms concurrently (Eidelman et al., 2010). Similarly, more variability in sleep duration has been found to predict more severe mood symptoms at a 12-month follow-up (Gruber et al., 2011). Thus, the adult literature suggests that variability in sleep has implications for short-term and long-term illness course in BD.

Poor stability and increased variability in sleep measures among BD adolescents relative to controls may be, in part, due to the effects of an irregular sleep schedule. One study showed that going to bed at different times each night was longitudinally related to greater depressive symptoms in a sample of adolescents diagnosed with bipolar spectrum disorders (Lunsford-Avery et al., 2012). Future studies should aim to incorporate indices of the regularity of sleep and daily routines, using indices such as the Social Rhythm Metric (Monk, Kupfer, Frank, & Ritenour, 1991) to characterize the daily context in which sleep instability and variability occur. This type of assessment may help to identify the triggers of unstable rhythms in youth with BD thereby aiding in treatment development. Future studies should also consider the potential irregularity of parental schedules and the impact this may have on household rules or structure surrounding the adolescent's bed and wake times. Given the large genetic contribution to risk for BD (McGuffin et al., 2003), it may be the case that the adolescent's parent is also affected with BD and experiencing sleep and circadian difficulties. Treatments that aim to improve unstable rhythms among adolescents with BD may be most beneficial when applied as a family intervention.

The importance of keeping regular daily routines and sleep-wake cycles to manage mood is the focus of Interpersonal and Social Rhythm Therapy (IPSRT; (Frank et al., 2005)). Results from clinical trials of IPSRT have shown that increasing regularization of daily rhythms has a preventative impact on relapse in adults (Frank et al., 2005). IPSRT has also been adapted for youth with bipolar disorder (Hlastala & Frank, 2006) and evidence is accruing to show that IPSRT improves sleep in youth at risk for BD (Goldstein et al., 2014) and reduces symptoms in adolescents and young adults with BD (Inder et al., 2015).

Poor sleep stability and increased sleep variability in the present sample may also be due to the effects of medications. In this study, all of the BD group participants and none of the control group participants were taking psychotropic medications, including antipsychotics, stimulants, and antidepressants. These medications are known to have sedating and activating properties. It is therefore possible that variation in medication regimen could have contributed to the sleep variability and instability observed among this sample of youth with BD. Subgroup analyses would be required to examine effects of classes of medications on sleep. The small size of the current sample limits the statistical power available for such analyses. Nevertheless, our results echo those from previous studies indicating that adolescents with BD experience more unstable and variable sleep relative to controls, suggesting that sleep stability may be an important feature of BD even early in the course of illness.

With regard to the effects of sleep disturbance on symptom progression, we hypothesized that sleep disturbances at T1 would contribute to more severe mood symptoms at T2 among youth with BD. Our findings provide polarity-specific support for this hypothesis. That is, we found that weekend awakenings and weekend wake time at T1 predicted depressive but not manic symptoms at T2 among youth with BD. A significant correlation between sleep and depression symptoms was not observed among controls, likely due to a very restricted range of mood symptoms in the control group.

It is notable that awakenings and wake time occurring specifically on the weekends were associated with increased follow-up depressive severity for those with BD. The current study is among few studies to provide a developmentally appropriate assessment of sleep by separating weekdays from weekends. Adolescents are known to keep different schedules on weekdays versus weekends, with weekdays representing typically restricted sleep schedules and weekends representing unrestricted sleep. If replicated, our finding that sleep loss on weekends is predictive of increased depression symptoms over time suggests that sleep disruptions during unrestricted sleep may represent a more enduring, trait-like sleep issue. It may be the case that youth who experience weekend sleep disruption would benefit most from IPSRT, which focuses on sleep-wake regularization for the purpose of increasing stability in circadian rhythms and sleep and, in turn, protecting against the risk of relapse (Ehlers, Frank, & Kupfer, 1988).

Although weekend sleep at T1 was predictive of depressive symptoms at T2 in this sample, it is also the case that there was a trend for mood symptoms to improve between T1 and T2 for the BD group, perhaps owing to the cumulative effects of treatment. Participants were enrolled in the study within 6-12 months of their first manic episode and, as such, had been receiving treatment for less than one year at the T1 assessment. By T2, one year later, a greater proportion of the BD sample was being treated with medications relative to T1. Although our findings are suggestive of a predictive relationship between sleep and mood, due to our measurement of sleep and symptoms at only two time points and one year apart, it is not possible to delineate the temporal sequence between sleep and symptom change. Future studies employing prospective longitudinal designs, with frequent assessments of sleep and symptoms, would help to clarify if sleep precedes symptom change or if sleep disturbance is concurrent to symptoms.

