See commentary by Gonzalez and Tohen

Circadian Rhythm Sleep-Wake Disorders Predict Shorter Time to Relapse of Mood Episodes in Euthymic Patients With Bipolar Disorder: A Prospective 48-Week Study

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ABSTRACT

Objective: Circadian rhythm dysfunction has been considered to be common in bipolar disorder (BD) and plays an important role in mood dysregulation in this disorder. However, no study has investigated whether circadian rhythm dysfunction would affect the clinical course of BD. The aim of this study was to test the hypothesis that circadian rhythm dysfunction could be a predictor of relapse in euthymic BD patients.

Methods: One hundred four euthymic outpatients with BD diagnosed according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), participated in this prospective follow-up study from August 2014 to April 2015. At baseline, data on demographic variables and clinical descriptive variables of bipolar disorder were ascertained via clinical interviews. The diagnoses of circadian rhythm sleep-wake disorders (CRSWDs) were made based on participants' sleep logs for 4 weeks and according to the International Classification of Sleep Disorders, Third Edition (ICSD-3). The BD symptoms of the subjects were evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS) and Young Mania Rating Scale (YMRS) scores every 4 weeks throughout the 48-week study period. Relapse of BD was defined as scores higher than the cutoff points (MADRS score ≥ 13 and YMRS score ≥ 7). The primary outcome was time to relapse of mood episodes.

Results: Thirty-four subjects met criteria for CRSWD at baseline, most frequently delayed sleep-wake phase disorder (n = 27). Of the total 104 subjects, 51 (49.0%) experienced relapse during the 48-week follow-up period. Multivariate Cox hazard regression analyses revealed that 2 or more previous mood episodes within the past year and comorbidity of CRSWD were significantly associated with the time to relapse of mood episodes ($P < .001$).

Conclusions: Comorbid CRSWD, mainly delayed sleep-wake phase disorder, could be a significant predictor of relapse in BD patients.

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Bipolar disorder (BD) is characterized by repeated relapse or recurrence of mood episodes in the clinical course of the disorder. Previous studies have reported that the rates of relapse or recurrence in BD were approximately one-third to one-half of patients with BD per year in spite of maintenance treatment.[1–3] It is important for clinicians to establish a strategy for preventing a new mood episode. Therefore, identifying predictors of relapse or recurrence in BD is necessary. Several studies have identified predictors of relapse or recurrence in BD patients. Prior number of mood episodes[2,4,5] and younger age at onset of BD[6] were suggested to predict recurrence or relapse of BD. Residual mood symptoms were also reported to be a predictor of the relapse or recurrence in BD in several studies.[2,7–9] However, it is still unclear which residual symptoms are associated with recurrence or relapse of BD. Further studies focusing on significant residual symptoms would be necessary to prevent a relapse or recurrence of BD in the clinical course of the disorder.

Circadian rhythm dysfunction has been considered as a common clinical feature of BD that plays an important role in mood regulation in BD.[10–13] Our previous study[14] revealed that one-third of euthymic BD patients had circadian rhythm sleep-wake disorders (CRSWDs),[14] indicating that circadian rhythm dysfunction could be a common residual symptom in euthymic BD patients. Dysfunction of biological rhythm was also reportedly associated with the severity of depressive symptoms and poor psychosocial function in BD.[15] Of note, some prospective studies suggested that evening circadian preference was a trait of BD[16] and that changes in sleep duration in euthymic BD were associated with relapse of mood episodes.[17,18] This finding implies that circadian rhythm dysfunction could be a candidate for a predictor of recurrence or relapse in BD.

However, no study has investigated whether circadian rhythm dysfunction would affect the clinical course of BD. Therefore, the aim of this study with a prospective 48-week design was to test the hypothesis that comorbid CRSWD could be a predictor of relapse in euthymic BD patients.

METHODS

Subjects

This study was approved by the ethics committee of Tokyo Medical University and conducted after obtaining written

Clinical Points

- Whether circadian rhythm dysfunction affects the clinical course of bipolar disorder has been unclear.
- Circadian rhythm dysfunction could be a target for the prevention of relapse in bipolar disorder.

