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Sleep, illness course, and concurrent symptoms in inter-episode bipolar disorder

Polina Eidelman, Lisa S. Talbot, June Gruber, Allison G. Harvey*

Department of Psychology, University of California, Berkeley, United States

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ABSTRACT

We investigated associations between sleep, illness course, and concurrent symptoms in 21 participants with bipolar disorder who were inter-episode. Sleep was assessed using a week-long diary. Illness course and symptoms were assessed via validated semi-structured interviews. Lower and more variable sleep efficiency and more variable total wake time were associated with more lifetime depressive episodes. Variability in falling asleep time was positively correlated with concurrent depressive symptoms. Sleep efficiency was positively correlated with concurrent manic symptoms. These findings suggest that inter-episode sleep disturbance is associated with illness course and that sleep may be an important intervention target in bipolar disorder.

1. Introduction

Sleep disturbance is a hallmark feature of bipolar disorder, occurring in both mania and depression. Sleep disturbance found in the inter-episode period has also been reported to be equivalent to that experienced by patients with chronic insomnia (Harvey, Schmidt, Scarna, Neitzert Semler, & Goodwin, 2005). A complex and varied presentation of sleep disturbances in bipolar disorder has been reported and includes a relatively high prevalence of insomnia (Harvey et al., 2005), hypersomnia (Kaplan & Harvey, 2009), reduced sleep need, and delayed phase sleep disorders (Staton, 2008). Thus, sleep variables of interest include total wake time (the total duration of sleep onset latency, duration of wake after sleep onset, and duration of early morning awakening; TWT), total sleep time (total duration of sleep over the course of the night; TST), sleep efficiency (the ratio of total sleep time to time spent in bed; SE), and variability in the timing of sleep.

Even with optimal psychiatric care, approximately 50% of recovered bipolar individuals relapse within 1 year (Perlis, et al., 2006) and almost all relapse within 4 years (Tohen, Waternaux, & Tsuang, 1990), most commonly into a depressive episode. Hence, focusing on potential predictors of illness course is a critical domain for research. Several lines of evidence suggest that sleep disturbance may be one such key predictor. First, disturbed sleep appears to be a predictor of increased symptoms in bipolar disorder (see Harvey, 2008 for review). Second, one night of sleep deprivation causes mania or hypomania in a proportion of bipolar individuals, with manic/hypomanic symptoms reported in as many as 75% of the sample in one study (e.g., Wehr, Sack, & Rosenthal, 1987). Third, sleep deprivation contributes to mood dysregulation and hypersensitive emotional responses in healthy controls as indexed by overactive amygdala response (Yoo, Gujar, Hu, Jolesz, & Walker, 2007). In addition to serving as a potential predictor of illness course, sleep disturbance in bipolar disorder is a particularly important research focus given the potential clinical implications of such research for treating this chronic and impairing disorder.

While several psychological therapies for bipolar disorder target sleep disturbance (see Harvey, 2008 for review), there remains significant room for improvement in treatment outcome (Miklowitz et al., 2007) and a need for basing treatments in empirical research (Salkovskis, 2002). Furthermore, bipolar disorder treatments have not yet taken advantage of advances made in the treatment of chronic insomnia, and several investigators (e.g., Harvey, 2008; Plante & Winkelman, 2008) have called for an empirical approach to integrating insomnia treatments into therapies for bipolar disorder. The treatment of sleep disturbance in bipolar disorder is often approached pharmacologically. However, there may be advantages to using psychological interventions to manage sleep disturbance in bipolar disorder, including the relative lack of side effects and the absence of adverse drug interactions with mood stabilizing medications. There is evidence that managing sleep disturbance psychologically has been a promising approach in unipolar depression. For instance, the use of cognitive behavioral therapy for insomnia in combination with antidepressant medication is

* Corresponding author. University of California, Department of Psychology, 2205 Tolman Hall #1650, Berkeley, CA 94720-1650, United States. Tel.: +1 510 642 7138.
E-mail address: aharvey@berkeley.edu (A.G. Harvey).