In a previous report on this sample, which focused exclusively on T1 data, cross-sectional associations were found between sleep loss and mania symptoms. Specifically, a greater number of awakenings was found to be associated with elevated and expansive mood and an increase in productivity, whereas more time spent awake during the night was related to a decreased need for sleep, increased goal directed activity, and increased productivity. In the current study, we found no effect of sleep disturbances on mania at a one year follow up. The absence of mania-specific effects may be due to the fact that most youth in this sample spent more time depressed than they did manic or to the fact that by T2, a greater percentage of the BD sample was being treated with medications relative to T1. Follow-ups during acute mania may be needed to observe the effect of sleep disturbances on mania.

Several limitations of this study should be acknowledged. First, the sample size was small, particularly given the attrition between T1 and T2. The small sample may have limited statistical power to detect group differences in sleep indices at T2. Replication with a larger sample and more frequent assessments of sleep and symptoms is warranted. Second, sleep was assessed using only self-report and with a non-standardized sleep questionnaire. As such, the information obtained is subject to the biases of retrospective reporting which may have contributed to between-group differences. Future studies should employ both subjective and objective measures of sleep (e.g., actigraphy). Third, half of our bipolar group had a lifetime comorbid diagnosis whereas none of control group had psychiatric comorbidities. Similarly, the majority of the BD group was taking medications (73.7% at T1 and 94.7% at T2), whereas none of the control group participants were taking any medications. Both psychiatric comorbidities and medication use may have confounded our sleep findings. Replication with a larger sample would allow for subgroup analysis to examine effects of comorbid psychiatric disorders and individual medications (or classes of medications) on sleep. Finally, as the sample was predominantly Caucasian and female, our results may have limited generalizability to a more diverse sample.

Despite these limitations, our findings suggest that weekend wakefulness is associated with long-term increases in depressive symptoms for youth with BD. Given that sleep loss is known to have adverse effects on illness course in adult BD, this study informs treatments in suggesting that treating wakefulness, particularly when it occurs during unrestricted sleep time on the weekends, may be an important therapeutic target for the alleviation and reduction of depression in youth with BD.

Acknowledgments

This research was supported by the National Institute of Mental Health (NIMH) Research Scientist Development Award K01MH100433 to AG and an NIMH R01MH105469, K23MH085919, the Klingenstein Third Generation Foundation, and American Psychiatric Association to MKS.

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Table 1
Demographic and Clinical Characteristics of 41 Study Participants Across Study Time Points

	T1		T2	
	BD (n=19)	Control (n=22)	BD (n=19)	Control (n=22)
Demographic characteristics				
Age in years, Mean (SD)	16.1 (1.75)	15.7 (1.48)	17.3 (1.86)	16.8 (1.40)
Female, n (%)	11 (57.9)	11 (52.4)	11 (57.9)	11 (52.4)
Caucasian, n (%)	13 (68.4)	12 (57.1)	13 (68.4)	12 (57.1)
Socioeconomic status, Mean (SD)	4.68 (0.58)	4.68 (0.58)	--	--
Pubertal development score, Mean (SD)	3.41 (0.33)	3.14 (0.62)	3.53 (0.36)	3.39 (0.48)
Clinical characteristics				
Current episode				
Manic/Hypomanic, n (%)	2 (10.5)	--	1 (5.3)	--
Depressed, n (%)	6 (31.6)	--	5 (26.2)	--
Mixed, n (%)	3 (15.8)	--	1 (5.3)	--
Inter-episode, n (%)	8 (42.1)	--	12 (63.2)	--
C-GAS score, Mean (SD)	55.5 (10.5)	93.7 (3.31)	61.1 (9.7)	91.1 (4.87)
YMRS score, Mean (SD)	18.4 (8.15)	0.26 (0.56)	14.3 (9.06)	0.75 (1.12)
CDRS-R score, Mean (SD)	45.6 (16.5)	18.2 (1.51)	37.4 (13.3)	19.0 (1.81)
Medications				
Antipsychotics, n (%)	13 (68.4)	--	16 (84.2)	--
Anticonvulsants, n (%)	9 (47.4)	--	10 (52.6)	--
SSRIs, n (%)	8 (42.1)	--	7 (36.8)	--
Stimulants, n (%)	7 (36.8)	--	8 (42.1)	--
Lithium, n (%)	3 (15.8)	--	7 (36.8)	--
Wellbutrin, n (%)	2 (10.5)	--	3 (15.8)	--
SARIs, n (%)	2 (10.5)	--	0 (0)	--
TCAs n (%)	1 (5.3)	--	1 (5.3)	--
TeCAs	0 (0)	--	3 (15.8)	--
Two or more classes of medications	12 (63.2)	--	15 (78.9)	--

