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Abnormal sleep duration associated with hastened depressive recurrence in bipolar disorder

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Abstract

Background: Abnormal sleep duration (ASD, < 6 or ≥ 9 h) is common in bipolar disorder (BD), and often persists beyond acute mood episodes. Few longitudinal studies have examined the ASD's impact upon BD illness course. The current study examined the longitudinal impact of ASD upon bipolar depressive recurrence/recovery.

Methods: Outpatients referred to the Stanford BD Clinic during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation at baseline, and with the Clinical Monitoring Form at monthly follow-ups for up to two years of naturalistic treatment. Prevalence and clinical correlates of ASD in 93 recovered (euthymic ≥ 8 weeks) and 153 depressed BD patients were assessed. Kaplan-Meier analyses (Log-Rank tests) assessed relationships between baseline ASD and longitudinal depressive severity, with Cox Proportional Hazard analyses assessing potential mediators.

Results: ASD was only half as common among recovered versus depressed BD outpatients, but was significantly associated with hastened depressive recurrence (Log-Rank $p=0.007$), mediated by lifetime anxiety disorder and attenuated by lifetime history of psychosis, and had only a non-significant tendency towards association with delayed depressive recovery (Log-Rank $p=0.07$). In both recovered and depressed BD outpatients, baseline ASD did not have significant association with any baseline BD illness characteristic.

Limitations: Self-reported sleep duration. Limited generalizability beyond our predominately white, female, educated, insured American BD specialty clinic sample.

Conclusions: Baseline ASD among recovered BD patients may be a risk marker for hastened depressive recurrence, suggesting it could be an important therapeutic target between mood episodes.

Keywords

Bipolar disorder; Sleep; Bipolar depression; Recurrence

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1. Introduction

Bipolar disorder (BD) is a severe and recurrent disorder that affects approximately 2.4% of the U.S. population, and entails a significant public health burden (Merikangas et al., 2007, 2011). Although mood elevation (mania or hypomania) is the defining aspect of bipolar disorder, depression is more pervasive (Judd et al., 2003, 2002). Despite advances in the treatment of BD, the risk of recurrence remains high (Gitlin et al., 1995; Goldberg et al., 1995; Perlis et al., 2006). Findings from both naturalistic studies and randomized clinical trials, indicate that one third to one half of recovered BD patients will experience a new mood episode within two years, even while receiving pharmacotherapy (Vazquez et al., 2015). Furthermore, BD is associated with substantive residual symptoms and persistent functional impairment between episodes (Altshuler et al., 2006; Coryell et al., 1993; Goldberg and Harrow, 2011; Joffe et al., 2004; MacQueen et al., 2003; Tohen et al., 2003; Vieta et al., 2008). These findings underscore the importance of identifying factors associated with recurrence risk and interepisode functional impairment. Identification of such factors could help lead to more effective treatments that lower or prevent vulnerability to recurrence and illness burden.

A considerable body of literature demonstrates the important role of disturbed sleep in BD (Harvey, 2008). Sleep disturbance is common in both depression and mood elevation. During depression individuals often experience hypersomnia or insomnia, whereas during mood elevation, individuals commonly experience insomnia or reduced need for sleep (DSM-5; American Psychiatric Association, 2013). Furthermore, research has shown that sleep disturbances persist between mood episodes in BD (Cretu et al., 2016; Gershon et al., 2012; Gruber et al., 2009; Harvey et al., 2005), contributing to both residual symptoms and functional impairment (Cretu et al., 2016; Gruber et al., 2009).

It has long been proposed that disturbed sleep may trigger episode recurrence in BD (Goodwin and Jamison, 1990; Wehr et al., 1987). Although there has been an extensive body of cross-sectional studies on sleep in bipolar disorder (Asaad et al., 2016; Banks et al., 2016; Baroni et al., 2012; Brill et al., 2011; Karthick et al., 2015; Rocha et al., 2013; Roybal et al., 2011; Russo et al., 2015; St-Amand et al., 2013; Steinan et al., 2016a; Walz et al., 2013), only a few longitudinal studies have examined the impact of sleep disturbances on BD illness course. In one such study, shorter sleep duration predicted worsening of depressive, but not manic symptoms, across a 6-month follow-up period in 54 adults with bipolar I disorder (BD-I) (Perlman et al., 2006). In another longitudinal study, 59 adults with BD provided daily reports of their mood, sleep duration and time in bed over 5 months. This study found shorter sleep duration or time in bed predicted increased next-day self-reported mania and longer sleep duration or time in bed predicted increased next-day self-reported depression (Bauer et al., 2006).