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associated with higher rates of remission than antidepressants alone in unipolar depressed individuals (Manber et al., 2008).

With the dual goals of further clarifying the role of sleep in bipolar disorder as well as developing an empirical basis for adapting current psychological treatments for sleep disturbance specifically for patients with bipolar disorder, the present study aimed to determine if inter-episode sleep/circadian variables in adult bipolar disorder are associated with illness course and concurrent symptoms. The first hypothesis was that greater inter-episode sleep disturbance would be correlated with a more severe and chronic illness course (i.e., earlier age at illness onset and more lifetime manic and depressive episodes). This was of interest as previous studies have indicated the importance of illness course as a predictor of future symptoms and impairment in bipolar disorder (Judd et al., 2002; Robinson & Ferrier, 2006) and have suggested that an earlier age at illness onset predicts more severe sleep disturbance in pediatric bipolar disorder (Mehl et al., 2006). The second hypothesis was that inter-episode sleep disturbance would be positively correlated with concurrent manic and depressive symptoms, based on evidence that sleep is critical for effective mood regulation (e.g., Harvey, 2008; Wehr et al., 1987; Yoo et al., 2007). For both the first and second hypotheses we sought to determine which specific sleep parameters were most important (e.g., TWT, TST, sleep efficiency, and variability in sleep), with an eye to identifying variables that might be targeted in intervention development. Following recent theories in pediatric bipolar disorder (Staton, 2008), the third hypothesis was that a tendency toward delayed phase sleep (measured via bedtime and falling asleep time) would be associated with a more chronic and severe illness course and more concurrent manic and depressive symptoms. We aimed to test these hypotheses in a diverse and representative sample. Given that bipolar disorder is typically associated with the presence of comorbid psychiatric diagnoses (Kessler, Chiu, Demler, & Walters, 2005), we enrolled participants with comorbid psychiatric illnesses.

2. Method

2.1. Participants

The majority of participants were recruited through advertisements, and several participants were also recruited via referrals. Of the 119 individuals screened, 21 chose not to enroll or were unable to be reached subsequently and 77 fell outside the inclusion criteria (specific details on the 77 excluded participants are presented below). Our final sample consisted of 21 participants diagnosed with bipolar disorder Type I ($n = 19$) or Type II ($n = 2$) according to the Structured Clinical Interview for DSM-IV-TR (SCID; First, Spitzer, Gibbon, & Williams, 1994). Inter-episode status was defined as a total score < 12 on the Clinician Rated Inventory of Depressive Symptomatology (IDS-C; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996), a total score < 8 on the Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), and not meeting SCID criteria for depression, mania, or hypomania in the month preceding the clinical interview. Additionally, we assessed for the presence of confounding sleep disorders using the Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2004) in combination with one night of polysomnography in the lab. Participants were excluded for: not being under psychiatric care (requirement of the ethics committee; $n = 23$); not meeting SCID criteria for bipolar disorder Type I or II ($n = 22$); not being inter-episode as per criteria noted above ($n = 17$); diagnosis of a current substance or alcohol abuse disorder ($n = 4$); severe medical illness ($n = 4$); and suspected confounding sleep disorder such as sleep apnea and restless leg syndrome ($n = 7$).

As bipolar disorder is typically associated with the presence of comorbid psychiatric diagnoses (Kessler et al., 2005), participants were not excluded on the basis of comorbid diagnoses other than current alcohol or substance abuse disorders. Current comorbidities included panic disorder ($n = 1$), agoraphobia ($n = 1$), social phobia ($n = 3$), specific phobia ($n = 6$), obsessive compulsive disorder ($n = 2$), post traumatic stress disorder ($n = 1$), generalized anxiety disorder ($n = 1$), anorexia nervosa ($n = 1$), bulimia nervosa ($n = 1$) and binge eating disorder ($n = 1$). Of 21 participants, 20 reported regular use of psychotropic medication including mood stabilizers ($n = 16$), antidepressants ($n = 17$), antipsychotics ($n = 10$) and anxiolytics ($n = 6$).