informed consent from the subject patients. Consecutive patients with bipolar disorder were recruited from among patients who visited the outpatient clinic of the Department of Tokyo Medical University Hospital from August 2014 to April 2015. There were 130 patients from 20 to 75 years old who met the criteria for bipolar I or II disorder according to *DSM-5*. Participants were eligible if they were euthymic as defined by the Young Mania Rating Scale[19] (YMRS; score < 7 points) and Montgomery-Asberg Depression Rating Scale[20] (MADRS; score < 13 points) for at least 8 weeks prior to the investigation. Exclusion criteria included the following: (*a*) current affective episodes, (*b*) shift work, (*c*) ongoing alcohol or substance abuse, (*d*) suicidal risk, (*e*) hospitalization in the previous 8 weeks, or (*f*) presence of visual impairments, which are likely to cause CRSWD.[21,22] Fifteen patients refused to participate in the study, and 11 patients met the exclusion criteria. Ultimately, 104 euthymic BD patients (BD I: n = 40, BD II: n = 64) were included in the present study. This study was part of a larger study conducted between August 2014 and January 2016, another part of which has already been published[14]; most subjects in the present study were also subjects in that previously published part of the larger study.[14]

Assessments

We collected data on demographic and clinical descriptive variables at baseline of this study through clinical interviews conducted by attending psychiatrists. This information included clinical descriptive variables of BD, family history of BD, and numbers of previous mood episodes. We collected information on medications from the clinical records, including mood stabilizers (lithium, lamotrigine, valproate, and carbamazepine), antipsychotics (olanzapine, quetiapine, and risperidone), selective serotonin reuptake inhibitors (paroxetine, sertraline, and escitalopram), serotonin-norepinephrine reuptake inhibitors (duloxetine), sedative antidepressants (trazodone and mirtazapine), benzodiazepine hypnotics, and non-benzodiazepine hypnotics (zolpidem, zopiclone, and eszopiclone). Assessment of subjective sleep disturbance was conducted by using the Pittsburgh Sleep Quality Index (PSQI).[23,24] The PSQI included the following subitems: sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), frequency of sleep disturbance (C5), use of sleep medication (C6), and daytime dysfunction (C7). The scores of these subitems range from 0 (no difficulty) to 3 (severe difficulty) and are summed to produce a global measure of sleep disturbance, with a higher score denoting poorer sleep quality (range, 0–21). All patients were asked to mark the sleeping time in shadowing sleep logs every day for 4 weeks. We accepted the sleep log if less than 10% percent of data were missing. The diagnoses of CRSWD were made using clinical interviews and shadowing sleep logs assessed by a single board-certified sleep specialist physician (Y.T.) according to the International Classification of Sleep Disorders, third edition (ICSD-3).[25] The subjects who met the criteria for CRSWD were additionally divided into subcategories of CRSWD. We show the diagnostic criteria of ICSD-3 as used in this study in Table 1.

All participants were followed up prospectively. Sleep logs were continuously recorded throughout the study period. The subjects were evaluated by MADRS and YMRS every 4 weeks throughout the 48-week study period. Relapse was defined as the cutoff points of MADRS score ≥ 13 and YMRS score ≥ 7.[26] We divided the subjects into 2 groups, namely, subjects who met the criteria of relapse during the study period (relapse group) and subjects who did not meet the criteria of relapse during the study period (no-relapse group). We also divided the subjects into 2 additional groups, subjects who met the criteria of CRSWD at the baseline of the study (CRSWD group) and subjects who did not meet the criteria of CRSWD at the baseline of the study (no-CRSWD group).

Statistical Analysis

The Mann-Whitney *U* test and χ^2 test or Fisher exact test were used for the comparison of characteristics, clinical variables, MADRS and YMRS scores, PSQI scores, and medication for BD between the relapse and no-relapse groups and between the CRSWD and no-CRSWD groups.

Cox proportional hazard regression (survival) analyses were used to examine the association between individual predictors and time to relapse. A univariate Cox proportional hazard regression analysis was conducted to estimate the crude hazard ratios of independent variables for time to relapse. We selected independent variables based on the significant differences in time to relapse in univariate Cox proportional hazard regression analyses between the relapse group and no-relapse group (age at baseline, PSQI total scores > 5, 2 or more previous episodes within the past year, and comorbid CRSWD). After we controlled for potential confounders, multivariate Cox proportional hazard regression models were applied to calculate the adjusted hazard ratios. We also performed sensitivity analyses of multivariate Cox proportional hazard regression analyses with 4 models (model 1: comorbid CRSWD; model 2: 2 or more previous episodes within the past year and comorbid CRSWD; model 3: age at baseline, 2 or more previous episodes within the past year, and comorbid CRSWD; model 4: PSQI total score > 5, age at baseline, 2 or more previous episodes within the past year, and comorbid CRSWD). SPSS version 24 software for Windows (SPSS Inc, Chicago) was used for all statistical analyses. A *P* value of less than .05 was considered to indicate a statistically significant difference.

