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ORIGINAL ARTICLE

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Correction of depression-associated circadian rhythm abnormalities is associated with lithium response in bipolar disorder

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Abstract

Background: Bipolar disorder (BD) is characterized by episodes of depression and mania and disrupted circadian rhythms. Lithium is an effective therapy for BD, but only 30%–40% of patients are fully responsive. Preclinical models show that lithium alters circadian rhythms. However, it is unknown if the circadian rhythm effects of lithium are essential to its therapeutic properties.

Methods: In secondary analyses of a multi-center, prospective, trial of lithium for BD, we examined the relationship between circadian rhythms and therapeutic response to lithium. Using standardized instruments, we measured morningness, diurnal changes in mood, sleep, and energy (circadian rhythm disturbances) in a cross-sectional study of 386 BD subjects with varying lithium exposure histories. Next, we tracked symptoms of depression and mania prospectively over 12 weeks in a subset of 88 BD patients initiating treatment with lithium. Total, circadian, and affective mood symptoms were scored separately and analyzed.

Results: Subjects with no prior lithium exposure had the most circadian disruption, while patients stable on lithium monotherapy had the least. Patients who were stable on lithium with another drug or unstable on lithium showed intermediate levels of disruption. Treatment with lithium for 12 weeks yielded significant reductions in total and affective depression symptoms. Lithium responders (Li-Rs) showed improvement in circadian symptoms of depression, but non-responders did not. There was no difference between Li-Rs and nonresponders in affective, circadian, or total symptoms of mania.

Conclusions: Exposure to lithium is associated with reduced circadian disruption. Lithium response at 12 weeks was selectively associated with the reduction of circadian depressive symptoms. We conclude that stabilization of circadian rhythms may be an important feature of lithium's therapeutic effects. Clinical Trials Registry: NCT0127253.

KEYWORDS
bipolar disorder, chronotype, circadian rhythm, lithium, sleep

1 | INTRODUCTION

Bipolar disorder (BD) is a devastating psychiatric disorder with an estimated prevalence of 1%–2%.[1] BD has a profound negative impact on social and occupational functioning and longevity, with an estimated suicide rate of 20–30 times higher than the general population.[2] Clinically, BD is characterized by episodes of depression and mania/hypomania with disturbances in sleep, mood, energy, appetite, motivation, and overall functioning. These changes in affective state, motivation, and reward processing are central features of the diagnostic criteria for both depressive and manic mood episodes.[2] Disturbances in rhythmic sleep and activity cycles are manifested in both depression and mania, suggesting that circadian dysfunction is another key pathological feature of BD. Depressive episodes are typically characterized by sleep disturbances (hypersomnia, insomnia, and sleep fragmentation) and decreased energy levels. Mania is defined by high energy, hyperactivity, and decreased need for sleep. BD patients also show trait instability in daily activity patterns during euthymia and state instability that predicts subsequent mood symptoms[3,4] whereby worsening sleep/activity disruption can predict mood relapse.[5,6] Thus, circadian disruptions encompass the full spectrum of BD affecting depression, mania, and euthymic (maintenance) periods.

Sleep-wake cycles reflect the behavioral outputs of circadian clocks in the central nervous system. The suprachiasmatic nucleus (SCN) located in the anterior hypothalamus serves as the "master pacemaker" and synchronizes circadian rhythms throughout the body to coordinate them with external environmental cues such as light (known as "zeitgebers"), and endogenous clocks in other tissues.[7,8] Photic input to the retina is transmitted by intrinsically photosensitive retinal ganglion cells expressing melanopsin.[9] Light signals are then relayed to the SCN and other brain clocks via direct projections from the retina. If circadian rhythms become desynchronized, this can lead to not only sleep-wake cycle disturbances but also adverse changes in mood and related behaviors.[7–9] Accordingly, patients with BD commonly show evidence of disrupted circadian rhythms and phase delay, commonly expressed as low trait morningness and a preference for an evening activity or evening chronotype.[3,4,10–15] Genetic studies have revealed polymorphisms in genes that encode the circadian clock and polygenic overlap between

activity rhythms, chronotype, and BD.[16,17] In retrospective studies, a significant association was observed between mood relapse and circadian disruption among BD subjects in maintenance treatment.[6,18] These results indicate that circadian disruption may have a role as a prognostic indicator of mood stability in BD.

