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RESEARCH ARTICLE

Association of Lithium Treatment with Biological Rhythms in Euthymic Patients with Bipolar Disorder

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ABSTRACT

Objective: Circadian rhythm disturbances are increasingly recognized as a core feature of bipolar disorder. Although lithium is a gold standard of maintenance treatment, clinical evidence regarding its association with sleep and biological rhythms remains limited. This study compared sleep quality, chronotype, and biological rhythms between euthymic patients with bipolar disorder receiving lithium and those under other treatments.

Materials and Methods: In this cross-sectional study, 83 euthymic outpatients with bipolar disorder (32 receiving lithium and 51 not receiving lithium) completed the Pittsburgh Sleep Quality Index (PSQI), Morningness–Eveningness Questionnaire (MEQ), and Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN). Multiple linear regression analyses examined whether lithium treatment was independently associated with biological rhythm measures after adjustment for age, sex, and subjective sleep quality. Associations between serum lithium concentrations and sleep/circadian measures were examined within the lithium group. Sensitivity analyses were performed using a therapeutic serum lithium concentration threshold (≥0.6 mmol/L).

Results: After adjustment for age, sex, and subjective sleep quality, lithium treatment was independently associated with lower BRIAN total scores (p=0.048) but not with MEQ scores. Serum lithium concentrations were not linearly associated with PSQI, MEQ, or BRIAN scores. In sensitivity analyses, therapeutic lithium exposure was associated with lower BRIAN total scores (p=0.011) and lower sleep, social, and eating domain scores (p=0.039, p=0.029, and p=0.036, respectively).

Conclusion: Lithium treatment was independently associated with lower biological rhythm disturbance, but not with subjective sleep quality or chronotype, in euthymic patients with bipolar disorder. These findings are consistent with the hypothesis that lithium treatment may be associated with greater biological rhythm stability beyond differences in subjective sleep quality; however, longitudinal studies are needed to clarify the temporal nature of this relationship.

Keywords: Bipolar disorder, circadian rhythms, lithium, sleep

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INTRODUCTION

Bipolar disorder (BD) is a chronic, recurrent psychiatric disorder affecting approximately 1% of the population worldwide and is among the leading causes of disability in young adults.[1] It is characterized by recurrent episodes of mania, hypomania, depression, or mixed states that substantially impair psychosocial functioning and quality of life. Although acute affective episodes define the clinical course of the disorder, many patients continue to experience residual symptoms, cognitive difficulties, and functional impairment during euthymic periods, highlighting that bipolar disorder is not merely an episodic illness but a chronic condition with a persistent clinical burden.[2–4]

Sleep disturbance is one of the core clinical features of bipolar disorder and represents a hallmark symptom across all phases of the illness. Reduced need for sleep is a diagnostic feature of mania, whereas insomnia and hypersomnia are common manifestations of bipolar depression. Moreover, sleep disturbance has been demonstrated to be prevalent during euthymia, even in patients on maintenance medication, and has been associated with poorer functioning, lower quality of life, and a greater risk of mood episode recurrence.[5,6] These findings suggest that sleep abnormalities may represent a trait-like feature of bipolar disorder rather than simply a state-dependent manifestation of acute mood episodes.

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Sleep is regulated by the interaction of two complementary physiological processes: the homeostatic sleep drive and the circadian timing system. The homeostatic process is the accumulation of sleep pressure during wakefulness, and the circadian system synchronizes sleep–wake timing to the external light–dark cycle via the central biological clock in the suprachiasmatic nucleus.[7] The circadian system regulates the sleep–wake cycle and coordinates numerous physiological functions, such as endocrine secretion, metabolism, immune function, autonomic activity, cognitive performance, and emotional regulation.[8,9] Therefore, circadian disruptions have widespread effects extending beyond sleep itself.