Table 1. Diagnostic Criteria of Subcategories of Circadian Rhythm Sleep-Wake Disorder (CRSWD)[a]

CRSWD Subgroup	Diagnostic Criteria
Delayed sleep-wake phase disorder	A. A significant delay in the phase of the major episode B. The symptoms are present for at least 3 months C. When patients choose a delayed sleep phase, they will exhibit improved sleep quality and duration for age and maintain a delayed sleep-wake phase D. Sleep log monitoring for at least 14 days demonstrates a delay in the timing of habitual sleep period E. The sleep disturbance is not better explained by other disorders
Non–24-hour sleep-wake rhythm disorder	A. A history of insomnia and/or excessive daytime sleepiness due to misalignment between the 24-hour light-dark cycle and the non-entrained endogenous circadian rhythm of sleep-wake propensity B. The symptoms are present for at least 3 months C. Sleep log monitoring for at least 14 days demonstrates a pattern of sleep and wake times that typically delay each day D. The sleep disturbance is not better explained by other disorders
Irregular sleep-wake rhythm disorder	A. A chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period B. The symptoms are present for at least 3 months C. Sleep log monitoring for at least 14 days demonstrates no major sleep episode and multiple irregular sleep bouts (at least 3) The sleep disturbance is not better explained by other disorders

[a]Based on The American Academy of Sleep Disorders.[25] All criteria must be met for the diagnosis of each disorder.

RESULTS

There were 34 subjects (32.7%) who met the criteria for CRSWD at the baseline (Table 1). According to the subcategories of CRSWD defined in this study, 27 patients met the criteria for delayed sleep-wake phase disorder, 6 patients met the criteria for non–24-hour sleep-wake disorder, and 1 patient met the criteria for irregular sleep-wake rhythm disorder. Of the total 104 subjects, 51 (49.0%) subjects experienced relapse during the 48-week follow-up period. In the relapse group, 32 patients (30.8%) experienced relapse of depressive episodes and 19 patients (18.3%) experienced manic or hypomanic relapse during the study period. Twelve subjects (11.5%) were lost to follow-up during the study period.

Among the comparisons of demographic and clinical descriptive variables for BD at the baseline in the study between the relapse group and no-relapse group, age at baseline and age at onset of BD in the relapse group were significantly lower than those in the no-relapse group (Table 2). MADRS scores and PSQI total scores, C1 scores, and C7 scores at baseline in the relapse group were significantly higher than those in the no-relapse group. The rates of having 2 or more previous mood episodes within the past year and comorbid CRSWD in the relapse group were higher than those in the no-relapse group (Table 2). No significant difference in other variables, including the use of psychotropic medication, was found between the 2 groups (Table 2).

Among the comparisons of demographic and clinical descriptive variables at baseline in the study between the CRSWD group and no-CRSWD group, age at baseline and age at onset of BD in the CRSWD group were significantly lower than those in the no-CRSWD group (Table 3). PSQI total scores, C1 scores, and C7 scores at baseline in the CRSWD group was significantly higher than that in the no-CRSWD group. The rate of having 2 or more previous mood episodes within the past year in the CRSWD group was higher than that in the no-CRSWD group. No significant difference in other variables, including the use of psychotropic medication, was found between the 2 groups (Table 3).

Survival analyses were performed using Cox proportional hazard regression analyses. Univariate Cox proportional hazard regression analyses revealed that age at baseline, PSQI total scores > 5, 2 or more previous episodes within the past year, and comorbid CRSWD were significantly associated with time to relapse of mood episodes (Table 4). Multivariate Cox proportional hazard regression analyses revealed that 2 or more previous episodes within the past year and comorbid CRSWD were significantly associated with time to relapse of mood episodes (Table 4).

Figure 1 shows the cumulative multivariate-adjusted hazard (age at the baseline, PSQI total scores > 5, and 2 or more previous episodes within the past year) for time to relapse of mood episode between BD patients with and without circadian rhythm sleep-wake disorder (Figure 1). The results of sensitivity analysis showed that there were similar results in all models (Table 5).

DISCUSSION

This prospective study may be the first focusing on circadian rhythm dysfunction as a candidate for predictor of relapse in euthymic BD patients. As presented, comorbid CRSWD, as well as 2 or more previous mood episodes within the past year, was significantly associated with the time to relapse of mood episode in euthymic BD patients. Because

Table 2. Comparison of Characteristics and Clinical Variables of BD Patients at Baseline Between the Relapse and No-Relapse Groups[a]