Lithium is hypothesized to act therapeutically by inhibiting glycogen synthase kinase 3B (GSK3B) and inositol monophosphatase to alter the metabolism of inositol tris-phosphate (IP_3). GSK3B regulates the stability of clock proteins such as REV-ERBα, PER2, CRY2, and CLOCK,[19–21] and preclinical studies indicate that lithium has direct effects on circadian rhythms. In both human and animal cell lines, lithium strengthens rhythms by increasing amplitude and slows rhythm cycles by lengthening period.[22,23] In a prospective study of BD patients on lithium monotherapy (LiM), baseline chronotype predicted early lithium response outcomes 12 weeks later.[24] Actigraphy studies have shown that good lithium responders (Li-Rs) show higher amplitude sleep/wake rhythms.[25] Similarly, case reports indicate the correction of rhythm abnormalities in the context of successful treatment with lithium.[26] These findings indicate that circadian factors might be a key determinant of therapeutic outcomes in BD. However, it has not yet been demonstrated in a prospective study that lithium corrects rhythm disruptions including sleep and energy symptoms, and/or how lithium's effects on circadian disruption relate to the therapeutic effects of the drug and clinical response.[19,27]

Presently, we addressed these unresolved issues in an exploratory study of a large, prospective lithium clinical trial. First, in a cross-sectional study, we assessed circadian disruption in BD patients who differed in history of past lithium exposure. The aim of this analysis was to characterize morningness and circadian disturbances as they relate to past lithium exposure and correlate these changes with mood stability. Next, we studied the relationship of circadian symptoms to lithium response by measuring changes in depression and mania in a 12-week prospective study of BD patients to determine the relationship between mood symptoms and circadian disruption over time. The overall hypothesis for both studies was that successful treatment of mood symptoms by lithium requires simultaneous resolution of circadian disruption.

2 | METHODS

2.1 | Clinical trial study design

PGBD was an 11-site prospective, nonrandomized open trial of LiM. The study was designed to identify genetic markers of lithium response during the maintenance phase in BD type I and details of the study have been published previously.[28,29] In brief, adult subjects (>18 years old) with BD type 1 could enter the study at any illness phase including depressed, manic, hypomanic, or mixed. To transition to LiM, subjects either switched to lithium from another medication or underwent dose adjustment of prior lithium treatment to optimize the likelihood of response to monotherapy. Euthymic subjects already on lithium either were continued on their previous regimen or, if taking another medication with lithium, were transitioned to LiM. Euthymic subjects not on lithium were not included. Subjects on nonlithium medications had them tapered off gradually for up to 12 weeks. Exclusion criteria included medical contraindications to lithium, clinically significant thyroid and renal impairment, pregnancy, noncompliance with contraception in women of childbearing potential, inpatient hospitalization, residential drug/alcohol treatment, or inability to comply with the study protocol. Subjects were enrolled into a 12-week stabilization phase during which time, the subject met with the study physician for clinical assessment every 2 weeks, lithium was initiated, and other drugs were gradually discontinued. Clinically stabilized subjects then transitioned to maintenance treatment for a total of 2-year follow-up. For this study, we focus on the early response to lithium. Li-Rs were subjects who successfully transitioned to the LiM maintenance phase by 12 weeks. Long-term (2-year) follow-up through maintenance has been reported previously and was not considered in these analyses.[29] Lithium nonresponders (Li-NR) were subjects who were unable to stabilize or suffered a mood relapse prior to entering maintenance. Mood stability was defined by the absence of a mood episode relapse and a score ≤2 on the Clinician Global Inventory for Bipolar Disorder (CGI-BP). Relapse was defined as the occurrence of a depressive or manic episode using DSM-IVTR criteria, or at the discretion of the clinician using a CGI-BP score ≥ 4 for two consecutive weeks. Upon relapse/failure to stabilize, Li-NR subjects were excluded from the study and any subsequent analyses.