Emerging evidence indicates that disturbances in circadian rhythm are a core feature of bipolar disorder. Bipolar disorder patients display abnormalities in sleep–wake timing, patterns of daily activity, melatonin secretion, and other circadian markers, many of which persist in euthymia.[10–13] In addition, genetic studies have consistently implicated several circadian clock genes, including CLOCK, ARNTL (BMAL1), PER, and CRY genes, in susceptibility to bipolar disorder, further supporting the involvement of circadian dysregulation in its pathophysiology.[14]

Lithium remains the gold-standard maintenance treatment for bipolar disorder and is one of the few pharmacological agents shown to be effective in preventing both manic and depressive recurrences while reducing suicide risk.[15] Despite decades of clinical use, its mechanisms of action are not yet fully understood and appear to differ from those of other mood stabilizers and psychotropic medications. In experimental studies, lithium has been shown to directly interact with the molecular circadian clock through inhibition of glycogen synthase kinase-3β (GSK-3β), causing changes in clock gene expression and stabilization of circadian rhythmicity.[16] These findings have led to the hypothesis that modulation of the circadian system may be responsible for the therapeutic effects of lithium. However, evidence from clinical studies investigating whether lithium treatment is associated with improved biological rhythm regulation, especially independently of its effects on sleep, remains limited. Distinguishing the effects of lithium on biological rhythms from its effects on sleep may provide further insight into the mechanisms underlying its mood-stabilizing properties.

Therefore, the present study aimed to compare sleep quality, chronotype, and biological rhythm disturbances between euthymic patients with bipolar disorder receiving lithium and those not receiving lithium. In addition, we examined whether lithium treatment was independently associated with biological rhythm disturbance after controlling for subjective sleep quality. Finally, among patients receiving lithium, we explored the relationship between serum lithium concentrations and sleep and circadian rhythm measures and performed a sensitivity analysis based on therapeutic serum lithium concentrations.

MATERIALS and METHODS

Study Design and Participants

This cross-sectional study included euthymic patients with bipolar disorder who were consecutively recruited from the outpatient psychiatry clinic of Istanbul Medeniyet University between October 2025 and May 2026. The study protocol was approved by the Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Research Ethics Committee (Approval No: 2025/0208; Date: 09.10.2025). All participants provided written informed consent before enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent revisions. Eligible participants were adults aged 18–65 years with a diagnosis of bipolar disorder who were receiving outpatient psychiatric treatment and were euthymic at the time of assessment. Additional inclusion criteria were the ability to read and write and the provision of written informed consent. Participants were excluded if they had: 1) a diagnosis of a schizophrenia spectrum disorder, 2) alcohol or substance use disorder, 3) intellectual disability, 4) a neurological disorder affecting cognitive functioning (e.g., dementia), 5) a shift-work schedule, 6) transmeridian travel within 2 weeks, or 7) unstable medical illnesses that could substantially affect sleep or circadian rhythm.

Diagnoses were confirmed by experienced psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Mood symptom severity was assessed using the Young Mania Rating Scale (YMRS) and the 17-item Hamilton Depression Rating Scale (HAM-D-17). Euthymia was defined as scores ≤7 on both the 17-item Hamilton Depression Rating Scale (HAM-D-17) and the Young Mania Rating Scale (YMRS). One participant in the lithium-treated group was excluded because of subsyndromal depressive symptoms. Consequently, all participants met the study definition of euthymia at the time of assessment.

Participants were classified into two groups according to whether they were receiving lithium treatment as part of their routine maintenance pharmacotherapy. Patients receiving lithium, either as monotherapy or in combination with other psychotropic medications, were assigned to the lithium group.

Patients not receiving lithium, irrespective of their other psychotropic medications, comprised the non-lithium group.

A power calculation based on the primary multiple regression model indicated that a minimum sample size of 81 participants would be required to detect a small-to-moderate effect (Cohen's f^2=0.10) with 80% power at a two-sided α level of 0.05, assuming one tested predictor and four predictors in the full model. The calculation was based on lithium treatment as the predictor of interest, with age, sex, and subjective sleep quality included as covariates.

Clinical Assessment

Sociodemographic and clinical information, including age, sex, educational level, marital status, smoking status, body mass index (BMI), medical comorbidities, and current psychotropic medications, was recorded using a structured clinical form.