In addition, three longitudinal studies examined relationships between sleep and illness course among patients in the National Institute of Mental Health-funded Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). First, Gruber et al. (2011) found that among adults with bipolar spectrum disorders (N=196), who had recovered clinical status at study entry, reduced sleep duration at study entry was associated

with increased manic symptoms, and more variable sleep duration was associated with increased manic and depressive symptoms, over a 12-month assessment period (Gruber et al., 2011). Second, Sylvia et al. (2012) found that reduced sleep duration, as measured using the sleep item from the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), was associated with increased risk of mood episode recurrence among 483 recovered adults with BD-I and bipolar II disorder (BD-II) (Sylvia et al., 2012). Third, Cretu et al. (2016) found that among 89 recovered patients with bipolar spectrum disorders, assessed when recovered using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), those classified as “poor sleepers” according to PSQI global score (i.e., with score > 5) had earlier mood episode recurrence over a one-year follow-up period (Cretu et al., 2016). Furthermore, the authors found that the relationship between poor sleep and episode recurrence was independent of residual mood symptoms, suggesting that poor sleep could represent an independent recurrence risk factor in BD. Taken together, these investigations suggested reduced sleep duration or quality could be important independent predictors of mood symptoms and episodes in BD.

The aim of the present study was to investigate the impact of abnormal sleep duration (ASD) on episode recurrence and recovery in a large, well-characterized sample of BD-I and BD-II outpatients. Although a handful of prior longitudinal studies have examined the impact of sleep duration on illness course in BD, all but one (Sylvia et al., 2012) followed patients for relatively short time periods (5–12 months). Sylvia et al. (2012) assessed sleep using an item drawn from a depression scale, which assessed specifically for reduced sleep duration. The present study examined impact of ASD upon BD illness course, assessing the effects of both long and short sleep duration.

2. Method

We included outpatients with BD-I or BD-II referred by community practitioners (primarily psychiatrists) to the Stanford University BD Clinic between 2000 and 2011. Patients were assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation (Sachs et al., 2003), which included the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (First et al., 1996) mood disorders module and Clinical Global Impression-Bipolar Version-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used to confirm bipolar and comorbid psychiatric disorder diagnoses. Clinical status at each follow-up visit was determined by symptom ratings on the STEP-BD Clinical Monitoring Form (CMF) (Sachs et al., 2002) while patients received measurement- and guideline-based naturalistic treatment (with monthly modal visit frequency) for up to two years.

Baseline ASD (mean of maximum and minimum duration in week prior to enrollment < 6 h or ≥ 9 h) was determined from available medical records and patient report, as assessed by the STEP-BD Affective Disorders Evaluation. Current mood symptoms were determined from patient report, as assessed by the STEP-BD Affective Disorders Evaluation at the time of enrollment, and clinician observation and reflected any mood symptoms in the ten days

prior to enrollment for the primary analysis, and mood symptoms thresholded for occurring on at least four or seven of the ten days prior to enrollment for the secondary analysis.

