Sleep and Bipolar Disorder:

Sleep Disturbance Across the Course of the Illness

By

Jennifer Christine Kanady

A thesis submitted in partial satisfaction of the requirements for the degree of

Master of Arts

in

Psychology

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Allison G. Harvey, Chair
Professor Stephen P. Hinshaw
Professor Sheri L. Johnson

Fall 2012
Abstract

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The present study examined the course of sleep disturbance across the lifespan of individuals with bipolar disorder, as well as the relationship between lifetime sleep disturbance and markers of illness severity. Individuals with inter-episode bipolar disorder and comorbid sleep disturbance (n = 48) completed the NIMH Retrospective Life-Charting Methodology (the life chart). The life chart assessed lifetime sleep disturbance and markers of illness severity. Across the course of the disorder, manic months were largely characterized by reduced sleep need and insomnia, depressive months were largely characterized by hypersomnia and insomnia, mixed months were largely characterized by reduced sleep need and hypersomnia, and inter-episode months were largely characterized by insomnia. A longer duration of sleep disturbance across inter-episode periods was associated with markers of a more severe course of the illness; namely, duration of lifetime manic and depressive symptoms. These data demonstrate that sleep disturbance is prevalent across the lifespan of individuals with bipolar disorder and the duration of sleep disturbance across inter-episode periods is associated with markers of illness severity. Hence, current sleep treatments should be adapted for use in bipolar disorder.

Keywords: Bipolar disorder, sleep disturbance, illness course, illness severity
Introduction

Bipolar I disorder is one of the 10 most disabling conditions worldwide (Murray & Lopez, 1996; World Health Organization, 2001) and has a lifetime prevalence of around 1.0% (Merikangas et al., 2011; Tohen & Angst, 2002; Weissman et al., 1996). Although there have been important advances in psychological and pharmacological treatments for bipolar disorder, it remains a severe and chronic psychiatric illness marked by significant mood disruption and functional impairment (Craighead, Milkowitz, Frank, & Vajk, 2002). Notably, individuals with bipolar disorder spend a considerable portion of their lives unwell (Angst & Sellaro, 2000), the risk of affective episode relapse remains high (Perlis et al., 2006a; Tohen, Watermaux, & Tsuang, 1990), and the lifetime rate of suicide attempts is 30% (Yuan-Who & Dilsaver, 1996). Furthermore, most individuals with bipolar disorder continue to experience mood lability, functional impairment, and other residual symptoms in the intervals between episodes, known as inter-episode periods (e.g., Harrow, Goldberg, Grossman, & Meltzer, 1990; Robb, Cookie, Devins, Young, & Joffe, 1997). Moreover, inter-episode impairment predicts relapse into either mania or depression (MacQueen et al., 2003). Therefore, it is important to identify pathways that may underlie mood disruption and functional impairment in bipolar disorder.

Sleep disturbance is among the most prominent correlates of mood disruption and functional impairment, yet there have been few studies that consider the complexity and variety of sleep disturbance across the lifespan. The present study aimed to fill these gaps in the literature in two ways. First, we examined sleep disturbance across the lifespan of individuals with bipolar disorder. Second, we clarified the relationship between lifetime sleep disturbance and markers of illness severity.

Sleep disturbance is a prevalent, yet variable, feature of bipolar disorder. Manic episodes are characterized by reduced sleep need (American Psychiatric Association, 2000; Clayton & Pitts, 1965), depressive episodes are characterized by insomnia and/or hypersomnia (American Psychiatric Association, 2000; Detre et al., 1972; Winokur, Clayton, & Reich, 1969), and mixed episodes are characterized by decreases in total sleep time (Cassidy, Murry, Forest, & Carroll, 1998). Sleep disturbance also persists during the inter-episode period; 70% of inter-episode individuals with bipolar disorder report clinically significant sleep disturbance, 55% meet strict diagnostic criteria for insomnia (Harvey, Schmidt, Scarna, Semler, & Goodwin, 2005), and 25% endorse symptoms of hypersomnia (Kaplan et al., 2011). Moreover, individuals with bipolar disorder are more likely to report a delayed sleep phase preference when compared to healthy individuals (Giglio et al., 2010; Stanton, 2008), and irregular sleep patterns are commonly reported (Eidelman, Talbot, Gruber, & Harvey, 2010; Jones, Hare, & Evershed, 2005; Millar, Espie, & Scott, 2004). Thus, individuals with bipolar disorder experience a variety of sleep disturbance across the different phases of the illness.