Residual depressive and manic symptom severity were assessed using the 17-item Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale (YMRS), respectively.[17,18]

Serum lithium concentrations were obtained from routine therapeutic drug monitoring performed during clinical follow-up. For patients receiving lithium treatment, the serum lithium concentration closest to the study assessment was recorded. For participants without a serum lithium measurement within the preceding three months, a routine therapeutic drug monitoring assessment was performed as part of standard clinical care. To explore whether therapeutic lithium exposure was associated with sleep and biological rhythm measures, an additional sensitivity analysis was performed using a serum lithium concentration threshold of 0.6 mmol/L, which was considered the lower limit of the therapeutic range.

Assessment of Sleep and Biological Rhythms

Pittsburgh Sleep Quality Index (PSQI)

Subjective sleep quality during the previous month was assessed using the Pittsburgh Sleep Quality Index (PSQI). The 19-item PSQI consists of seven component scores evaluating subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.[19] Total scores range from 0 to 21, and higher scores indicate poorer subjective sleep quality. The Turkish version of the PSQI has demonstrated good validity and reliability, with a Cronbach's α value of 0.80.[20]

Morningness–Eveningness Questionnaire (MEQ)

Chronotype was assessed using the Morningness–Eveningness Questionnaire (MEQ). Higher scores indicate a greater preference for morningness, whereas lower scores indicate greater eveningness.[21] In general, scores of 59–86 indicate morning type, 42–58 intermediate type, and 16–41 evening type. The Turkish validity and reliability study was conducted by Agargun et al.,[22] with a Cronbach's α value of 0.81. Because of the moderate sample size of the study, MEQ scores were analyzed as a continuous variable rather than categorizing participants into chronotype groups.

Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)

Biological rhythm disturbances were evaluated using the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN). The BRIAN assesses disturbances across four domains, including sleep, activity, social rhythms, and eating patterns. Three additional items assess individual chronotype preference.[23] The total scale score is calculated by summing the subscale scores. Higher scores indicate greater disruption of biological rhythms. The Turkish validity and reliability study was conducted by Aydemir et al.,[24] with a Cronbach's α value of 0.90.

Statistical Analysis

Statistical analysis were performed using IBM SPSS Statistics version 30.0.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean±standard deviation (SD) for continuous variables and frequencies (percentages) for categorical variables. Normality was assessed using visual inspection of histograms and Q-Q plots together with the Shapiro-Wilk test. Baseline sociodemographic and clinical characteristics were compared between the lithium and non-lithium groups using independent-samples t tests or Welch's t tests for continuous variables, as appropriate, and χ^2 tests for categorical variables. Cohen's d was calculated to estimate effect sizes for continuous variables. Sleep quality (PSQI), chronotype (MEQ), and biological rhythm (BRIAN) scores were initially compared between groups using unadjusted group comparisons. Subsequently, separate multiple linear regression analyses were conducted to determine whether lithium treatment was independently associated with MEQ and BRIAN scores after adjustment for prespecified covariates such as age, sex, and PSQI.

Subjective sleep quality was included as a covariate because the primary aim was to determine whether lithium treatment was associated with biological rhythms beyond differences in subjective sleep quality. Multicollinearity among predictors was assessed using tolerance and variance inflation factor (VIF) values. Among patients receiving lithium treatment,

Table 1. Sociodemographic and clinical characteristics of participants

	Lithium (n=32)	Non-lithium (n=51)	p
Sociodemographic characteristics			
Age, years	36.75±13.26	42.50±11.01	0.036
Female sex, n (%)	24 (75.0)	35 (68.6)	0.533
Education level, n (%)			
Primary school	8 (25.0)	12 (23.5)	
High school	10 (31.3)	14 (27.5)	
University	14 (43.8)	25 (49.0)	0.890
Marital status, n (%)			
Single	17 (53.1)	24 (47.1)	
Married	12 (37.5)	23 (45.1)	
Divorced/Widowed	3 (9.4)	4 (7.8)	0.790
BMI, kg/m²	30.42±5.43	29.32±6.74	0.451
Current smoker, n (%)	16 (51.6)	29 (56.9)	0.643
Medical comorbidity, n (%)	19 (59.4)	26 (51.0)	0.455
Clinical characteristics			
YMRS score	0.50±1.58	0.33±0.65	0.510
HAM-D score	2.54±2.27	2.78±2.30	0.646