As described below, clinical characteristics of participants were evaluated and prospective clinical course of participants meeting diagnostic criteria for either current recovery (euthymic 8 weeks) or depression (a current major depressive episode) at enrollment were assessed. The STEP-BD protocol and the subsequent similar Stanford-specific Assessment, Monitoring, and Centralized Database protocol were approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation. Trained medical and research staff collected data on 6 demographic parameters and 19 illness characteristics/current mood symptoms. The demographic parameters assessed were: (A) Age (in years); (B) Gender; (C) Race/Ethnicity; (D) Education; (E) Marital Status; and (F) Employment status. The illness characteristics/current mood symptoms/current psychotropic medications assessed were: (1) Lifetime anxiety disorder; (2) Lifetime alcohol/substance use disorder; (3) Lifetime eating disorder; (4) Lifetime personality disorder; (5) Bipolar II Disorder; (5 A) Lifetime psychosis (which is very commonly associated with Bipolar I Disorder); (5B) Lifetime prior psychiatric hospitalization (which is also very commonly associated with Bipolar I Disorder); (6) One first-degree relative with mood disorder; (7) Onset age (in years); (8) Childhood (age < 13 years) onset; (9) Illness duration (in years); (10) Long illness duration (> 15 years); (11) Episode accumulation (> 10 prior mood episodes); (12) Lifetime suicide attempt; (13) Rapid cycling (> 4 episodes) in prior year; (14) CGI-BP-OS; current (i.e., any in the prior 10 days); and (15) Sadness; (16) Anhedonia; (17) Euphoria; (18) Irritability; and (19) Anxiety.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 23.0 software (IBM Corp.; Armonk, NY) on an Apple MacBook Air computer (Apple Corporation, Cupertino, CA). Prevalence and clinical correlates of baseline ASD were examined in currently recovered (i.e., euthymic 8 weeks) and currently depressed (i.e., with a current major depressive episode) patients. Analytical baseline statistics included Fisher's Exact Test comparisons of categorical data and independent-sample t-test comparisons of continuous variables. Primary longitudinal analyses consisted of Kaplan-Meier survival analyses (Log-Rank tests), which compared times to recurrence and recovery in patients with versus without baseline ASD. We used the standard approaches of censoring patients with mood elevation prior to depressive recurrence in assessing time to depressive recurrence, and censoring patients with depressive prior to mood elevation recurrence in assessing time to mood elevation recurrence (Tohen et al., 1990). Secondary metrics included for patients with versus without baseline ASD were Kaplan-Meier estimated recurrence/recovery rates for significant longitudinal depressive associations. Additional secondary analyses included Cox proportional hazard analyses (hazard ratios (HRs) and 95% confidence intervals (CIs)) for recurrence and recovery, as well as for potential mediators of statistically significant longitudinal illness findings. To select parameters for entry into mediator models, univariate Cox proportional hazard analyses were performed for all 25 (6 demographic and 19 clinical) assessed parameters. Parameters with $p < 0.05$ were entered into a forward stepwise procedure, and covariates were included in the model if $p < 0.05$. Additionally, Cox proportional hazard analyses with time-dependent covariates were used to further characterize statistically significant associations between the presence or

absence of baseline ASD and depressive recurrence and recovery. To facilitate comparisons with prior studies, we also calculated observed and Kaplan-Meier estimated overall (all patients, any episode) recurrence/recovery rates. We used a two-tailed significance threshold with $p < 0.05$, with no correction for multiple comparisons.

3. Results

Table 1 includes demographics, illness characteristics, and current mood symptoms of currently recovered and currently depressed patients, stratified by presence or absence of baseline ASD. Our sample included 93 (18.5%) recovered patients and 149 (29.6%) depressed patients, from our entire cohort of 503 outpatients, with the remaining 261 patients excluded for the following reasons: Having recovering (i.e., euthymic < 8 weeks; $N=102$, 20.3%), subsyndromal depression/mood elevation (i.e., > 2 threshold level depressive or mood elevation symptoms, but NOT meeting DSM-IV criteria for a syndromal mood episode; $N=89$, 17.7%), or syndromal mood elevation (i.e., hypomanic, manic, or mixed episodes; $N=54$, 10.7%) clinical status, and not having adequate baseline sleep data and/or satisfying inclusion criteria ($N=16$, 3.2%).

In our sample, the rate of baseline ASD was only approximately half as high among 93 recovered versus 149 depressed patients (30.1% versus 59.7%, Chi-Square=20.1, $df=1$, $p < 0.0001$). However, the ratio of patients with long: short sleep duration was not statistically different in recovered versus depressed patients (19:9 versus 63:26, Chi-square =0.1, $df=1$, $p=0.77$).

3.1. Demographics and illness characteristics/current mood symptoms in recovered patients with versus without baseline abnormal sleep duration

Among 93 recovered patients, baseline ASD was significantly less (less than half) common than no baseline ASD (30.1% versus 69.9%, Binomial test, $p < 0.0001$). Among the 28 recovered patients with baseline ASD, approximately twice as many ($N=19$, 67.9%) had long (≥ 9 h) versus short (< 6 h) ($N=9$, 32.1%) sleep duration (Chi-Square=3.6, $df=1$, $p=0.06$). No assessed demographic parameter and no illness characteristic/current mood symptom in Table 1 was significantly associated with baseline ASD among recovered patients.