Sleep disturbance is important, as it is one possible pathway to mood disruption and functional impairment. First, disrupted sleep patterns are associated with the onset of mood episodes. For example, experimentally induced sleep deprivation is associated with the onset of mania or hypomania in a proportion of individuals with bipolar disorder (e.g., Columbo, Benedetti, Barbini, Campori, & Smeraldi, 1999; Wehr, Sack, & Rosenthal, 1987; Wu & Bunney, 1990), and sleep disturbance is the most common prodrome for mania and the sixth most common prodrome for depression (Jackson, Cavanagh, & Scott, 2003). Second, bipolar disorder is a disorder of mood regulation (Kruger, Seminowicz, Goldapple, Kennedy & Mayberg, 2003), and accruing evidence demonstrates that sleep disturbance undermines the capacity to regulate mood (e.g., Dingés et al., 1997; Totterdell, Reynolds, Parkinson, & Briner, 1994). Specific to
bipolar disorder, inter-episode hypersomnia (Kaplan et al., 2011), short sleep duration (Barbini, Bertelli, Columbo, & Smeraldi, 1996; Gruber et al., 2009; Leibenluft, Albert, Rosenthal, & Wehr, 1996), long sleep duration (Gruber et al., 2009), and sleep variability (Eidelman et al., 2010) are all associated with mood symptoms. Third, suicide rates are high in bipolar disorder (e.g., Yuan-Who & Dilsaver, 1996), and sleep disturbance is a risk factor for suicidal behavior (e.g., Arargun, Kara, & Solmaz, 1997; Bernert et al., 2005; Chellappa & Arujo, 2007; Hall & Platt, 1999; McCall et al., 2010; Wojnar et al., 2009). Fourth, there is some evidence that lifetime prevalence of sleep disturbance is associated with future mood disruption. For example, the lifetime prevalence of insomnia in young adults predicts future incident of major depressive episodes (Breslau, Roth, Rosenthal, & Adreski, 1997). However, much less is known about how lifetime prevalence of sleep disturbance affects the course of bipolar disorder.

In the present study we aimed to begin the process of addressing two important gaps relating to sleep and bipolar disorder. The first aim was to examine the course of sleep disturbance across affective episodes and inter-episode periods. Previous studies examining sleep disturbance in bipolar disorder typically focused on a single mood episode or a single period of time. This is one of the first studies to examine the course of sleep disturbance across the lifespan of individuals with bipolar disorder. The types of sleep disturbance examined were: insomnia, hypersomnia, reduced sleep need, delayed sleep phase, and irregular sleep patterns. Based on previous research, it was hypothesized that across the course of the disorder (a) manic months would be largely characterized by reduced sleep need, (b) depressive months would be largely characterized by insomnia and/or hypersomnia, (c) mixed months would be largely characterized by insomnia or reduced sleep need, (d) inter-episode months would be largely characterized by insomnia, (e) both delayed sleep phase and irregular sleep patterns would be reported within and between mood episodes.

The second aim was to examine the association between lifetime sleep disturbance and markers of illness severity. For the purpose of this study, lifetime sleep disturbance was defined as the duration of sleep disturbance across inter-episode periods. The rationale for a focus on the inter-episode period was threefold. First, individuals continue to suffer from significant symptomatology and impairment during the inter-episode period (e.g., Harrow et al., 1990; MacQueen et al., 2003). Second, this impairment is concerning because it predicts relapse into either mania or depression (MacQueen et al., 2003). Third, the mechanisms that underpin this impairment have been minimally researched. For the purpose of this study, markers of bipolar illness severity included the duration of manic and depressive symptoms across the lifespan, and the number of mood-related hospitalizations. Based on previous research, it was hypothesized that a longer duration of sleep disturbance would be associated with markers of a more severe course of the illness.

Methods

Participants

Forty-eight individuals with bipolar disorder, type I were examined (age: 36.8 ± 11.3 years; education: 15.5 ± 3.7 years; 29F). Ethnicity and race of the participants reflected the diversity of Alameda County (63% Caucasian, 11.1% African American, 9.3% Asian, 9.3% more than one ethnicity, 3.7% declined to answer, 1.9% American Indian/Alaska Native, 1.9% other). Individuals with a diagnosis of bipolar disorder, type I were recruited. Bipolar I diagnoses were confirmed by the research team based on DSM-IV-TR criteria (American Psychiatric Association, 2000), as established by the Structured Clinical Interview for Axis I Disorders
(SCID; First, Spitzer, Gibbon, & Williams, 1995). A psychiatrist consultant verified all diagnoses. Participants were inter-episode (i.e., not currently manic or depressed) at the time of the assessment. An inter-episode period was defined by a score of 24 or less on the Inventory of Depressive Symptomatology – Clinician Rating (IDS-C) and a score of 12 or less on the Young Mania Rating Scale (YMRS), which are standard measures and cutoffs in the bipolar literature (Rush, Gullion, Basco, Jarrett, & Trivedi, 1996; Young, Biggs, Ziegler, & Meyer, 1978).