BMI: Body mass index; YMRS: Young mania rating scale; HAM-D: Hamilton depression scale

Spearman's rank correlation coefficients were calculated to examine associations between serum lithium concentrations and PSQI, MEQ, and BRIAN scores. As a prespecified sensitivity analysis, lithium exposure was redefined according to therapeutic serum lithium concentrations. Patients with serum lithium levels ≥0.6 mmol/L were compared with all remaining participants (patients receiving non-lithium treatment and lithium-treated patients with serum concentrations <0.6 mmol/L). The adjusted regression analyses described above were repeated using this definition of therapeutic lithium exposure. In exploratory analyses, separate regression models were additionally performed for each BRIAN subdomain (sleep, activity, sociality, and eating patterns). A two-tailed p value<0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 83 euthymic patients with bipolar disorder were included, comprising 32 patients receiving lithium-containing treatment regimens and 51 receiving non-lithium treatment regimens. Patients receiving lithium were younger than those receiving non-lithium treatment (36.8±13.3 vs. 42.5±11.0 years, p=0.036). The two groups did not differ with respect to gender, educational attainment, marital status, body mass index, smoking status, medical comorbidity, or residual depressive and manic symptom severity (all p>0.05) (Table 1).

Table 2. Sleep and biological rhythm characteristics according to lithium treatment

	Lithium (n=32)	Non-lithium (n=50)	p	Effect size
PSQI total	7.00±5.45[1]	6.69±4.60[2]	0.788	0.06
MEQ total	51.72±7.39	51.45±9.54[2]	0.893	0.03
BRIAN total	35.09±8.12	38.90±13.42[2]	0.116	-0.33
BRIAN sleep	10.34±2.72	11.72±4.08	0.070	-0.38
BRIAN activity	9.75±3.36	10.74±4.58	0.263	-0.24
BRIAN social	7.47±2.21	8.04±3.45	0.364	-0.19
BRIAN eating	7.53±2.54	8.45±3.27[2]	0.183	-0.31

Values are presented as mean±standard deviation. [1]: n=31 because of missing data; [2]: n=49 because of missing data. PSQI: Pittsburgh sleep quality index; MEQ: Morningness–eveningness questionnaire; BRIAN: Biological rhythms interview of assessment in neuropsychiatry

Regarding current pharmacological treatment, combination pharmacotherapy was common in both the lithium and non-lithium groups [23 (71.9%) and 38 (74.5%), respectively; p=0.791]. Antipsychotic use was reported in 22 (68.8%) patients in the lithium group and 46 (90.2%) in the non-lithium group (p=0.013), while olanzapine/quetiapine use was comparable between groups [15 (46.9%) and 28 (54.9%), respectively; p=0.476]. Antidepressant use was reported in 5 (15.6%) patients in the lithium group and 15 (29.4%) in the non-lithium group (p=0.153). Benzodiazepine use was rare, with only two patients in the overall sample receiving clonazepam (1 mg/day), both of whom were in the non-lithium group. Anticonvulsant mood stabilizer use was more frequent in the non-lithium group [29 (56.9%)] than in the lithium group [2 (6.3%); p<0.001].

Sleep and Biological Rhythm Characteristics

In unadjusted analyses, no statistically significant between-group differences were observed in subjective sleep quality, chronotype, or biological rhythm measures (Table 2). However, patients receiving lithium consistently demonstrated numerically lower BRIAN total and subscale scores than those receiving non-lithium treatment.

PSQI total scores were significantly correlated with BRIAN total scores (Spearman's ρ=0.609, p<0.001) and with all BRIAN subdomains, including sleep (ρ=0.622), activity (ρ=0.556), social (ρ=0.498), and eating rhythms (ρ=0.408; all p<0.001).