2.2. Measures

2.2.1. Sleep diary

Sleep variables were assessed using a week-long daily sleep diary. Each morning, participants indicated their sleep onset latency, duration of wake after sleep onset, and duration of early morning awakening in minutes for the preceding night. These were summed to comprise total wake time (TWT) for each night. Participants also indicated their bedtime, their arising time, and their total sleep time (TST) for each night. Sleep efficiency was calculated by dividing TST by time in bed (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). The standard deviation of each sleep measure was used as an index of variability. TWT, TST, sleep efficiency, bedtime, and falling asleep time (bedtime plus sleep onset latency) were averaged for the week. In an attempt to add to the evidence derived from questionnaires that circadian disturbances are central in bipolar disorder (Staton, 2008), we utilized participants' bedtime and falling asleep times as proxies for a potential tendency toward delayed phase. We emphasize that there are limitations associated with both questionnaire and sleep diary measures of circadian rhythm disorders. However, there are also significant ethical difficulties associated with utilizing the gold standard approach to assessing circadian rhythms in bipolar individuals, an issue to which we return in the discussion.

2.2.2. Illness course

We assessed illness course (age of bipolar disorder onset and the number of lifetime manic and depressive episodes) using the National Institute of Mental Health retrospective Life-Charting Methodology (NIMH-LCMr; Leverich & Post, 1993). The NIMH-LCMr procedure involves charting a participant's course of illness by using important dates, occurrences, and events as anchor points. This process allows for capturing mild to severe hypomanic/manic and depressive episodes while taking a systematic approach that limits the impact of current mood and retrospective recall bias. The NIMH-LCMr has been well validated, and its assessment of manic and depressive symptoms correlates highly with clinician-rated symptoms and Global Assessment of Functioning (Denicoff, Smith-Jackson, Disney, & et al, 1997; Leverich & Post, 1993).

2.2.3. Concurrent symptoms

The IDS-C (Rush et al., 1996) and YMRS (Young et al., 1978) assessed depressive and manic symptoms present over the week of sleep diary completion. The IDS-C total score is based on 28 items, with scores less than 12 indicating no clinical depression. The IDS-C has good psychometric properties and is widely used in medical and research settings (Rush et al., 1996). The YMRS consists of 11 items, with scores less than 8 indicating no clinical mania/hypomania. The YMRS has good psychometric properties, including inter-rater reliability of 0.93 and predictive validity of 0.66 (Young et al., 1978).

2.3. Procedures

Individuals who responded to an advertisement or were referred to the study completed a screen determining potential eligibility. Those appearing to be eligible were mailed or emailed the sleep diary. Participants called into the lab with their responses each morning following diary completion in order to time-stamp the data. The day following sleep diary completion, the SCID-IV, IDS-C, YMRS, NIMH-LCMr, and demographics and medication self-report questionnaires were administered. Only data from individuals who were determined to be eligible at this visit was retained for analysis.

2.4. Data analysis

Bivariate correlations were used to examine associations between sleep diary variables and illness course and concurrent manic and depressive symptoms.

3. Results

The average age of the sample was 37.0 years old (SD = 10.65). The majority of the sample was female (85.7%), single (47.6%), college educated (66.7%), Caucasian (71.4%), and employed (81%). Average TWT ranged from 12.83 to 193.00 min ($M = 72.79$) with a standard deviation of 48.88, average TST ranged from 264.67 to 546.86 min ($M = 414.36$) with a standard deviation of 68.28, and average SE ranged from 61% to 96% ($M = 85.35\%$) with a standard deviation of 9.29. Mean bedtime was 11:37PM (SD = 71.40 min) and mean falling asleep time was 12:20AM (SD = 68.40 min). The sample had a mean age of illness onset of 18.76 years (SD = 9.53), 8.71 lifetime manic episodes (SD = 7.64), and 10.52 depressive episodes (SD = 10.05). On average, participants scored 3.30 (SD = 2.20) on the YMRS and 6.95 (SD = 3.36) on the IDS-C.