Participants were required to be on a stable medication regimen for at least four weeks prior to enrollment in the study and under the care of a treating physician or nurse practitioner who manages mood. All participants were at least 18 years old and reported English fluency, which was necessary as all aspects of the protocol were in English.

Participants also presented with a current complaint of insomnia. Insomnia was defined as a subjective report of difficulty falling asleep (>30 minutes), difficulty maintaining sleep (wake after sleep onset >30 minutes), and/or waking up too early (early morning awakening >30 minutes), with associated daytime complaints, at least three times a week for at least one month. These criteria reflect a combination of Research Diagnostic Criteria (Edinger et al., 2004), International Classification of Sleep Disorders (ICSD-2; American Academy of Sleep Medicine, 2005) and DSM-IV-TR standards (American Psychiatric Association, 2000). In addition to meeting criteria for insomnia, 7% of the participants met strict diagnostic criteria for hypersomnia and 12% for delayed sleep phase. These statistics reflect the heterogeneity of sleep disturbance in this sample.

Participants were excluded from the study if they (a) were diagnosed with alcohol or substance abuse/dependence within the past three months as defined by the DSM-IV-TR (American Psychiatric Association, 2000); (b) were diagnosed with current post-traumatic stress disorder as defined by the DSM-IV-TR (American Psychiatric Association, 2000); (c) had an active or progressive physical illness or neurological degenerative disease; (d) had evidence of sleep apnea, restless legs syndrome or periodic limb movements during sleep; (e) were employed as an overnight shift worker in the last six months; (f) presented as a current suicidal risk, specifically if the participant endorsed active suicidal intent and/or had a specific suicide plan; (g) made a suicide attempt within the past 6 months; (h) presented as a current homicidal risk (as assessed by treating physician); and/or (i) were pregnant or breast-feeding mothers.

**Measures**

**Structured Clinical Interview for DSM-IV-TR.** The Structured Clinical Interview for DSM-IV-TR (SCID; First, Spitzer, Gibbon, & Williams, 1995) is a semi-structured interview designed to assess DSM-IV-TR diagnostic criteria for Axis I disorders. The SCID has been shown to have good reliability (Skre, Onstad, Torgersen, & Kringlen, 1991; Williams et al., 1992). Trained psychology doctoral students administered the SCID to all participants to assess current and lifetime Axis I disorders and to confirm a bipolar disorder, type I diagnosis. Fifteen randomly selected audiotapes of SCID interviews were rated by a set of independent reviewers in order to check diagnostic reliability. Rating matched 99.3% (κ = 0.99) of the primary diagnoses made by the original interviewer. This indicates strong intrarater reliability, though the use of a “skip-out” strategy (implemented if initial required criteria for a particular disorder were not met) may have reduced the number of potential disagreements with the original interviewer.

**Duke Structured Interview for Sleep Disorder.** The Duke Structured Interview for Sleep Disorders (DSISD; Edinger et al., 2004) is a semi-structured interview used to assess research diagnostic criteria for sleep disorders. The DSISD has been shown to have good reliability and validity (Edinger et al., 2009). Again, 14 randomly selected audiotapes of DSISD interviews
were rated by a set of independent reviewers for diagnostic reliability. Ratings matched 99.4% (κ = 0.99) of the primary diagnoses made by the original interviewer. This indicates strong interrater reliability.

**Young Mania Rating Scale.** The Young Mania Rating Scale (YMRS; Young et al., 1978) is an 11-item measure used to assess the severity of manic symptoms. Specifically, the YMRS was developed to assess the severity of (a) elevated mood, (b) increased motor activity, (c) increased sexual interest, (d) decreased need for sleep, (e) increased irritability, (f) increased speech, (g) increased distractibility, (h) increased goal-directed behavior, (i) disruptive and/or aggressive behavior, (j) appearance, and (k) insight. Each item is rated on a five-point scale and a higher YMRS score indicates more severe manic symptoms. The YMRS is a sensitive measure, and has been shown to have good reliability and validity (Young et al., 1978).