2.2 | Baseline characterization of circadian phenotypes in medication groups

All subjects were administered the full version of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego auto questionnaire (TEMPS-A,[30]). Eleven items were selected from the TEMPS-A that ask questions related to sleep, diurnal mood variation, and energy (items 8, 21, 22, 23, 31, 32, 37, 50, 63, 101, 102). In order to estimate baseline circadian disruption, these items were individually scored and coded as absent/present. The sum of these items endorsed by a subject was used to calculate a circadian disruption index (CDI) to estimate overall circadian disruption. CDI ranged from 0 to 11 with higher numbers indicating a greater degree of disruption. Subjects were also given the basic language morningness scale (BALM), a validated measure for estimating chronotype, and surrogate marker for the circadian phase.[31]

2.3 | Prospective changes in mood symptoms during lithium pharmacotherapy

All subjects were assessed with the QIDS-SR and CARS-M to measure symptoms of depression and mania.[32,33] Circadian depression symptoms were defined as those directly related to sleep, energy, and concentration that are known to be regulated by the circadian clock. Six

items (1–4, 10, and 14) were scored 0–3 for a range of 0–18. Typically for the QIDS-SR, the items 1–4 related to sleep are scored to count only the most severe item. However, the items are not perfectly correlated and may capture distinct elements of the circadian rhythm (phase and amplitude). Since we were especially interested in sleep information, we modified the QIDS-SR scoring system and counted each of these items independently for purposes of calculating depressive circadian symptoms. As a comparison, we examined QIDS-SR items 5, 11,12,13, that pertain to negative affective symptoms (feelings of sadness, poor self-appraisal, anhedonia, and suicidal thoughts). Other items focused on appetite, weight changes, feelings of restlessness, and psychomotor slowing were not considered separately as they are ambiguously related to both circadian and noncircadian systems; however, these items were included in the total QIDS-SR score that was calculated according to standard procedures.[33] A similar scheme was developed to assess manic symptoms. Three items from the CARS-M (items 3, 8–9) related to activity, energy, and sleep were considered together as circadian manic symptoms and were scored 0–5 for a range of 0–15. For comparison, three other items related to euphoria, irritability, and grandiosity (items 1–2, 7) were scored separately as positive affective symptoms, likewise scored 0–5 for a range of 0–15. Other symptoms related to the thought process, speech, insight, and delusions were not scored separately but were included in the total score CARS-M score that was calculated according to standard procedures.[32]

2.4 | Statistical analysis

To reduce the number of statistical comparisons in the cross-sectional study, total CDI score and BALM were analyzed as the primary outcome variables to assess circadian disruption and morningness, respectively. Individual components of the CDI score were evaluated post-hoc for descriptive purposes and regarded as secondary measures. Mean group differences in the total CDI score and morningness were compared using ANCOVA with age, sex, race as covariates to determine statistical significance (defined as $p < 0.05$). A second model added two additional covariates (baseline QIDS-SR and CARS-M scores) to control for confounding of circadian function caused by mood symptoms. Afterward, a correlation matrix was constructed to examine the relationship between individual CDI items with each other and with morningness. For these secondary, descriptive analyses, an uncorrected $p < 0.05$ was used to define significantly correlated factors. A principal component analysis (PCA) was performed to examine clustering among CDI items. In the prospective study, to normalize comparison across various symptom scores and control for differences in starting symptom severity between Li-R and Li-NR, all symptom scores were transformed to z-scores based on the baseline level for each group. Changes in symptom categories (circadian, affective, and total) over time were assessed separately for depression and mania using ANCOVA with age, sex, race as covariates. Group differences between Li-R and Li-NR were compared over time. Sample size decreased over time as subjects advanced to maintenance, relapsed, or were declared treatment failures. There was no effort made to impute missing results following a subject dropout.

3 | RESULTS

3.1 | Clinical and demographic characteristics

Baseline demographics were examined separately for the larger cross-sectional study and the prospective lithium response study. Patients in the cross-sectional study were classified into four groups: stable on LiM, stable on lithium polytherapy with one or more other medications (LiP), unstable on lithium (ULi), and unstable on other medication (UOM). In the larger cross-sectional study, BD patients from the UOM group were on average younger and more likely to be from a non-European ethnic background compared with the other groups (Table 1). Only a fraction of the UOM subjects (88/153) went on to participate in the prospective study. There were no significant differences in demographic features between UOM subjects who did/did not participate. In the prospective study, there were no significant differences between Li-R and Li-NR in age, sex, or racial group (Table 1).