Variable	Relapse Group (n = 51)	No-Relapse Group (n = 53)	*P* Value
Age at baseline, mean ± SD, y	43.9 ± 12.5	49.5 ± 15.5	.042
Sex (male/female), n/n (% male)	20/31 (39.2)	23/30 (43.4)	.695
Age at BD onset, mean ± SD, y	26.3 ± 12.0	32.8 ± 11.7	.007
Living alone (yes/no), n/n (% yes)	13/38 (25.5)	9/44 (17.0)	.341
College graduate (yes/no), n/n (% yes)	24/27 (47.1)	26/27 (49.1)	.700
Employed (yes/no), n/n (% yes)	13/38 (25.5)	18/35 (15.1)	.402
Family history of BD (yes/no), n/n (% yes)	12/39 (23.5)	8/45 (34.0)	.325
Two or more previous episodes within the past year (yes/no), n/n (% yes)	24/27 (47.1)	7/46 (13.2)	< .001
Circadian rhythm sleep-wake disorders (yes/no)	27/24 (52.9)	7/46 (13.2)	< .001
Type of BD (I/II), n/n (% BD I)	17/34 (33.3)	23/30 (43.4)	.319
MADRS score, mean ± SD	4.9 ± 4.1	3.3 ± 3.6	.028
YMRS score, mean ± SD	2.0 ± 2.0	1.8 ± 2.1	.676
PSQI total score, < 5/≥5, n/n	41/10	33/20	.052
PSQI total score, mean ± SD	8.7 ± 3.6	7.0 ± 3.5	.018
C1: sleep quality	1.3 ± 1.1	0.9 ± 1.1	.040
C2: sleep latency	1.3 ± 1.1	1.1 ± 1.1	.211
C3: sleep duration	1.3 ± 1.1	1.2 ± 1.1	.434
C4: habitual sleep efficiency	0.8 ± 0.9	0.8 ± 1.1	.892
C5: frequency of sleep disturbance	0.8 ± 0.5	0.7 ± 0.4	.760
C6: use of sleep medication	2.2 ± 1.3	2.2 ± 1.3	.804
C7: daytime dysfunction	0.9 ± 1.2	0.3 ± 0.8	.003
Medications			
Lithium (yes/no), n/n (% yes)	17/34 (33.3)	14/39 (26.4)	.522
Lamotrigine (yes/no), n/n (% yes)	25/26 (49.0)	19/34 (35.8)	.234
Valproate (yes/no), n/n (% yes)	5/46 (9.8)	12/41 (22.6)	.111
Carbamazepine (yes/no), n/n (% yes)	4/47 (7.8)	6/47 (11.3)	.742
Olanzapine (yes/no), n/n (% yes)	3/48 (5.9)	6/47 (11.3)	.489
Quetiapine (yes/no), n/n (% yes)	4/47 (7.8)	6/47 (11.3)	.742
Risperidone (yes/no), n/n (% yes)	2/49 (3.9)	2/51 (3.8)	1.000
SSRI/SNRI (yes/no), n/n (% yes)	8/43 (15.7)	7/46 (13.2)	.785
Sedative antidepressants (yes/no), n/n (% yes)	3/48 (58.8)	4/49 (7.5)	1.000
Benzodiazepine hypnotics (yes/no), n/n (% yes)	28/23 (54.9)	30/23 (42.9)	1.000
Non-benzodiazepine hypnotics (yes/no), n/n (% yes)	21/30 (41.2)	20/33 (37.7)	.841
Lithium + benzodiazepine or non-benzodiazepine hypnotics (yes/no), n/n (% yes)	17/34 (33.3)	12/41 (22.6)	.276
Lamotrigine + benzodiazepine or non-benzodiazepine hypnotics (yes/no), n/n (% yes)	21/30 (41.2)	16/37 (30.2)	.307

[a]The Mann-Whitney *U* test was used for the comparison of continuous variables between the 2 groups, and the χ^2 test or Fisher exact test was used for the comparison of categorical variables between the 2 groups.

Abbreviations: BD = bipolar disorder, CRSWD = circadian rhythm sleep-wake disorder, MADRS = Montgomery-Asberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, YMRS = Young Mania Rating Scale.

our CRSWD subjects mostly had delayed sleep-wake disorder and there were no subjects with other subcategories of CRSWD (advanced sleep-wake phase disorder and shift work disorder), it is difficult to generalize our results to all CRSWD patients. Although we did not evaluate the differences in the effects on time to relapse of mood episode between subcategories of CRSWD because of the small numbers of subjects, there could be some differences between the subcategories of CRSWD. All of the subjects with non–24-hour sleep-wake rhythm disorder (n = 6) and irregular sleep-wake rhythm disorder (n = 1) experienced relapse of mood episodes during the study period, implying that these subcategories might be more likely to relapse in the clinical course of BD.