Table 3. Multiple linear regression analyses examining the association between lithium treatment and biological rhythm measures[1]

	B (SE)	95% CI for B	β	p	Adjusted R^2
MEQ total	0.432 (1.990)	-3.54, 4.40	0.025	0.829	0.055
BRIAN total	-4.534 (2.251)	-9.02, -0.05	-0.193	0.048	0.341
BRIAN sleep	-1.653 (0.706)	-3.06, -0.25	-0.226	0.022	0.318
BRIAN activity	-1.001 (0.826)	-2.65, 0.65	-0.120	0.230	0.280
BRIAN social	-0.871 (0.654)	-2.18, 0.43	-0.140	0.187	0.184
BRIAN eating	-1.035 (0.659)	-2.35, 0.28	-0.169	0.121	0.167

[1]: Each model was adjusted for age, sex, and PSQI total score. Lithium treatment status was dummy-coded as 1 = lithium and 0 = non-lithium; therefore, negative coefficients indicate lower scores among patients receiving lithium. SE: Standard error; CI: Confidence interval; MEQ: Morningness–eveningness questionnaire; BRIAN: Biological rhythms interview of assessment in neuropsychiatry

Multivariable Regression Analyses

After adjustment for age, sex, and subjective sleep quality, lithium treatment was independently associated with lower biological rhythm disturbance, as reflected by lower BRIAN total scores (β=-0.193, p=0.048) (Table 3). No independent association was observed between lithium treatment and chronotype assessed using the MEQ (β=0.025, p=0.829). Exploratory analyses further demonstrated an independent association between lithium treatment and the BRIAN sleep domain (β=-0.226, p=0.022), whereas the remaining BRIAN subdomains were not significantly associated with lithium treatment.

Serum Lithium Concentrations

Among patients receiving lithium treatment, serum lithium concentrations were not significantly correlated with PSQI, MEQ, or BRIAN total scores (all p>0.05) (Table 4). Likewise, exploratory correlation analyses showed no significant associations between serum lithium concentrations and any of the individual BRIAN subdomains, including sleep, activity, social, or eating rhythms (all p>0.05).

Sensitivity Analyses

Of the 32 patients receiving lithium, 23 (71.9%) had serum lithium concentrations ≥0.6 mmol/L. To examine whether therapeutic lithium exposure was more strongly associated with biological rhythm disturbance than lithium treatment status alone, sensitivity analyses were performed after classifying lithium-treated patients according to a serum lithium concentration threshold of ≥0.6 mmol/L. Therapeutic lithium exposure was independently associated with lower BRIAN total scores (β=-0.244, p=0.011), whereas no association was observed with chronotype (p=0.554). Exploratory analyses additionally demonstrated significant associations with the BRIAN sleep, social, and eating domains, while the association with the activity domain did not reach statistical significance (p=0.079) (Table 5).

Table 4. Correlations between serum lithium levels and sleep and biological rhythm measures

	Spearman's ρ	p
PSQI total	0.036	0.850
MEQ total	-0.127	0.497
BRIAN total	-0.088	0.640
BRIAN sleep	0.046	0.807
BRIAN activity	-0.001	0.994
BRIAN social	-0.256	0.165
BRIAN eating	-0.101	0.590

PSQI: Pittsburgh sleep quality index; MEQ: Morningness eveningness questionnaire; BRIAN: Biological rhythms interview of assessment in neuropsychiatry

DISCUSSION

To our knowledge, this is one of the few clinical studies to compare sleep quality, chronotype, and biological rhythm disturbances between euthymic patients with bipolar disorder receiving lithium and those not receiving lithium while accounting for subjective sleep quality. The principal findings were fourfold. First, although unadjusted comparisons did not reveal significant between-group differences, lithium treatment was independently associated with lower biological rhythm disturbance after adjustment for age, sex, and subjective sleep quality. Second, lithium treatment was not associated with subjective sleep quality or chronotype. Third, serum lithium concentrations were not linearly associated with sleep or circadian measures. Finally, the association between lithium and biological rhythm disturbance became stronger when lithium exposure was defined according to therapeutic serum

Table 5. Associations between therapeutic lithium exposure and biological rhythm measures[1]

	B (SE)	95% CI for B	β	p	Adjusted R^2
MEQ total	-1.286 (2.163)	-5.60, 3.03	-0.067	0.554	0.057
BRIAN total	-6.229 (2.391)	-11.00, -1.46	-0.244	0.011	0.368
BRIAN sleep	-1.623 (0.773)	-3.16, -0.08	-0.204	0.039	0.308
BRIAN activity	-1.580 (0.886)	-3.35, 0.19	-0.174	0.079	0.301
BRIAN social	-1.541 (0.689)	-2.92, -0.17	-0.229	0.029	0.226
BRIAN eating	-1.504 (0.705)	-2.91, -0.10	-0.226	0.036	0.189