3.2. Demographics and illness characteristics/current mood symptoms in depressed patients with versus without baseline abnormal sleep duration

Among 149 depressed patients, baseline ASD was significantly more common than no baseline ASD (59.7% versus 40.3%, Binomial test, $p=0.02$). Among the 89 depressed patients with ASD, more than twice as many ($N=63$, 70.8%) had long (≥ 9 h) versus short (< 6 h) ($N=26$, 29.2%) sleep duration (Chi-Square=15.4, $df=1$, $p < 0.0001$). Depressed patients with versus without baseline ASD were significantly younger (33.9 ± 12.9 versus 40.1 ± 13.6 years, $t=2.8$, $df=147$, $p=0.005$) and had a significantly lower rate of female gender (52.8% versus 73.3%, Chi-Square=6.4, $df=1$, $p=0.016$). In contrast, no other assessed demographic and no illness characteristic/current mood symptom in Table 1 was significantly associated with baseline ASD among depressed patients.

3.3. Baseline abnormal sleep duration in relationship to time to and frequency of recurrence

Baseline ASD was significantly associated with hastened depressive recurrence (Log-Rank $p=0.007$) in 28 versus 65 recovered patients with versus without baseline ASD (Fig. 1). Baseline ASD was also significantly associated with hastened depressive recurrence using Cox Proportional Hazard analysis (HR=2.6; 95% CI 1.3, 5.4; $p=0.009$). Hastened depressive recurrence in patients with versus without baseline ASD was mediated by lifetime anxiety disorder (HR=3.8; 95% CI 1.7, 8.8; $p=0.002$) and attenuated by lifetime history of psychosis (HR=0.36; 95% CI: 0.16, 0.81, $p=0.01$). No other illness characteristic or current mood symptom in Table 1, not even fatigue, mediated the relationship between baseline ASD and hastened depressive recurrence.

The association of baseline ASD with hastened depressive recurrence was significant in the first year (HR=2.7; 95% CI 1.2, 5.9; $p=0.014$), driven by lifetime anxiety disorder (HR=4.0; 95% CI 1.6, 10.3; $p=0.004$) and attenuated by lifetime history of psychosis (HR=0.4; 95% CI: 0.2, 0.96, $p=0.04$), but not in the second year. Patients with versus without baseline ASD had a significantly higher (i.e., more than twice as high with non-overlapping 95% CI) two-year Kaplan-Meier estimated depressive recurrence rate of 72.3% (95% CI=50.0–94.6%) versus 34.8% (95% CI=20.3–49.3%). Importantly, baseline long sleep duration was significantly associated with hastened depressive recurrence in 19 versus 74 recovered patients with versus without baseline long sleep duration (Log-Rank $p=0.015$, not illustrated), mediated by lifetime anxiety disorder (HR=4.4; 95% CI 1.9, 10.3; $p=0.001$) and attenuated by lifetime history of psychosis (HR=0.39; 95% CI 0.17, 0.88; $p=0.02$). In contrast, baseline short sleep duration was not significantly associated with hastened depressive recurrence in 9 versus 84 recovered patients with versus without baseline short sleep duration (Log-Rank $p=0.36$, not illustrated).

The association between baseline ASD and hastened any mood episode recurrence in 28 versus 65 recovered patients was also significant (Log-Rank $p=0.03$, HR=1.9; 95% CI 1.1–3.3; $p=0.03$, not illustrated), attenuated by episode accumulation (HR=0.5; 95% CI 0.3, 0.90; $p=0.02$). Patients with versus without baseline ASD had a nonsignificantly higher (i.e., with overlapping 95% CIs) two-year Kaplan-Meier estimated any mood episode recurrence rate of 81.4% (95% CI=64.5–98.3%) versus 58.4% (95% CI=44.3–72.5%). In contrast, the association between baseline ASD and time to mood elevation recurrence in 28 versus 65 recovered patients was not significant (Log-Rank $p=0.36$, HR=1.6; 95% CI 0.58–4.4; $p=0.37$, not illustrated). The observed and Kaplan-Meier estimated overall (all patients, any episode type) 2-year recurrence rates were 52.7% and 65.7% (95% CI 54.3–77.1%), respectively. As expected, the observed and Kaplan-Meier estimated overall (all patients, any episode type) 1-year recurrence rates were lower at 41.9% and 49.6% (95% CI 38.4–60.8%), respectively.