Previous studies have implied that circadian rhythm dysfunction could affect mood episodes of BD patients in the clinical course of the disorder. Social rhythm dysregulation was reportedly associated with the early onset of mood episode in bipolar spectrum individuals.[27] A 4-year longitudinal study[16] reported that frequent sleep changes were observed in the BD group (n = 257) and were dependent on the changes in mood state, compared to the healthy controls (n = 55) and the non-BD psychiatric patients with disorders that included major depressive disorder and anxiety disorder patients (n = 105). Of note, Perlman et al[18] reported that changes in sleep duration at the baseline observational period predicted depressive but not manic symptoms in a 6-month prospective study with 54 BD subjects. These studies were in line with the results of our study and suggested that circadian rhythm dysfunction could be a predictor of relapse in BD patients.

Although the causal relationships between changes in sleep-wake phase and relapse of mood episodes in BD are still unclear, there could be pathophysiologic relationships between the 2 factors. A previous study[28] indicated that changes in sleep pattern occurred prior to those in mood pattern in BD patients, suggesting that sleep dysregulation might affect manic and/or depressive symptoms and onset of mood episodes in BD patients. Sleep quality of bipolar disorder was not only affected by circadian rhythm, but also affected by personality traits and stressful life events.[29] Although our results showed that there was no significant association between relapse of mood episodes and gender, previous studies have suggested that sleep[30] and gender[31] are both important factors in influencing the clinical course of BD. Interestingly, Saunders et al[32] revealed in a longitudinal study that poor sleep quality predicted worse mood outcome only in female bipolar disorder patients, suggesting that sleep and circadian rhythm may be altered by ovarian hormones.[33] Of note, a recent study[34] revealed that biochemical circadian rhythm assessed by salivary cortisol, circadian gene expression extracted from buccal epithelial cells, and physical and sleep-wake activity assessed by actigraphy were associated with circadian phase advance in acute manic episodes of BD patients and circadian phase delay in acute mixed and depressive episodes of BD patients, respectively. Considering these findings, circadian rhythm dysfunction could be a pathophysiologic mechanism in BD and could affect the clinical course of BD, including relapse of mood episodes.

Consistent with the results of our study, a larger number of previous mood episodes has been reported as a predictor of relapse

Table 3. Comparison of Characteristics and Clinical Variables of BD Patients at Baseline Between the Groups With and Without CRSWD[a]

Variable	BD Patients With CRSWD (n = 34)	BD Patients Without CRSWD n = 70	*P* Value
Age at baseline, mean ± SD, y	40.1 ± 13.1	49.8 ± 14.0	< .001
Sex (male/female), n/n (% male)	14/20 (41.2)	29/41 (41.4)	1.000
Age at BD onset, mean ± SD, y	23.2 ± 11.4	32.8 ± 13.1	< .001
Living alone (yes/no), n/n (% yes)	11/23 (32.4)	13/57 (18.6)	.140
College graduate (yes/no), n/n (% yes)	17/17 (50.0)	34/36 (48.6)	1.000
Employed (yes/no), n/n (% yes)	11/23 (32.4)	20/50 (28.6)	.820
Family history of BD (yes/no), n/n (% yes)	10/24 (29.4)	10/60 (14.3)	.109
Two or more previous episodes within the past year (yes/no), n/n (% yes)	21/13 (61.8)	13/57 (18.6)	< .001
Relapse of mood episode (yes/no), n/n (% yes)	27/7 (79.4)	24/46 (34.3)	< .001
Time to relapse, mean ± SD, wk	12.9 ± 6.2	18.2 ± 10.2	.034
Type of BD (I/II), n/n (% BD I)	12/22 (35.3)	28/42 (40.0)	.674
MADRS score, mean ± SD	5.0 ± 4.3	3.6 ± 3.8	.103
YMRS score, mean ± SD	1.9 ± 1.9	1.9 ± 2.1	.899
PSQI total score, < 5/≥5, n/n	30/4	44/26	.010
PSQI total score, mean ± SD	9.1 ± 3.3	7.2 ± 3.6	.007
C1: sleep quality	1.5 ± 1.1	0.9 ± 1.0	.006
C2: sleep latency	1.4 ± 1.1	1.1 ± 1.1	.107
C3: sleep duration	1.4 ± 1.1	1.2 ± 1.0	.311
C4: habitual sleep efficiency	0.9 ± 1.0	0.8 ± 1.0	.698
C5: frequency of sleep disturbance	0.8 ± 0.5	0.7 ± 0.4	.300
C6: use of sleep medication	2.0 ± 1.4	2.3 ± 1.3	.347
C7: daytime dysfunction	1.2 ± 1.3	0.4 ± 0.8	.001
Medications			
Lithium (yes/no), n/n (% yes)	13/21 (38.2)	18/52 (25.7)	.253
Lamotrigine (yes/no), n/n (% yes)	16/18 (47.1)	28/42 (40.0)	.531
Valproate (yes/no), n/n (% yes)	4/30 (11.8)	13/57 (18.6)	.573
Carbamazepine (yes/no), n/n (% yes)	4/30 (11.8)	6/64 (8.6)	.725
Olanzapine (yes/no), n/n (% yes)	1/33 (2.9)	8/62 (11.4)	.265
Quetiapine (yes/no), n/n (% yes)	2/32 (5.9)	8/62 (11.4)	.492
Risperidone (yes/no), n/n (% yes)	1/33 (2.9)	3/67 (4.3)	1.000
SSRI/SNRI (yes/no), n/n (% yes)	5/29 (14.7)	10/60 (14.3)	1.000
Sedative antidepressants (yes/no), n/n (% yes)	1/33 (2.9)	6/64 (8.6)	.422
Benzodiazepine hypnotics (yes/no), n/n (% yes)	15/19 (44.1)	43/27 (61.4)	.140
Non-benzodiazepine hypnotics (yes/no), n/n (% yes)	14/20 (41.2)	27/43 (38.6)	.833
Lithium + benzodiazepine or non-benzodiazepine hypnotics (yes/no), n/n (% yes)	10/24 (29.4)	19/51 (27.1)	.819
Lamotrigine + benzodiazepine or non-benzodiazepine hypnotics (yes/no), n/n (% yes)	13/21 (38.2)	24/46 (34.3)	.827