Given that the sample size was 21 participants, statistical power was fairly low. Analyses were powered to detect large effect sizes. However, r-values in the medium effect size range did not reach statistical significance. Correlations between sleep variables, illness course, and concurrent manic and depressive symptoms are reported in Table 1. Average SE was significantly negatively correlated with the number of lifetime depressive episodes. Variability in SE (as indexed by the standard deviation) and variability in TWT were positively correlated with the number of lifetime depressive episodes. Although not statistically significant, variability in bedtime was also positively correlated with the number of lifetime depressive episodes ($r = 0.42$). Additionally, variability in falling asleep time was positively correlated with concurrent depressive symptoms (IDS-C score), while average SE was positively correlated with concurrent manic symptoms (YMRS score). To check if sleep symptoms assessed by the YMRS and IDS-C were driving these correlations, analyses were recalculated excluding items assessing sleep disturbance (items 4 on the YMRS and 1–4 on the IDS-C). The correlations between variability in falling asleep time and depressive symptoms, and between SE and manic symptoms remained significant. Additionally, although not statistically significant, a negative correlation ($r = -0.42$) between TWT and manic symptoms emerged once the item assessing sleep disturbance was removed from the YMRS score. TST and bedtime were not significantly correlated with illness course or concurrent symptoms. Additionally, age of illness onset and the number of lifetime manic episodes were not significantly correlated with sleep.

4. Discussion

This study investigated whether inter-episode sleep/circadian variables are associated with illness course and concurrent symptoms in bipolar disorder. Our hypothesis that greater inter-episode sleep disturbance would correlate with a more chronic and severe illness course was partially supported. Specifically, having experienced a greater number of depressive episodes was associated with poorer and more variable sleep efficiency and with more variable TWT. Additionally, although the correlation was not statistically significant, a greater number of depressive episodes was also associated with more variability in bedtime. These findings raise the possibility that an unstable sleeping pattern, particularly as indicated by poor and variable sleep efficiency and TWT, may be a correlate of or contributor to a depressive bipolar disorder illness course. It may be the case that experiencing a greater number of depressive episodes, which are marked by disturbed sleep, leads to spending more time in bed than is spent sleeping, possibly as the bed comes to be associated with poor sleep and depression. Alternately, spending excessive time awake in bed may have detrimental effects on mood. Indeed, in recent discussions of hypersomnia, we have suggested that excessive time in bed (i.e., poor sleep efficiency) may contribute to depression through associated interpersonal, occupational, and self-esteem problems (Kaplan & Harvey, 2009). Perhaps an escalating vicious cycle may develop between a tendency toward experiencing depression and an inconsistent and disturbed sleep pattern.

One finding partially supported our second hypothesis that greater inter-episode sleep disturbance would be associated with more concurrent manic and depressive symptoms. Specifically, variability in falling asleep time was positively correlated with concurrent depressive symptoms. The potential conclusions we can draw from this correlation are tentative given that this was the only significant correlation to support our hypothesis. However, this finding is consistent with the idea discussed above that a tendency toward experiencing depressive symptoms may be associated with

Table 1
Correlations between sleep diary variables, illness course, and manic and depressive symptoms.