**Inventory of Depressive Symptomatology, Clinician Rating.** The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C; Rush et al., 1996) is a widely used 30-item instrument for assessment of depressive symptoms. The IDS-C includes all nine symptoms for major depressive disorder based on the DSM-IV-TR, including affective, behavioral, cognitive and motivational symptoms. The IDS-C also includes commonly associated symptoms for major depressive disorder such as anxious and irritable mood. Melancholic and atypical features of major depressive disorder are also assessed by the IDS-C (e.g., hypersonia). Each item is rated on a four-point scale and a higher IDS-C score indicates more severe depressive symptoms. The IDS-C has demonstrated good reliability and validity (Rush et al., 1996).

**The Insomnia Severity Index.** The Insomnia Severity Index (ISI; Morin, 1993) is a seven-item scale used to evaluate the severity of insomnia. The seven items of the ISI specifically assess the severity of sleep onset and sleep maintenance difficulties, satisfaction with current sleep patterns, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and degree of distress or concern caused by sleep problems. Each item is rated on a five-point scale and a higher score indicates more severe insomnia. The ISI has demonstrated good reliability, validity, and has strong psychometric properties (Bastien, Vallieres, & Morin, 2001).

**The NIMH Retrospective Life-Charting Methodology – Modified.** The National Institute of Mental Health Retrospective Life-Charting Methodology (the life chart; Leverich & Post, 1993) is a validated and standard measure of recording retrospective features of bipolar disorder including the number, duration, and severity of mood episodes, inter-episode periods, and medication use (e.g., Denicoff et al., 1997; Eidelman et al., 2010; Roy-Byrne, Post, Uhde, Porcu, & Davis, 1985). For the present study, the life chart was modified to include comorbid sleep disturbance; namely: insomnia, hypersonia, reduced sleep need, delayed sleep phase, and irregular sleep patterns. Insomnia was defined as a subjectively perceived difficulty initiating sleep, maintaining sleep, waking up too early, or sleep that is chronically poor in quality, and occurs despite adequate opportunity and circumstances for sleep, resulting in distress or daytime impairment (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2000). Hypersonia was defined as a subjectively perceived sleep disturbance characterized by persistent and excessive daytime sleepiness and abnormally prolonged sleep periods, resulting in distress or daytime impairment (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2000). Reduced sleep need was defined as sleeping very little, but feeling energized despite the inadequate amount of sleep (American Psychiatric Association, 2000). Delayed sleep phase was defined as a circadian rhythm disorder in which the major sleep episode is two or more hours later relative to the desired bedtime, which causes difficulty waking
at the desired time along with subsequent distress or daytime impairment (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2000). Last, irregular sleep patterns were defined as inconsistent and fragmented sleep and an erratic sleep-wake routine, resulting in distress or daytime impairment (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2000).

The life chart was completed collaboratively with the participant and a psychology doctoral student interviewer. To aid in life chart administration and participant recollection, the participant was provided with definitions of mild, moderate, and severe mood episodes; definitions of the different types of sleep disturbance; a list of commonly prescribed medications in bipolar disorder; and a list of life events that aided in recollection (e.g., high school graduation, loss of a job). Furthermore, participants were asked to consult diaries, medical records, doctors, friends, and family members to further ensure recollection and accuracy. The life chart was used to examine the course of sleep disturbance across affective episodes and inter-episode periods, as well as markers of illness severity. These data were collected using month-to-month units across the course of a participant’s lifespan. For the purpose of this study, markers of illness severity included the duration of manic and depressive symptoms across the lifespan, and the number of mood-related hospitalizations.

Procedure
Participants were recruited through Internet advertisements and flyers distributed to psychiatric clinics in the community. Participants were first screened over the phone. Once determined eligible, they were invited for a detailed in-person assessment. Written informed consent procedures were completed, and sociodemographic information was collected. Bipolar disorder I and insomnia diagnoses were confirmed using the SCID and DSISD. The SCID and the DSISD were also used to determine comorbid Axis I disorders and comorbid sleep disorders. The IDS-C and the YMRS were administered in order to determine the severity of current mood symptoms and to confirm an inter-episode state. The ISI was also administered to determine the severity of current insomnia symptoms. The life chart was completed during the in-person assessment.