[a]The Mann-Whitney *U* test was used for the comparison of continuous variables between the 2 groups, and the χ^2 test or Fisher exact test was used for the comparison of categorical variables between the 2 groups.

Abbreviations: BD = bipolar disorder, CRSWD = circadian rhythm sleep-wake disorder, MADRS = Montgomery-Asberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, YMRS = Young Mania Rating Scale.

and recurrence of BD in several studies.[2,4,5] On the other hand, residual mood symptoms, assessed by the MADRS and YMRS in our study, did not show the association to the time to relapse of mood episodes; however, residual mood symptoms were suggested as a predictor of mood episodes in the Systematic Treatment Enhancement Program for Bipolar Disorder study.[2] One possible explanation for this inconsistency is that circadian rhythm dysfunction could be a significant residual symptom in euthymic BD patients and might affect relapse of mood episodes in BD more than any other residual symptoms in BD patients.

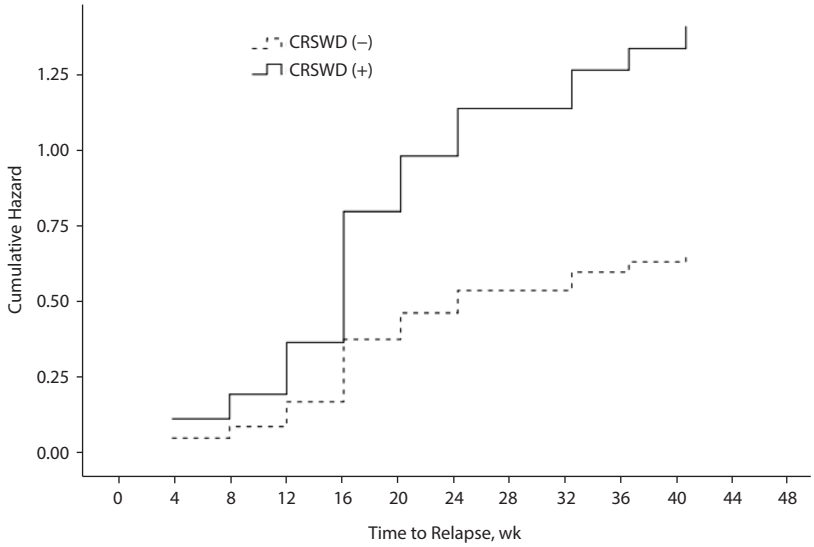
This study has several limitations. First, because this study was conducted with a relatively small sample size in a single university hospital, it may be difficult to generalize these results to all BD patients. Second, because this study was conducted in a naturalistic design, treatment was not controlled and did not necessarily follow specific contemporary practice guidelines. Third, although there was no significant difference in psychotropic medication among the BD subjects, some medications might affect circadian rhythm and clinical course of the BD subjects. Fourth, we did not use structured interviews for sleep disorders because there is no official structured interview. The lack of structured interviews for sleep disorders and psychiatric disorders in this study might have underdiagnosed comorbid sleep and psychiatric disorders as confounding factors. In addition, we did not evaluate physical comorbidities that might be confounding factors. Fifth, although we used the definitions of remission and relapse of mood episode with cutoff points on the MADRS (13 points) and YMRS (7 points) according to several previous studies,[26,35] there were a lot of different definitions in previous studies, including