	Age at onset	Lifetime manic episodes	Lifetime depressive episodes	YMRS (Mania)	IDS-C (Depression)	YMRS minus sleep items	IDS-C minus sleep items
Sleep diary	*r*	*r*	*r*	*r*	*r*	*r*	*r*
Average TWT	0.02	0.15	0.05	−0.11	0.25	−0.42	0.03
Average TST	−0.09	−0.14	−0.25	0.06	−0.01	0.13	0.03
Average SE	0.08	−0.39	−0.60**	0.46*	−0.27	0.44*	0.00
Variability of TWT	−0.14	0.32	0.58**	−0.34	0.23	−0.29	0.22
Variability of TST	−0.22	−0.15	0.03	0.10	0.14	0.03	0.06
Variability of SE	−0.10	0.22	0.50*	−0.29	0.24	−0.30	0.17
Average bedtime	−0.03	−0.05	−0.32	0.26	0.14	0.20	0.17
Average falling asleep time	−0.06	0.16	0.09	0.29	0.23	0.14	0.23
Variability of bedtime	−0.12	0.18	0.42	0.05	0.15	−0.07	0.23
Variability of falling asleep time	−0.36	0.19	0.01	−0.03	0.54*	−0.14	0.70**

Note: *$p \leq 0.05$; **$p \leq 0.005$.

more unstable sleep patterns. Additionally, in contrast to our hypothesis, we also found a higher level of manic symptoms to be associated with increased sleep efficiency. This is surprising because sleep efficiency is typically considered to be a sign of good sleep; the higher the sleep efficiency, the larger the portion of the time spent in bed is spent sleeping. Additionally, although not statistically significant, we found a negative correlation of medium size between TWT and manic symptoms other than sleep disturbance (total YMRS score excluding the item assessing sleep disturbance), suggesting that those individuals who were experiencing more manic symptoms also spent less time awake at night trying to sleep. These findings raise the possibility that experiencing more manic symptoms may be associated with a greater likelihood of leaving the bed during awakenings in the night or getting up earlier in the morning and starting the day rather than attempting to return to sleep. It is possible that this behavior may be related to the excessive goal-directed activity that has been observed in inter-episode bipolar disorder (Johnson, Ruggero, & Carver, 2005). This possible link between sleep efficiency and manic symptoms during the inter-episode period warrants further investigation.

Our third hypothesis was that tendency toward delayed phase would be associated with a more severe and chronic illness course and with more concurrent symptoms. This hypothesis was not supported. It is possible that the fairly low percentage of participants (20%) reporting a bedtime or falling asleep time that was later than 1 AM likely resulted in a reduced range in the data set, limiting the possibility of significant correlations emerging. On the one hand, this is a potential limitation. On the other hand, perhaps the low number of individuals with late bedtimes may indicate that a tendency toward delayed phase may be less prevalent in, and central to, bipolar disorder than has been theorized. If the latter turns out to be true, these findings would be in contrast to the recent emphasis on delayed phase as a core deficit in bipolar disorder (Staton, 2008) and to questionnaire data from adults with bipolar disorder (Mansour et al., 2005). Future studies using questionnaire data to assess tendency toward a delayed phase may benefit from considering bedtime, falling asleep time, and midsleep time, particularly on days when individuals' sleep schedules are not constrained by their work schedule. Data identifying which of the days the diary was kept were such unconstrained days was not available in the present study. We emphasize that the gold standard method for assessing circadian phase is the direct measurement of the circadian clock (i.e., through melatonin) in a forced desynchronization protocol (Dijk & Cajochen, 1997). Given the involved nature of this method, it might be considered unethical to ask an individual with bipolar disorder to participate, and anyone who could successfully complete the protocol may well not be representative of most bipolar individuals. Thus, although neither questionnaire nor diary data are the gold standards for assessing tendency toward delayed phase, they are reasonable proxies. Importantly, the mixed data obtained with these methods warrants further investigation of the hypothesis that a delayed phase contributes to the onset and maintenance of bipolar disorder.