3.2 | Lithium exposure in BD patients is associated with reduced CDI

Since low trait morningness has been associated with BD in previous studies,[12,16] we looked at chronotype across groups. After adjusting for demographic factors, the LiM group had the highest morningness scores, followed by LiP and ULi, respectively (Table 2). The UOM group showed significantly lower morningness scores (Figure 1A). We then analyzed CDI in the same four groups to assess

TABLE 1 Demographic features of the bipolar disorder patients initiating lithium treatment

Group	Total *N*	Mean age	Male sex *N* (%)	European ancestry *N* (%)
Cross-sectional study				
Unstable Other Medication (UOM)	153	39.7*	69 (45.1)	99 (64.7)*
Unstable lithium (ULi)	72	40.8	27 (37.5)	63 (87.5)
Stable-Lithium Polytherapy (LiP)	66	44.1	28 (42.4)	58 (87.8)
Stable-Lithium Monotherapy (LiM)	95	45.8	46 (48.4)	84 (88.4)
Statistical test		ANOVA $p < 0.005$	Chi-squares NS	Chi-squares $p < 0.0001$
Prospective study				
Li-R	44	38.6	17 (38.6)	31 (70.4)
Li-NR	44	40.1	18 (40.1)	27 (61.3)
Statistical test		*T*-test NS	Chi-squares NS	Chi-squares NS

Abbreviations: Li-NR, lithium nonresponder; Li-R, lithium responder.
*$p < 0.05$.

disruptions in sleep, activity, and diurnal changes in effect. CDI differed significantly across the four medication groups. LiM patients had the lowest CDI (3.1 ± 0.22), whereas LiP and ULi groups had similar CDI scores of 4.7 ± 0.29 and 4.8 ± 0.31, respectively. UOM patients had the highest CDI burden of 6.15 ± 0.16 significantly higher than any of the other three groups (Figure 1A). While depressive and manic symptoms were positively associated with CDI, the group differences in CDI remained significant after additional covariates for manic and depressive symptoms were added to the model. Upon examination of the individual symptoms, the group differences were consistently and significantly higher in the UOM group and lower in the LiM group across the majority (9/11) of items (Table 2). Individual CDI items were highly interrelated (Figure 1B) and fell into one of three clusters (Figure 1C): The first included items related to low energy (low energy, sleep >9 h, often tired), the second related to instability in sleep/wake cycles (mood and energy shift, sleep need varies, diurnal mood changes-better in the evening, sleep not restful, early insomnia). The first two clusters were significantly negatively correlated with morningness (Figure 1B). The third cluster related to excess energy states (rarely feeling tired, sleep <6 h, diurnal mood changes-better in the morning) and was not correlated with morningness (Figure 1B). Altogether, these data suggest that any past exposure to lithium, even in patients not fully responsive to the drug, is associated with greater morningness and a reduced burden of circadian disruption, and that mood stability is positively associated with these indicators of circadian rhythm.

TABLE 2 Chronotype and circadian disruption and in lithium-treated patients with bipolar disorder. Chronotype was estimated by quantifying morningness using the Basic Language Morningness scale (BALM). BALM scores range from 13 to 55 with higher scores indicating greater morningness. Individual components of the circadian index are reported for each BD group. CDI components were selected from items on the TEMPS-A scale and scored absent (1) or present (0). Group values indicate the proportion of positive scores and group mean for each component.

Circadian trait	UOM	ULi	LiP	LiM	ANOVA
Morningness	31.2	32.9	36	38.5	***
Rarely tired	0.43	0.43	0.5	0.52	NS
Sleep < 6 h	0.44	0.39	0.26	0.31	*
Diurnal mood AM > PM	0.55	0.47	0.50	0.38	***
Low energy	0.63	0.44	0.44	0.20	***
Sleep > 9 h	0.43	0.33	0.30	0.20	**
Often tired	0.73	0.54	0.46	0.29	***
Sleep not restful	0.72	0.54	0.47	0.23	***
Diurnal mood PM > AM	0.61	0.4	0.39	0.24	NS
Mood and energy shift	0.90	0.74	0.71	0.46	***
Early insomnia	0.75	0.58	0.61	0.29	***

Abbreviations: LiM, stable on lithium monotherapy; LiP, stable on lithium polytherapy; ULi, unstable on lithium; UOM, unstable on other medication.

*$p < 0.05$; **$p < 0.005$; ***$p < 0.0001$.