Analysis Plan
To examine the hypotheses, two sets of analyses were conducted. In the first set, the life chart data were collapsed into several variables: (a) the total number of manic, depressive, mixed and inter-episode months across the lifespan; and (b) the total number of manic, depressive, mixed and inter-episode months with comorbid insomnia, hypersomnia, reduced sleep need, delayed sleep phase and irregular sleep patterns. From these variables, percentages were calculated to evaluate the hypotheses of aim one: (a) the percentage of manic months across the lifespan with comorbid reduced sleep need; (b) the percentage of depressive months across the lifespan with comorbid insomnia and/or hypersomnia; (c) the percentage of mixed months across the lifespan with comorbid insomnia and reduced sleep need; (d) the percentage of inter-episode months across the lifespan with comorbid insomnia; and (e) the percentage of affective and inter-episode months across the lifespan with comorbid delayed sleep phase and irregular sleep patterns. For comparison purposes, we also examined the percentage of manic, depressive, mixed and inter-episode months characterized by each type of sleep disturbance.

In the second set of analyses, lifetime sleep disturbance was examined by calculating the duration of sleep disturbance across all inter-episode periods. The duration of each type of sleep disturbance was examined individually. This procedure resulted in a total of five lifetime sleep disturbance variables: the duration of insomnia, hypersomnia, reduced sleep need, delayed sleep
The Course of Sleep Disturbance Across Bipolar Disorder

phase, and irregular sleep patterns across inter-episode periods. Markers of illness severity were calculated by: (1) computing the duration of manic and depressive symptoms across the lifespan; and (2) totaling the number of mood-related hospitalizations across the lifespan. This procedure resulted in a total of three markers of illness severity.

To examine the association between lifetime sleep disturbance and markers of illness severity, bivariate partial correlations were calculated, controlling for participant age. Partial correlations were computed for each variable of lifetime sleep disturbance and each marker of illness severity individually. To reduce the likelihood of a Type I error, a Bonferroni correction for multiple comparisons was applied. Two-sided significance was set at p<0.003.

Results

Participant Characteristics.

Bipolar disorder and sleep disturbance descriptive data for the 48 participants are presented in Table 1 and Table 2, respectively. Notably, the average age of onset for sleep disturbance was significantly earlier than the average age of onset for mood disturbance, t(47)=2.74, p<0.01.

The Course of Sleep Disturbance Across Affective Episodes and Inter-episode Periods.

Percentages were calculated to examine the prevalence of insomnia, hypersomnia, reduced sleep need, delayed sleep phase, and irregular sleep patterns across affective episodes and inter-episode periods. Results are depicted in Figure 1. Across the course of the disorder, manic months were largely characterized by reduced sleep need and insomnia, depressive months were largely characterized by hypersomnia and insomnia, and mixed months were largely characterized by reduced sleep need, hypersomnia, and insomnia. No mixed months were characterized by a lack of sleep disturbance. Over half of inter-episode months were characterized by insomnia and approximately one third were characterized by no sleep disturbance. Finally, delayed sleep phase and irregular sleep patterns were the least common features of each type of affective episode and the inter-episode period.

The Relationship between Lifetime Sleep Disturbance and Markers of Illness Severity.

Bivariate partial correlations, controlling for participant age, were calculated to examine the relationship between lifetime sleep disturbance and markers of illness severity. Results are presented in Table 3. Results discussed here are all significant at the p<0.003 level.

Lifetime sleep disturbance was calculated by examining the duration of each type of sleep disturbance across inter-episode periods. The duration of insomnia across inter-episode periods was moderately—but significantly—correlated with the duration of manic and depressive symptoms. There was a non-significant trend (p=0.009) suggesting that duration of inter-episode insomnia is related to number of mood-related hospitalization. Longer duration of hypersomnia across inter-episode periods was largely associated with longer duration of depressive symptoms. Reduced sleep need, delayed sleep phase, and irregular sleep patterns across inter-episode periods were not significantly correlated with any marker of illness severity.

Discussion

The present study was designed to clarify and extend knowledge about sleep and bipolar
disorder by addressing the complexity and impact of sleep disturbance across the lifespan. This was accomplished by addressing two specific aims. The first aim was to examine the course of sleep disturbance across affective episodes and inter-episode periods. Across the course of the disorder, approximately 65% of manic months were characterized by reduced sleep need. This finding is consistent with previous research (e.g., Cassidy et al., 1998; Clayton & Pitts, 1965; Hudson, Lipinski, Frankenburg, Grochocinski, & Kupfer, 1988). Interestingly, insomnia occurred in nearly a quarter of manic months. Whereas some studies have reported sleep continuity problems during mania (Hudson et al., 1988; Linkowski & Mendelwicz, 1993; Winokur & Tanna, 1969), to the best of our knowledge, the present study is the first to suggest that distress or impairment is associated with these sleep problems. Recall that sleep continuity and distress or impairment are required for a diagnosis of insomnia (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2000). Together, these findings suggest that insomnia is a common feature of mania.