Several researchers have suggested that cognitive behavioral approaches for insomnia be applied to bipolar disorder while including calls for an empirical approach to adapting existing interventions and developing new interventions (Harvey, 2008; Plante & Winkelman, 2008). As one step in this direction, we found that sleep efficiency and TWT and their variability were significantly associated with lifetime history of depressive episodes and with concurrent symptoms. Given the chronic and treatment-resistant nature of bipolar depression (Sachs, et al., 2007), it is important to target variables such as sleep disturbance that are potential contributors to depressive illness course in bipolar disorder. Sleep efficiency and variability in sleep may be particularly noteworthy variables to consider given that the goal of two empirically supported treatments for insomnia, stimulus control and sleep restriction, is to increase sleep efficiency and regularize the sleep–wake cycle (Morin et al., 2006). Stimulus control and sleep restriction are the most thoroughly empirically tested and supported treatments for insomnia (Morin et al., 2006). They are thought to target conditioned night-time anxiety and arousal. Rather than staying in bed when having trouble falling asleep at the beginning of the night or after an awakening in the middle of the night, patients treated with stimulus control and sleep restriction are encouraged to leave the bed and bedroom when they cannot sleep, attempting to initiate or resume sleep only when they feel that sleep is imminent. Additionally, patients set a regular waking time for the morning regardless of the time they actually fall asleep. If this approach were trialed in patients with bipolar disorder, manic symptoms would need to be carefully monitored as both stimulus control and sleep restriction may involve a mild form of short-term sleep deprivation, which could place individuals with bipolar disorder at risk for increased manic symptoms (Harvey, 2008). This is particularly important given the present findings linking increased manic symptoms with increased sleep efficiency.

A number of potential limitations must be noted. First, we recognize that our discussion needs to be tempered because of the relatively small sample ($n = 21$). However, we emphasize that our chosen participant group can be difficult to recruit and retain, and that a strength of our approach was its inclusion of a detailed characterization of sleep, including many of the "gold standard" measures (Buysse et al., 2006). Given the sample size, we carefully considered our approach to multiple statistical comparisons. On the one hand, not correcting for multiple comparisons increases the risk of Type I error. On the other hand, applying a correction for multiple comparisons increases the risk of Type II error. On balance, we elected not to correct for multiple comparisons as we were more concerned with decreasing the risk of Type II error because links between variables considered in this study have not previously been investigated (Nakagawa, 2004). Given our goal of identifying potential treatment targets for interventions designed to address sleep disturbance in bipolar disorder, we believe it was important to investigate associations between a variety of sleep variables and clinical factors. We hope these findings will allow future investigations to take a more targeted approach enabling fewer statistical tests. Second, we relied on self-report for assessing sleep disturbance. Future studies should try to replicate these findings with objective naturalistic sleep measures such as actigraphy. Third, we assessed sleep over the course of one week. It is possible that a longer duration of sleep assessment (2 weeks or longer) would have yielded a more accurate impression of participants' sleep. Fourth, although the NIMH-LCMr is a well-validated measure of bipolar illness course, it is retrospective and is potentially subject to recall bias. It may be the case that those individuals who were experiencing more disturbed sleep and were more prone to mood disturbance were more likely to recall negative past experiences. Supplementing such a measure with data collected from medical records would be useful in future research. Fifth, our sample was primarily recruited via advertisements. It is possible that the socioeconomic or clinical characteristics of individuals responding to research advertisements may differ from the larger population of bipolar individuals. Thus, future investigations of bipolar disorder should utilize multiple recruitment strategies. Sixth, there are potentially confounding effects of psychotropic medications on sleep. However, given that no medication taken by our participants is consistently associated with sedating/activating effects, any possible effects of medications on sleep are likely to have been randomly distributed in the sample. In addition, side

effects often wear off or diminish as individuals continue on a medication course (Talbot, Hairston, Eidelman, Gruber, & Harvey, 2009). In spite of these limitations, we believe that our findings support the theory that sleep disturbance may be a potential trait marker of bipolar disorder, and they extend previous research by raising the importance of SE and sleep variability as critical sleep parameters in bipolar disorder.

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