[1]: Adjusted for age, sex, and PSQI total score. Therapeutic lithium exposure was defined as a serum lithium concentration ≥0.6 mmol/L (n=23) and dummy-coded as 1 = serum lithium concentration ≥0.6 mmol/L and 0 = otherwise. SE: Standard error; CI: Confidence interval; MEQ: Morningness–eveningness questionnaire; BRIAN: Biological rhythms interview of assessment in neuropsychiatry

concentrations, suggesting that clinically effective lithium exposure may be more relevant than serum concentration itself.

Our findings suggest that the association between lithium treatment and biological rhythm disturbance may extend beyond differences in subjective sleep quality. Sleep and circadian rhythms are closely related but represent distinct physiological systems. Sleep quality primarily reflects the subjective experience of sleep and homeostatic sleep regulation, whereas biological rhythm measures capture the regularity and synchronization of daily behavioral rhythms, including sleep, activity, social interaction, and eating patterns. Although PSQI and BRIAN are conceptually overlapping measures, particularly because the BRIAN includes a sleep domain, the association between lithium treatment and BRIAN total score persisted after adjustment for PSQI. Notably, PSQI was significantly correlated with both BRIAN total and sleep-domain scores. Thus, the observed association with broader biological rhythm disturbance does not appear to be explained solely by differences in subjective sleep quality.

This interpretation is biologically plausible. Experimental studies have consistently demonstrated that lithium directly modulates the molecular circadian clock through inhibition of glycogen synthase kinase-3β (GSK-3β), thereby altering the phosphorylation and stability of several core clock proteins, including REV-ERBα, BMAL1, PER2, and CRY2. The molecular effects of lithium result in enhanced amplitude and stabilization of circadian rhythms in both animal models and cellular systems.[25] Unlike many psychotropic medications whose circadian effects are considered secondary to symptomatic improvement, lithium appears to exert direct effects on the molecular mechanisms regulating circadian rhythmicity. Our findings demonstrating an independent association between lithium treatment and biological rhythm disturbance in euthymic patients are consistent with these experimental observations. Nevertheless, the cross-sectional design does not allow us to determine whether the observed association reflects these molecular circadian mechanisms.

Clinical studies examining the relationship between lithium treatment and circadian functioning have yielded heterogeneous findings. Previous investigations using actigraphy, melatonin secretion, and self-report measures have generally suggested that lithium treatment is associated with greater stability of rest–activity rhythms, larger amplitude, and improved regularity of daily behavioral patterns, although findings have not been entirely consistent across methodologies and clinical populations.[26–28] These inconsistencies may partly reflect differences in mood state, illness stage, concomitant medications, and the circadian measures employed. Our findings extend this literature by demonstrating that, even among euthymic patients receiving routine maintenance treatment, lithium use was independently associated with lower biological rhythm disturbance after accounting for subjective sleep quality. The lack of association with chronotype further suggests that lithium may primarily improve circadian rhythm stability rather than alter intrinsic circadian preference.

Interestingly, lithium treatment was associated with lower BRIAN scores but not with chronotype as measured by the MEQ. Previous clinical studies investigating the association between lithium treatment and chronotype have yielded inconsistent results. Two relatively small cross-sectional studies found greater morningness among patients treated with lithium compared with patients taking other psychotropic medications, but a larger study of 525 patients found no difference in chronotype by lithium treatment status.[29–31] Consistent with the latter findings, we did not find an association between lithium treatment and MEQ scores, suggesting that lithium may affect the stability of biological rhythms rather than an individual's circadian preference. This difference is clinically relevant. Chronotype is a person's preferred timing of sleep and activity and is considered a relatively stable trait influ-

enced by genetic and environmental factors. In contrast, the BRIAN assesses the regularity of behavioral rhythms across multiple domains of daily life, including sleep, activity, social rhythms, and eating patterns.[23] Consequently, it may capture changes in the organization of daily rhythms that are not necessarily reflected by measures of chronotype. The findings suggest that lithium treatment may be more closely associated with the stability and regularity of biological rhythms than with circadian preference. This pattern is consistent with the hypothesis that lithium treatment may be related to circadian rhythm stability rather than chronotype modification.