Depressive months were largely characterized by hypersomnia (43.6%) and insomnia (39.1%), findings that are consistent with prior work (for review see Harvey, 2008; Plante & Winkelman, 2008). The prevalence of hypersomnia was similar to previous reports in bipolar depression, which have ranged from 38% (Akiskal & Benazzi, 2005) to 78% (Detre et al., 1972). Previous estimates of insomnia in bipolar depression vary considerably across studies (e.g., Casper et al., 1985; Winokur, Clayton, & Reich, 1969), with one study reporting 100% of depressed bipolar patients experiencing insomnia (Winokur et al., 1969). The prevalence of insomnia in the present study falls within the lower end of the range of previous studies. Notably, there is variability in prevalence estimates of hypersomnia and insomnia across studies. These discrepancies likely arise because of differences in measurements and definitions used. Future studies should consider using operationalized research diagnostic criteria to increase uniformity across studies of sleep disturbance prevalence. (Edinger et al., 2004; Kaplan & Harvey, 2009).

Relative to depression and mania, sleep during mixed episodes has been less-extensively characterized (see Harvey, 2008). To the best of our knowledge, only one study has reported that mixed episodes were associated with decreases in total sleep time (Cassidy et al., 1998). In the present study, approximately half of mixed months were marked by reduced sleep need and roughly a third by insomnia. Moreover, over a third of mixed months were characterized by hypersomnia. Finally, in contrast to manic, depressive, and inter-episode months, months spent in mixed states were characterized by sleep disturbance 100% of the time. Clearly, further research is needed to investigate the prevalence and impact of sleep disturbance during mixed states.

Across the course of the disorder and consistent with the literature (e.g., Brill, Penagaluri, Roberts, Gao, & El-Mallakh, 2011; Harvey et al., 2005) over half of inter-episode months were characterized by insomnia. Importantly, in unipolar depression, insomnia is a robust predictor for the development of future depressive episodes (e.g., Breslau et al., 1997). Therefore, insomnia may be an important target for intervention in bipolar disorder. Notably, approximately one-third of the inter-episode months were characterized by no sleep disturbance. It might be interesting to examine if individuals with no sleep disturbance during an inter-episode state have a less severe course of the illness relative to individuals with inter-episode sleep disturbance.

The percentage of months with delayed sleep phase and irregular sleep patterns across affective episodes and inter-episode periods was lower than expected (4.3 – 10.9% and 6.0 - 15.1%, respectively). Previous studies have demonstrated a tendency toward delayed sleep phase in as many as 49% of individuals with bipolar disorder (Giglio et al., 2010), and key
interventions treat instability of circadian rhythms (e.g., Frank, Swartz, & Kupfer, 2000; Malkoff-Schwartz et al., 2000). Hence, these two findings are quite surprising and require replication.

The second aim was to examine the relationship between lifetime sleep disturbance and markers of illness severity. As hypothesized, lifetime sleep disturbance, defined as the duration of sleep disturbance across inter-episode periods, was associated with markers of a more severe course of the illness. Relative to the other types of sleep disturbance, insomnia was the strongest correlate of markers of illness severity. Longer duration of insomnia across inter-episode periods was positively correlated with duration of manic and depressive symptoms and showed a non-significant trend for number of mood-related hospitalizations. These findings align with accruing evidence of an association between insomnia and mood (Buysee et al., 2007; Morin, Rodrigue, & Ivers, 2003).

Consistent with previous studies (Kaplan et al., 2011), duration of hypersomnia across inter-episode periods was largely associated with duration of depressive symptoms. This contributes to previous research by raising the possibility that duration of hypersomnia may play a role in the course of bipolar depression. Even so, we emphasize that this association may not be interpreted causally.

A particularly noteworthy finding was that the average age of onset for sleep disturbance was significantly earlier than the average age of onset for mood disturbance. This result is consistent with previous literature demonstrating that sleep disturbance was one of the earliest symptoms observed in pediatric bipolar disorder (Faedda, Baldessarini, Glovinsky, & Austin, 2004) and is an antecedent to the onset of bipolar disorder in a subset of high risk youth (Duffy et al., 2007). Moreover, there is a parallel finding that is quite robust in unipolar depression. Multiple longitudinal studies have reported that sleep disturbance often precedes episodes of depression and may be a risk factor for first and recurrent episodes of depression (e.g. Breslau et al., 1997; Ford & Kamerow; Perlis et al., 2006b; Weissman, Greenwald, Nino-Murcia, & Dement, 1997). Taken together, these findings suggest that sleep disturbance may be an early marker for bipolar disorder and an ideal target for early intervention.