3.3 | Circadian and noncircadian depressive and manic symptoms in patients treated with lithium

We then examined the clinical course of 88 UOM BD subjects as they began lithium treatment and were followed prospectively over 12 weeks. Outcomes among this group were split evenly with 44 patients successfully stabilizing (Li-R) and another 44 failing to stabilize or relapsing (Li-NR; Figure S1). Li-R and Li-NR were similar in baseline CDI (mean ± SEM) Li-R 5.7 ± 0.3 versus Li-NR 6.04 ± 0.3, trait morningness (mean BALM ± SEM): Li-R 33.0 ± 1.3 versus Li-NR 32.0 ± 1.3, and serum lithium levels (mean meq/ml ± SEM): Li-R 0.61 ± 0.03 versus Li-NR 0.59 ± 0.03. None of these were significantly different between groups. Depressive symptoms in both Li-R and Li-NR at baseline were moderate and not significantly different between groups (mean QIDS-SR ± SEM): 11.0 ± 0.9 Li-R versus 11.4 ± 0.8 Li-NR. Manic symptoms in both groups were mild and not significantly different between groups (mean CARS-M ± SEM): Li-R 8.1 ± 1.0 versus Li-NR 8.5 ± 0.9. After starting lithium, depression was gradually and significantly reduced in the Li-R group across all measures: total, affective, and circadian symptoms, and the degree of improvement was similar for the circadian symptoms and noncircadian symptoms alike (Figure 2A). In Li-NR, total and affective depressive symptoms also significantly improved in a manner similar to the Li-R patients. However, among Li-NR, the reduction of circadian depressive symptoms by lithium was attenuated and failed to improve significantly over time (Figure 2B). In other words, the failure of circadian depressive symptoms to resolve was specifically associated with subsequent destabilization/relapse and dropout of Li-NR patients from the study. Symptoms of mania were tracked in the same way over 12 weeks of treatment with lithium (Figure 2C,D). Unlike depressive symptoms, manic symptoms across all measures (total, affective, and circadian) significantly improved in both the Li-R and Li-NR groups.

4 | DISCUSSION

Circadian disruption is a hallmark of BD, with prominent roles in both the depressive (e.g., insomnia, low energy) and manic (e.g., high energy, decreased need for sleep) illness phases. In maintenance treatment of BD, circadian rhythm disorders and insomnia are common predictors of mood relapse.[5] While lithium is widely accepted as an effective treatment for BD and has effects on the circadian clock, it has not been clearly established that lithium is effective specifically for the treatment of circadian rhythm disruptions such as insomnia and low energy, or that restoration of rhythms is necessary for an overall favorable response to lithium treatment. The results of this exploratory study on the early stages of lithium response suggest that compared with BD patients on other medications, any therapeutic exposure to lithium is associated with improvements in circadian rhythm disruption independently of mood symptoms, even in patients who are not fully stabilized. When studied prospectively over 12 weeks, improving circadian function is associated with the overall resolution of depressive symptoms and favorable response to lithium.[34] Taken together,