Table 4. Cox Proportional Hazard Ratio Estimates for a Multivariate Model for Predictors of Time to Relapse

Variable	Crude Hazard Ratio (95% CI)	*P* Value	Adjusted Hazard Ratio (95% CI)	*P* Value
Age at baseline, y	0.97 (0.95–0.99)	.009	1.00 (0.80–1.02)	.879
Sex (female)	1.18 (0.67–2.06)	.574		
Age at BD onset, y	0.99 (0.97–1.01)	.232		
Living alone (yes)	1.49 (0.81–2.73)	.197		
College graduate (yes)	1.08 (0.62–1.88)	.781		
Employed (yes)	0.95 (0.53–1.72)	.088		
Family history of BD (yes)	2.79 (0.77–2.79)	.251		
Two or more previous episodes within the past year (yes)	3.35 (1.92–5.84)	< .001	2.59 (1.26–5.34)	.010
CRSWD (yes)	2.94 (1.69–5.03)	< .001	1.89 (1.03–3.50)	.039
Type of BD (bipolar II)	1.38 (0.77–2.47)	.280		
MADRS score	1.06 (0.99–1.13)	.100		
YMRS score	1.03 (0.90–1.17)	.682		
PSQI total score > 5	2.06 (1.00–4.24)	.049	1.68 (0.80–3.55)	.173

Abbreviations: BD = bipolar disorder, CI = confidence interval, CRSWD = circadian rhythm sleep-wake disorder, MADRS = Montgomery-Asberg Depression Rating Scale, PSQI = Pittsburgh Sleep Quality Index, YMRS = Young Mania Rating Scale.

Figure 1. Cumulative Hazard for Time to Relapse Between Bipolar Disorder Patients With and Without Circadian Rhythm Sleep-Wake Disorder (CRSWD)[a]



[a]CRSWD was significantly associated with time to relapse of mood disorder in multivariate Cox proportional hazard analysis (adjusted hazard ratio = 1.89; 95% CI, 1.03–3.50; *P* = .039).

Table 5. Sensitivity Analysis for Cox Proportional Hazard Analysis

Variable	Model 1, Crude Hazard Ratio (95% CI)	Model 2, Adjusted Hazard Ratio (95% CI)	Model 3, Adjusted Hazard Ratio (95% CI)	Model 4, Adjusted Hazard Ratio (95% CI)
Circadian rhythm sleep-wake disorders (yes)	2.94** (1.69–5.03)	2.14* (1.18–3.88)	2.14* (1.18–3.88)	1.89* (1.03–3.50)
Two or more previous episodes within the past year (yes)		2.58* (1.42–4.69)	2.54* (1.22–5.27)	2.59* (1.26–5.34)
Age at baseline, y			1.00 (0.98–1.02)	1.00 (0.80–1.02)
PSQI total score > 5				1.68 (0.80–3.55)

*$P < .05$.
**$P < .01$.
Abbreviation: PSQI = Pittsburgh Sleep Quality Index.

recommendations of the International Society for Bipolar Disorders Task Force,[36] because of insufficient consensus for the definitions of remission and relapse in BD. Sixth, we did not use objective measures of circadian rhythm, such as actigraphy, measurement of core body temperature, endogenous melatonin secretion, and expression of clock genes. Further investigation will be needed to confirm the relationship between CRSWD and clinical course of BD.

In conclusion, the results of this study revealed that circadian rhythm dysfunction, mainly delayed sleep-wake phase disorder, could be a significant predictor of relapse in BD patients. It is important for clinicians to focus on sleep-wake dysregulation in a clinical setting of BD treatment. Chronobiological treatment focusing on circadian rhythm dysfunction should be developed to prevent relapse and recurrence of BD.