Another notable finding was that serum lithium concentrations were not linearly associated with biological rhythm measures. However, when patients were classified according to a therapeutic serum lithium threshold (≥0.6 mmol/L), the association with biological rhythm disturbance became stronger and extended to several BRIAN domains. Although exploratory, this observation raises the possibility that associations with biological rhythm stability may be more apparent at therapeutically relevant lithium concentrations than across serum lithium concentrations considered as a continuous measure. Such a threshold effect would also be consistent with clinical practice, in which therapeutic efficacy is generally expected once serum lithium concentrations reach the recommended maintenance range.

Interestingly, the sensitivity analyses suggested that the association between lithium treatment and biological rhythms was not confined to a single behavioral domain but extended across sleep, social, and eating rhythms, with a similar trend observed for activity rhythms. Although these analyses are exploratory, this pattern may suggest that lithium treatment is associated with the overall temporal organization of daily behaviors rather than isolated effects on sleep alone. This interpretation is in line with the social zeitgeber hypothesis, which posits that the regularity of daily routines, including sleep, meals, physical activity, and social interactions, plays a central role in maintaining circadian stability and reducing vulnerability to mood episodes in bipolar disorder. Rather than being associated with a particular circadian output, lithium treatment may be associated with greater synchronization across multiple behavioral rhythms and greater stability of the circadian system as a whole. Nevertheless, this interpretation should be considered preliminary and requires investigation in prospective longitudinal studies.

Our study has several strengths. Participants were restricted to euthymic patients, minimizing the confounding effect of acute mood symptoms on sleep and circadian measures. In addition, we distinguished subjective sleep quality from broader biological rhythm disturbance and evaluated serum lithium concentrations in addition to treatment status. Furthermore, by adjusting for subjective sleep quality, we specifically examined whether the association between lithium and biological rhythms was independent of its potential effects on sleep, providing a more direct evaluation of circadian rhythm.

Several limitations should also be acknowledged. First, the cross-sectional design precludes causal inference, and it cannot be determined whether lithium treatment improves biological rhythms or whether patients with more stable biological rhythms are more likely to remain on lithium treatment. Second, many patients in the lithium group were also receiving additional psychotropic medications as part of routine clinical care. Although this reflects real-world clinical practice and enhances the generalizability of our findings, the independent contribution of lithium cannot be completely separated from that of concomitant medications. Importantly, several psychotropic agents, including atypical antipsychotics, anticonvulsants, and antidepressants, have also been reported to influence sleep architecture and circadian rhythm regulation. Therefore, residual confounding related to concomitant pharmacotherapy cannot be excluded. Third, although adjustment for PSQI allowed us to examine whether the association with biological rhythm disturbance persisted after accounting for subjective sleep quality, some conceptual overlap between PSQI and BRIAN should be acknowledged because the BRIAN includes a sleep domain. Moreover, biological rhythms and sleep were assessed using validated subjective and interview-based measures rather than objective circadian measures, such as actigraphy, dim-light melatonin onset, or core body temperature. Finally, the relatively small sample size may have limited the statistical power to detect small between-group differences, especially in the unadjusted analyses.

CONCLUSION

In conclusion, lithium treatment was independently associated with lower biological rhythm disturbance, but not with subjective sleep quality or chronotype, in euthymic patients with bipolar disorder. Associations with biological rhythm disturbance were more pronounced when lithium exposure was defined using a therapeutic serum concentration threshold. Together, these findings are consistent with the hypothesis that lithium treatment may be associated with greater biological rhythm stability beyond differences in subjective sleep quality. Longitudinal studies incorporating objective circadian measures are needed to determine the temporal and potentially mechanistic nature of this relationship.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Medeniyet University Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Research Ethics Committee (No: 2025/0208, Date: 09/10/2025).

Informed Consent: All participants provided written informed consent before enrolment.

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