The current findings should be interpreted within the context of certain limitations. Perhaps the key major limitation is that this study was retrospective. The course of sleep disturbance and markers of illness severity were recorded using the NIMH Retrospective Life-Charting Methodology. Although ample recollection aids were provided, the accuracy of participant recollection could not be verified. Longitudinal studies are needed. However, although longitudinal studies are methodologically sound, conducting such studies is time-consuming, costly, and logistically difficult. Previous literature suggests that it may be possible to retrospectively collect details about severe life events over as much as a 5-year period (Brown & Harris, 1982) and that interview formats that include easy to recall anchor points are able to elicit life event information over periods ranging from 1-16 years (Roy-Byrne, Geraci, & Udhe, 1987). Moreover, although we utilized a retrospective design, many of our results are consistent with previous cross-sectional and prospective reports that did not rely on long periods of recall.

A second limitation is that participants presented with current sleep disturbance. Although we intentionally recruited a sleep-disturbed sample in order to establish the prevalence of sleep disturbance across the course of the disorder, the results may not be generalizable. Third, medications prescribed for bipolar disorder affect mood and sleep. Ninety-seven percent of individuals with bipolar disorder report taking at least one medication (Hirschfeld, Lewis, & Vornick, 2003). Therefore, a non-medicated sample would not be feasible to recruit and would
not be representative of the majority of individuals with bipolar disorder. Fourth, these data are correlational and the direction of the relation between sleep disturbance and markers of illness severity has not been established.

In sum, these findings demonstrate that sleep disturbance is a prevalent and variable feature across affective episodes and inter-episode periods of bipolar disorder. Additionally, a longer duration of sleep disturbance across the lifespan and across inter-episode periods is associated with a more severe course of the illness. In light of these results, it is recommended that current treatments for sleep disturbance should be adapted for use in bipolar disorder (see Harvey, 2011; Plante et al., 2008, for review).
Acknowledgments

I would like to thank the members of the Golden Bear Sleep and Mood Research Clinic. I would like to extend a special thank you to Adriane Soehner and Jason Lee, who helped with the administration of the life chart; Siena Duarte, Rebecca Roos, Anita Satish and Alana Aquilino, who helped with data entry; Kerrie Hein, who coordinated this study; and especially Allison Harvey, my very supportive mentor. I would also like to thank the National Science Foundation Graduate Research Fellowship for providing me with the means to conduct my research.
References


Table 1
Descriptive Data Regarding Illness Course

<table>
<thead>
<tr>
<th>Bipolar Disorder Variables</th>
<th>Average ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset (years)</td>
<td>21.1 ± 9.3</td>
</tr>
<tr>
<td>Number of inter-episode months</td>
<td>173.7 ± 120.4</td>
</tr>
<tr>
<td>Mania</td>
<td></td>
</tr>
<tr>
<td>Number of Episodes</td>
<td>4.7 ± 5.4</td>
</tr>
<tr>
<td>Duration of Episodes Summed Across Episodes (months)</td>
<td>3.3 ± 4.4</td>
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<tr>
<td>Duration of Mild Symptoms Across Lifespan (months)</td>
<td>31.0 ± 49.7</td>
</tr>
<tr>
<td>Duration of Moderate Symptoms Across Lifespan (months)</td>
<td>10.5 ± 14.6</td>
</tr>
<tr>
<td>Duration of Severe Symptoms Across Lifespan (months)</td>
<td>4.2 ± 5.9</td>
</tr>
<tr>
<td>Current Manic Symptoms (YMRS score)</td>
<td>3.6 ± 3.2</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Number of Episodes</td>
<td>6.4 ± 8.4</td>
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<tr>
<td>Duration of Episodes Summed Across Episodes (months)</td>
<td>4.7 ± 4.3</td>
</tr>
<tr>
<td>Duration of Mild Symptoms Across Lifespan (months)</td>
<td>36.5 ± 60.0</td>
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<tr>
<td>Duration of Moderate Symptoms Across Lifespan (months)</td>
<td>18.2 ± 24.2</td>
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<tr>
<td>Duration of Severe Symptoms Across Lifespan (months)</td>
<td>10.9 ± 15.8</td>
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<td>Current Depressive Symptoms (IDS-C score)</td>
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<tr>
<td>Mixed</td>
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<tr>
<td>Number of Episodes</td>
<td>0.9 ± 1.7</td>
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<tr>
<td>Duration of Episodes Summed Across Episodes (months)</td>
<td>2.0 ± 1.5</td>
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<td>Duration of Mild Symptoms Across Lifespan (months)</td>
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<td>Duration of Moderate Symptoms Across Lifespan (months)</td>
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<td>Duration of Severe Symptoms Across Lifespan (months)</td>
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<tr>
<td>Number of Hospitalizations</td>
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</tr>
<tr>
<td>Total Medications Prescribed Across the Lifespan</td>
<td>7.5 ± 4.7</td>
</tr>
</tbody>
</table>
### Table 2
Descriptive Data Regarding Sleep Disturbance Course