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REFERENCES

1. Keller MB, Lavori PW, Coryell W, et al. Bipolar I: a five-year prospective follow-up. *J Nerv Ment Dis*. 1993;181(4):238–245.
2. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Am J Psychiatry*. 2006;163(2):217–224.
3. Gitlin MJ, Swendsen J, Heller TL, et al. Relapse and impairment in bipolar disorder. *Am J Psychiatry*. 1995;152(11):1635–1640.
4. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry*. 1990;47(12):1106–1111.
5. de Dios C, Gonzalez-Pinto A, Montes JM, et al. Predictors of recurrence in bipolar disorders in Spain (PREBIS study data). *J Affect Disord*. 2012;141(2–3):406–414.
6. Yatham LN, Kauer-Sant'Anna M, Bond DJ, et al. Course and outcome after the first manic episode in patients with bipolar disorder: prospective 12-month data from the Systematic Treatment Optimization Program For Early Mania project. *Can J Psychiatry*. 2009;54(2):105–112.
7. Tohen M, Bowden CL, Calabrese JR, et al. Influence of sub-syndromal symptoms after remission from manic or mixed episodes. *Br J Psychiatry*. 2006;189(6):515–519.
8. Kleindienst N, Greil W. Inter-episodic morbidity and drop-out under carbamazepine and lithium in the maintenance treatment of bipolar disorder. *Psychol Med*. 2002;32(3):493–501.
9. De Dios C, Ezquiaga E, Agud JL, et al. Subthreshold symptoms and time to relapse/recurrence in a community cohort of bipolar disorder outpatients. *J Affect Disord*. 2012;143(1–3):160–165.
10. Melo MC, Abreu RL, Linhares Neto VB, et al. Chronotype and circadian rhythm in bipolar disorder: a systematic review. *Sleep Med Rev*. 2017;34:46–58.
11. Ng TH, Chung KF, Ho FY, et al. Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: a systematic review and meta-analysis. *Sleep Med Rev*. 2015;20:46–58.
12. Murray G, Harvey A. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord*. 2010;12(5):459–472.
13. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatry*. 2008;165(7):820–829.
14. Takaesu Y, Inoue Y, Murakoshi A, et al. Prevalence of circadian rhythm sleep-wake disorders and associated factors in euthymic patients with bipolar disorder. *PLoS One*. 2016;11(7):e0159578.
15. Pinho M, Sehmbi M, Cudney LE, et al. The association between biological rhythms, depression, and functioning in bipolar disorder: a large multi-center study. *Acta Psychiatr Scand*. 2016;133(2):102–108.
16. Seleem MA, Merranko JA, Goldstein TR, et al. The longitudinal course of sleep timing and circadian preferences in adults with bipolar disorder. *Bipolar Disord*. 2015;17(4):392–402.
17. Leibenluft E, Albert PS, Rosenthal NE, et al. Relationship between sleep and mood in patients with rapid-cycling bipolar disorder. *Psychiatry Res*. 1996;63(2–3):161–168.
18. Perlman CA, Johnson SL, Mellman TA. The prospective impact of sleep duration on depression and mania. *Bipolar Disord*. 2006;8(3):271–274.
19. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
20. Asberg M, Montgomery SA, Perris C, et al. A comprehensive psychopathological rating scale. *Acta Psychiatr Scand suppl*. 1978;57(271):5–27.
21. Sack RL, Lewy AJ, Blood ML, et al. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. *J Clin Endocrinol Metab*. 1992;75(1):127–134.
22. Lockley SW, Skene DJ, Arendt J, et al. Relationship between melatonin rhythms and visual loss in the blind. *J Clin Endocrinol Metab*. 1997;82(11):3763–3770.
23. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
24. Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res*. 2000;97(2–3):165–172.
25. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
26. Steinan MK, Krane-Gartiser K, Langsrud K, et al. Cognitive behavioral therapy for insomnia in euthymic bipolar disorder: study protocol for a randomized controlled trial. *Trials*. 2014;15(1):24.
27. Shen GH, Alloy LB, Abramson LY, et al. Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. *Bipolar Disord*. 2008;10(4):520–529.
28. Bauer M, Grof P, Rasgon N, et al. Temporal relation between sleep and mood in patients with bipolar disorder. *Bipolar Disord*. 2006;8(2):160–167.
29. Saunders EF, Novick DM, Fernandez-Mendoza J, et al. Sleep quality during euthymia in bipolar disorder: the role of clinical features, personality traits, and stressful life events. *Int J Bipolar Disord*. 2013;1(1):16.
30. Gruber J, Miklowitz DJ, Harvey AG, et al. Sleep matters: sleep functioning and course of illness in bipolar disorder. *J Affect Disord*. 2011;134(1–3):416–420.
31. Saunders EF, Nazir R, Kamali M, et al. Gender differences, clinical correlates, and longitudinal outcome of bipolar disorder with comorbid migraine. *J Clin Psychiatry*. 2014;75(5):512–519.
32. Saunders EF, Fernandez-Mendoza J, Kamali M, et al. The effect of poor sleep quality on mood outcome differs between men and women: a longitudinal study of bipolar disorder. *J Affect Disord*. 2015;180:90–96.
33. Bailey M, Silver R. Sex differences in circadian timing systems: implications for disease. *Front Neuroendocrinol*. 2014;35(1):111–139.
34. Moon JH, Cho CH, Son GH, et al. Advanced circadian phase in mania and delayed circadian phase in mixed mania and depression returned to normal after treatment of bipolar disorder. *EBioMedicine*. 2016;11:285–295.
35. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162(7):1351–1360.
36. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disord*. 2009;11(5):453–473.