3.4. Baseline abnormal sleep duration in relationship to time to and frequency of recovery

Baseline ASD only non-significantly tended to be associated with time to depressive recovery (Log-Rank $p=0.07$) in 89 versus 60 depressed patients with versus without baseline

ASD (not illustrated). Baseline ASD also only non-significantly tended to be associated with time to depressive recovery using Cox Proportional Hazard analysis (HR=1.5; 95% CI 0.97–2.4; $p=0.07$) and was not significantly associated with rate of depressive recovery. Similarly, baseline long sleep duration was not significantly associated with time to depressive recovery (Log-Rank $p=0.24$) in 63 versus 86 depressed patients with versus without baseline long sleep duration (not illustrated), and baseline short sleep duration was also not significantly associated with time to depressive recovery (Log-Rank $p=0.29$) in 26 versus 123 depressed patients with versus without baseline short sleep duration (not illustrated).

Moreover, baseline ASD was not significantly related to time to recovery from mood elevation (Log-Rank $p=0.81$, not illustrated) or from any mood (Log-Rank $p=0.12$, not illustrated) episode. The observed and Kaplan-Meier estimated overall (all patients, depressive episode) 2-year recovery rates were 53.0% and 82.4% (95% CI 73.8–91.0%), respectively. As expected, the observed and Kaplan-Meier estimated overall (all patients, depressive episode) 1-year recovery rates were lower at 40.9% and 44.2% (95% CI 34.6–53.8%), respectively.

4. Discussion

Disturbed sleep is a common and prognostic feature of BD, yet few longitudinal studies have examined the impact of sleep duration on illness course among recovered BD patients. Our findings show that among recovered outpatients with BD-I and BD-II, ASD is common (30.1%) and associated with hastened depressive recurrence over a two-year follow up period. This study supports previous findings in showing that sleep disturbance is not only prevalent between episodes of BD (Gershon et al., 2012; Gruber et al., 2009; Harvey et al., 2005; Millar et al., 2004), but also an important predictor of episode recurrence (Cretu et al., 2016; Sylvia et al., 2012). Although there is an extensive literature on sleep disturbance in BD, only a few longitudinal studies have examined the impact of sleep disturbance on BD illness course. We extend prior findings in examining the longitudinal risk for episode recurrence prospectively over two years, and in focusing on sleep duration, rather than general sleep disturbance, as a specific predictor of depressive episode recurrence.

In addition, our findings highlight the particular importance of long sleep duration (≥ 9 h per night) in BD. Among both recovered and depressed BD outpatients with ASD, we found that more than twice as many individuals reported long compared to short sleep duration. Long sleep duration has been only sparsely explored in BD, despite evidence that long sleep duration is common in BD not only during periods of depression (Steinan et al., 2016b), but also during periods of euthymia (Kaplan et al., 2011; Millar et al., 2004), suggesting that it may be an important feature of illness even between mood episodes. Furthermore, using cross-sectional analysis, long sleep duration (also defined as ≥ 9 h per night) has been associated with more severe depressive symptoms and impaired functioning, relative to normal sleep (defined as 6.5–8.5 h per night), among BD outpatients (Gruber et al., 2009). Extending these findings to the prediction of episode relapse, we found that long sleep duration was significantly associated with hastened depressive relapse among recovered BD outpatients over the two-year follow up period. That is, ASD predicted depressive

recurrence, even when confining consideration to ASD patients with abnormally long sleep duration.

Because only a small number (9 of 28) of our recovered patients with baseline ASD had short (rather than long) sleep duration we were unable to conduct meaningful comparisons between short versus long sleep duration to determine which form of ASD was more strongly associated with depressive recurrence. However, our finding that most recovered patients with ASD had long sleep duration was consistent with the notion that hypersomnia is a hallmark of bipolar depression, suggesting that long sleep duration may be an important target for treatment. To date, only a handful of longitudinal studies have examined the impact of sleep duration on illness course in BD, and most of these studies have focused exclusively on short sleep duration as a risk factor for symptom change or episode recurrence (Gruber et al., 2011; Perlman et al., 2006; Sylvia et al., 2012). Our findings highlight the importance of long sleep duration in BD, and suggest that research attention should be directed to long sleep duration as a possible risk marker for depressive recurrence in BD.