<table>
<thead>
<tr>
<th>Sleep Disturbance Variables</th>
<th>Average ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>18.5 ± 9.6</td>
</tr>
<tr>
<td>Duration of Insomnia Across Lifespan (months)</td>
<td>109.7 ± 124.7</td>
</tr>
<tr>
<td>Current Insomnia Symptoms (ISI score)</td>
<td>14.7 ± 5.3</td>
</tr>
<tr>
<td>Duration of Hypersomnia Across the Lifespan (months)</td>
<td>29.4 ± 57.3</td>
</tr>
<tr>
<td>Duration of Reduced Sleep Need Across Lifespan (months)</td>
<td>17.6 ± 24.3</td>
</tr>
<tr>
<td>Duration of Delayed Sleep Phase Across Lifespan (months)</td>
<td>13.8 ± 55.0</td>
</tr>
<tr>
<td>Duration of Irregular Sleep Patterns Across Lifespan (months)</td>
<td>18.7 ± 44.0</td>
</tr>
</tbody>
</table>
Figure 1
The Course of Sleep Disturbance Across Affective Episodes and Inter-episode Periods

<table>
<thead>
<tr>
<th>Affective Episode</th>
<th>Mania</th>
<th>Depression</th>
<th>Mixed</th>
<th>Inter-episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>11.5% ± 24.9</td>
<td>20.8% ± 34.4</td>
<td>15.1% ± 32.0</td>
<td>30.5% ± 31.8</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>13.8% ± 29.8</td>
<td>3.9% ± 15.8</td>
<td>10.9% ± 30.3</td>
<td>6.0% ± 19.0</td>
</tr>
<tr>
<td>Reduced Sleep Need</td>
<td>23.3% ± 35.6</td>
<td>4.3% ± 15.4</td>
<td>32.2% ± 45.7</td>
<td>6.2% ± 13.1</td>
</tr>
<tr>
<td>Delayed Sleep Phase</td>
<td>43.6% ± 42.5</td>
<td>43.6% ± 42.5</td>
<td>33.7% ± 44.5</td>
<td>5.2% ± 9.6</td>
</tr>
<tr>
<td>Irregular Sleep Patterns</td>
<td>51.1% ± 46.7</td>
<td>30.5% ± 31.8</td>
<td>51.1% ± 46.7</td>
<td>7.9% ± 18.1</td>
</tr>
<tr>
<td>No Sleep Disturbance</td>
<td>65.5% ± 40.5</td>
<td>43.6% ± 42.5</td>
<td>51.1% ± 46.7</td>
<td>55.9% ± 35.8</td>
</tr>
</tbody>
</table>
Table 3
Correlations Between Lifetime Sleep Disturbance and Markers of Illness Severity

<table>
<thead>
<tr>
<th></th>
<th>Duration of Manic Symptoms</th>
<th>Duration of Depressive Symptoms</th>
<th># of hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Across the Inter-episode Periods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.45**</td>
<td>0.43**</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>-0.01</td>
<td>0.61**</td>
<td>0.01</td>
</tr>
<tr>
<td>Reduced Sleep Need</td>
<td>0.20</td>
<td>0.22</td>
<td>-0.01</td>
</tr>
<tr>
<td>Delayed Sleep Phase</td>
<td>0.08</td>
<td>0.14</td>
<td>-0.02</td>
</tr>
<tr>
<td>Irregular Sleep Patterns</td>
<td>0.07</td>
<td>-0.02</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Note. Partial correlation coefficients, controlling for age are presented.*

** p < 0.003