T1, Time 1; T2, Time 2; SD, standard deviation; Pubertal development score based on Pubertal Development Scale; C-GAS, Children's Global Assessment Scale; YMRS, Young Mania Rating Scale. CDRS-R, Child Depression Rating Scale - Revised. SSRI, selective serotonin reuptake inhibitor; SARI, serotonin antagonist reuptake inhibitor; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant. Valid percents are reported. Two control group participants were missing YMRS scores.

Table 2
Means, Standard Deviations, and Ranges for Sleep Variables of 41 Study Participants
Across Study Time Points

	T1		T2	
	BD (n=19)	Control (n=22)	BD (n=19)	Control (n=22)
Weekday Sleep				
Sleep onset latency (min)				
Mean (SD)	23.9 (16.7)	20.0 (18.7)	29.2 (37.9)	20.6 (17.1)
Range	5-60	0-60	0-120	5-60
No. awakenings				
Mean (SD)	1.05 (1.18)	0.50 (0.76)	0.47 (0.77)	0.65 (0.81)
Range	0-4	0-2	0-2	0-3
Wake time (min)				
Mean (SD)	11.7 (18.9)	1.35 (2.52)	26.0 (77.0)	7.72 (10.9)
Range	0-75	0-10	0-300	0-30
Weekend Sleep				
Sleep onset latency (min)				
Mean (SD)	34.1 (68.0)	14.1 (17.4)	19.6 (22.1)	17.6 (18.0)
Range	0-300	0-60	0-75	0-60
No. awakenings				
Mean (SD)	0.88 (1.17)	0.45 (0.76)	0.39 (0.61)	0.35 (0.75)
Range	0-4	0-2	0-2	0-3
Wake time (min)				
Mean (SD)	10.6 (22.7)	1.58 (2.76)	3.25 (5.69)	3.06 (6.10)
Range	0-90	0-10	0-20	0-20

Note. SD, standard deviation. Two control group participants were missing weekday onset latency and weekday number of awakenings at T1. One bipolar group participant was missing weekday wake time and weekend sleep onset latency at T1.

Table 3
Pearson's Product Moment Correlations for T1-T2 Sleep Variables by Group

	BD (n=19)	Controls (n=22)
Weekdays		
Sleep onset latency	0.19	0.56 [*]
No. awakenings	0.46 [*]	0.54 [*]
Wake time	0.10	0.74 ^{**}
Weekends		
Sleep onset latency	0.03	0.61 ^{**}
No. awakenings	0.29	0.69 ^{**}
Wake time	-0.03	0.53 [*]

Note.

^{*}
^{*} = $p < .05$,

^{**}
^{**} = $p < .01$.

Table 4
Multiple Regression Using T1 Weekend Number of Awakenings to Predict T2 Depressive Symptoms While Controlling for T1 Depressive Symptoms

	<i>t</i>	<i>p</i>	β	95% CIs for β	F	df	<i>p</i>	Adjusted R ²
Overall model					26.292	3,37	.000	.661
T1 CDRS-R	1.296	.203	.204	-.089, .404				
Group	-3.182	.003	-.490	-22.720, -5.032				
T1 Weekend Number of Awakenings	2.897	.006	.297	1.158, 6.564				

Note. CDRS-R, Child Depression Rating Scale - Revised.

Table 5
Multiple Regression Using T1 Weekend Wake Time to Predict T2 Depressive Symptoms While Controlling for T1 Depressive Symptoms

	<i>t</i>	<i>p</i>	β	95% CIs for β	F	df	<i>p</i>	Adjusted R ²
Overall model					22.758	3,37	.000	.632
T1 CDRS-R	1.363	.182	.217	-.081, .412				
Group	-2.937	.006	-.466	-21.415, -3.910				
T1 Weekend Wake Time	2.941	.006	.310	.047, .255				

Note. CDRS-R, Child Depression Rating Scale - Revised.