In our sample of depressed patients, those with baseline ASD were significantly younger and had a significantly lower rate of female gender, relative to depressed patients without baseline ASD. In contrast, no other assessed demographic and no illness characteristic or current mood symptom was significantly associated with baseline ASD among depressed patients. Similarly, among recovered BD patients, no assessed demographic parameter and no illness characteristic or current mood symptom was significantly associated with baseline ASD. As such, the findings of our study suggest that ASD's impact upon depressive recurrence may be relatively independent of residual symptoms or other commonly considered unfavorable illness characteristics. This is consistent with findings by Cretu et al. (2016), in which the relationship between poor sleep, as assessed by the PSQI, and episode recurrence was found to be independent of residual mood symptoms (Cretu et al., 2016). Our finding that the effect of ASD on hastened depressive recurrence was mediated by lifetime anxiety disorder is also consistent with prior studies, which document that anxiety disorders are highly prevalent (Pavlova et al., 2015; Simon et al., 2004) and account for significant illness burden (Sala et al., 2012) in BD.

Our study has several notable strengths and limitations. Among the strengths are a well-characterized sample, which was assessed for BD, current clinical status/mood symptoms, and a range of illness characteristics, using clinician-administered interviews. Another strength of the study is the longitudinal design, in which patients were monitored for mood episode recurrence over a two-year period. However, our findings also need to be considered in light of several limitations. First, our measure of sleep duration was based on self-reported sleep duration. This assessment was limited in scope and susceptible to recall bias. Future research needs to incorporate objective sleep assessments such as polysomnography and/or actigraphy, and use sleep diaries, to more comprehensively and objectively assess sleep disturbance, and reduce potential recall bias. Second, we did not account for the effects of medications on baseline ASD. However, in a previous study by Sylvia et al. (2012) examining the impact of reduced sleep duration on course of illness in recovered BD patients, only use of anticonvulsants was associated with reduced sleep duration, whereas

use of other medications (e.g., lithium or atypical antipsychotics) was unrelated to sleep duration. Third, pooling patients with abnormally short and long sleep duration may have obscured potential differences between the two subgroups. Although additional analysis indicated that long sleep duration was associated with hastened depressive recurrence in recovered patients with versus without baseline long sleep duration ($p=0.015$), the small number of recovered patients with short sleep duration ($n=9$) precluded adequately-powered assessment of relationships between short sleep and time to mood episode recurrence as well as comparisons between short versus long sleepers with respect to recurrence risk. Fourth, relatively few patients in our sample were assessed with mood elevation at study entry ($n=51$). As a result, we had insufficient statistical power to adequately assess the effects of baseline ASD on time to mood elevation recovery. Similarly, relatively few of the patients who were recovered at study entry, subsequently developed mood elevation ($n=25$), limiting statistical power to assess associations between baseline ASD and mood elevation recurrence. Replication with a larger sample is warranted. Similarly, recruitment of the sample from a single clinic limited sample size and generalizability of findings, warranting replication with larger cohorts from multiple sites. Finally, our data are left truncated. As such, we did not account for how long prior to baseline patients had been recovered or depressed, respectively.

Despite limitations, the present study is one of few to investigate longitudinal impact of baseline ASD on recurrence risk in a substantial sample of well-characterized recovered BD patients. Our findings suggest that interepisode ASD is informative for the prediction of illness course in BD. As such, increased monitoring of sleep duration between episodes may help to identify patients at particular risk for depressive recurrence and thereby allow timely interventions to manage sleep difficulties, including methods for normalizing sleep duration and improving sleep quality, and potentially delay or prevent episode recurrence.

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Abnormal Sleep Duration (< 6 or ≥ 9 hours) Associated with Hastened Depressive Recurrence

Fig. 1. Abnormal sleep duration associated with hastened depressive recurrence.

Two-year survival analysis of time to depressive recurrence in recovered bipolar disorder patients indicated significantly hastened depressive recurrence in patients with (N=28, black line on bottom) versus without (N=65, gray line on top) abnormal sleep duration (< 6 or ≥ 9 h, Log-Rank $p=0.007$). Abnormal sleep duration was also significantly associated with hastened depressive recurrence using Cox Proportional Hazard analysis (Hazard Ratio (HR)=2.6 (95% Confidence Interval (CI)=1.3, 5.4, $p=0.009$). Lifetime anxiety disorder (HR=3.8, 95% CI=1.7, 8.8, $p=0.002$) drove and lifetime history of psychosis (HR=0.36; 95% CI=0.16, 0.81, $p=0.01$) attenuated hastened depressive recurrence in patients with versus without abnormal sleep duration.

Demographics, illness characteristics, and current mood symptoms in recovered and depressed bipolar disorder outpatients with and without baseline abnormal sleep duration.

Table 1

	Recovered with ASD 28 (30.1 ****)	Recovered without ASD 65 (69.9)	Depressed with ASD 89 (59.7*)	Depressed without ASD 60 (40.3)
<i>N</i> (% , stratified)				
<i>Demographics</i>				
A. Age (years, mean $\pm$ SD)	36.8 $\pm$ 12.8	37.1 $\pm$ 14.2	33.9 $\pm$ 12.9 **	40.1 $\pm$ 13.6
B. Female (%)	53.6	55.4	52.8 *	73.3
C. Caucasian (%)	75.0	80.0	83.2	91.7
D. College degree (%)	57.1	64.6	42.7	55.0
E. Married (current, %)	42.9	40.0	32.6	46.7
F. Full time Employment (current, %)	32.1	30.8	24.7	28.3
<i>Comorbid disorders (lifetime, %)</i>				
1. Anxiety	57.1	44.6	76.4	78.3
2. Alcohol/substance use	35.7	53.9	61.8	55.0
3. Eating	17.9	6.2	13.5	25.0
4. Personality	7.1	7.7	15.7	13.3
<i>Other illness characteristics</i>				
5. Bipolar II disorder (%)	50.0	33.9	64.0	60.0
5A. Psychosis (lifetime, %)	32.1	52.3	40.5	28.3
5B. Psychiatric Hospitalization (lifetime, %)	39.3	47.7	29.2	21.7
6. One 1° relative w mood disorder (%)	46.4	49.2	57.3	61.7
7. Onset age (years, mean $\pm$ SD)	17.0 $\pm$ 8.4	20.2 $\pm$ 9.2	16.2 $\pm$ 6.4	18.5 $\pm$ 9.4
8. Childhood (age < 13 years) Onset (%)	25.0	10.8	24.7	21.7
9. Illness duration (years, mean $\pm$ SD)	19.5 $\pm$ 14.1	17.1 $\pm$ 13.2	17.5 $\pm$ 13.6	21.2 $\pm$ 12.2
10. Long illness duration (15 years, %)	57.1	47.7	48.3	63.3
11. Episode accumulation (10, lifetime, %)	53.6	47.7	60.7	78.3
12. Suicide attempt (lifetime, %)	32.1	26.2	31.5	38.3
13. Rapid cycling (4 episodes in prior year, %)	10.7	7.7	27.0	31.7
14. CGI-BP-OS (current, mean $\pm$ SD)	2.4 $\pm$ 0.8	2.1 $\pm$ 0.7	5.4 $\pm$ 0.7	5.3 $\pm$ 0.8
<i>Mood symptoms (in prior 10 days, %)</i>				

	Recovered with ASD	Recovered without ASD	Depressed with ASD	Depressed without ASD
15. Sadness	17.9	18.5	87.6	91.7
16. Anhedonia	25.0	10.8	94.4	95.0
17. Euphoria	14.3	12.3	27.0	28.3
18. Irritability	42.9	32.3	67.4	68.3
19. Anxiety	46.4	36.9	85.4	73.3

* p < 0.05,

** p < 0.01,

***

p < 0.0001 with versus without baseline ASD. ASD indicates abnormal sleep duration. **Boldface** font indicates parameters with statistically significant relationships with baseline ASD. *Italic* font indicates parameters associated with bipolar I subtype. Missing data among recovered patients: 7.5% for 10 prior episodes, 0.0–4.3% for other parameters. Missing data among depressed patients: 7.4% for 10 prior episodes, 0.0–0.7% for other parameters. CGI-BP-OS indicates Clinical Global Impression for Bipolar Disorder-Overall Severity; SD indicates standard deviation.