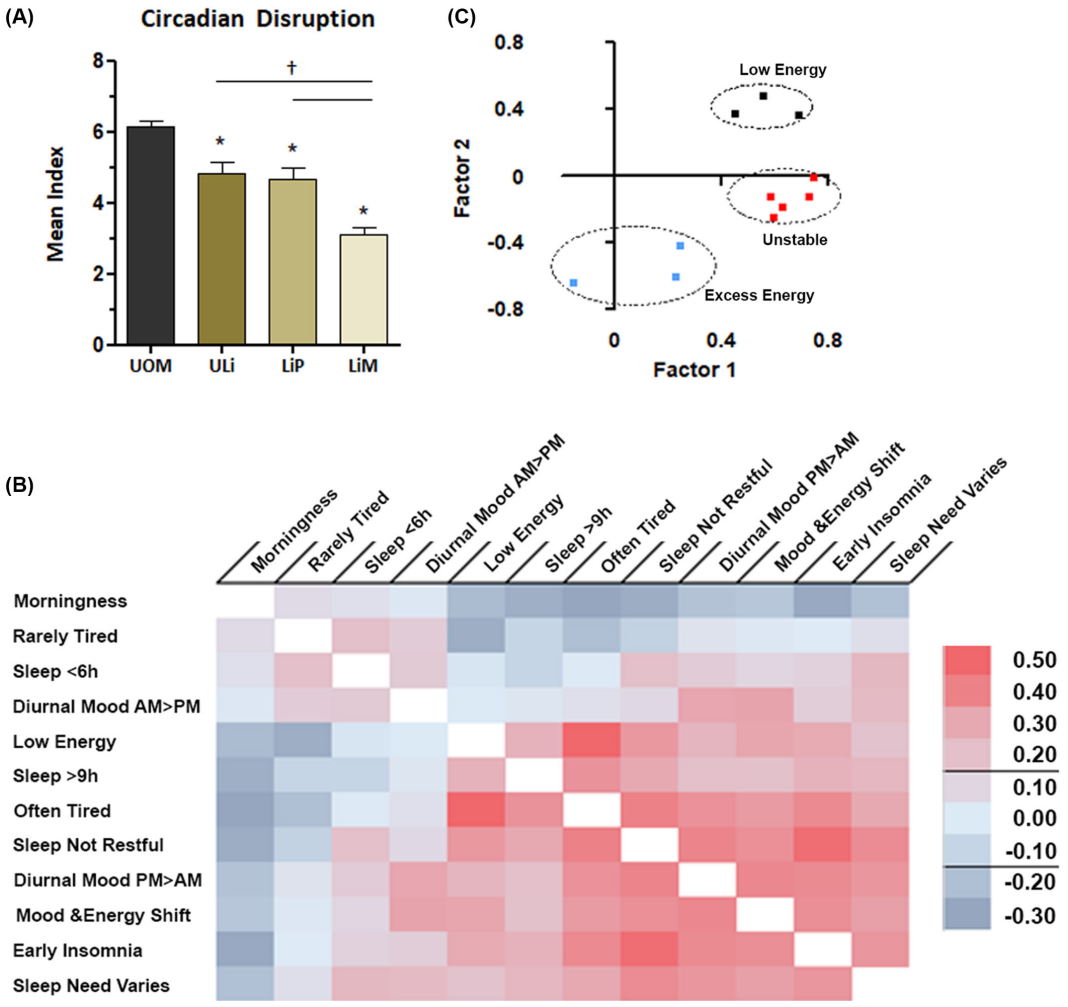

FIGURE 1 (A) Lithium exposure is associated with less circadian disruption. The total circadian disruption index (CDI) score is shown for each BD patient group (group mean CDI ± SEM). After controlling for demographic variables, analysis by ANCOVA showed significant group differences ($p < 0.001$). Group differences remained significant ($p < 0.001$) after additional covariates for depressive and manic symptoms are added to the model. Post hoc test indicated significant differences between the UOM group versus each of the three lithium-treated groups (all $p < 0.05$, indicated by *). Furthermore, LiM had significantly lower CDI versus LiP and ULi (all $p < 0.05$, indicated by †). (B) Correlation matrix showing the relationship among chronotype and components of the circadian disruption index. Low energy states mostly negatively correlated with morningness. High energy states mostly showed no significant correlation with morningness. Key: red = positive correlation, blue = negative correlation. The darker the color the stronger the correlation. Cutoff for nominal statistical significance (uncorrected $p < 0.05$) is indicated by lines in the key. (C) Results of clustering by the first two PCA components showed that CDI items cluster into three groups corresponding to low energy, unstable sleep/activity cycles, and excess energy states. Data suggest CDI items are meaningfully related to chronotype and conceptually coherent.

these findings indicate that actions of lithium on the circadian clock, especially improvements in sleep and energy may be essential for achieving initial mood stability early in the treatment of BD.

Morning chronotype is commonly associated with a variety of mental health outcomes including better response to lithium and overall well-being.[24,35] LiM subjects stable on lithium monotherapy at the time of initial assessment had higher trait morningness and approximately 50% less circadian disruption compared with UOM subjects without previous lithium exposure. Smaller but significant differences in CDI were also seen in LiM compared with LiP and ULi patients, indicating that the lithium-responsive LiM BD group had comparatively less circadian disruption compared with lithium nonresponsive or previously untreated BD patients. Patients with past exposure to lithium but with unstable mood symptoms or requiring additional medications to stabilize were characterized by less morningness and more circadian disruption compared to patients who were psychiatrically stable on lithium monotherapy. While there were significant demographic differences between groups, especially in the UOM group, differences in circadian disruption remained significant after statistical correction for these. Group differences in symptom burden of depression and mania may account for some of the variance in circadian disruption but does not fully explain it. Our data, therefore, suggest that there are effects of lithium exposure on the circadian disruption that are independent of changes in mood. However, the cross-sectional design of this part of the study could not distinguish between pharmacological effects of lithium on rhythms and individual differences in circadian rhythms that predated treatment.

To better characterize the pharmacological effects of lithium, we prospectively followed a cohort of BD subjects newly undergoing

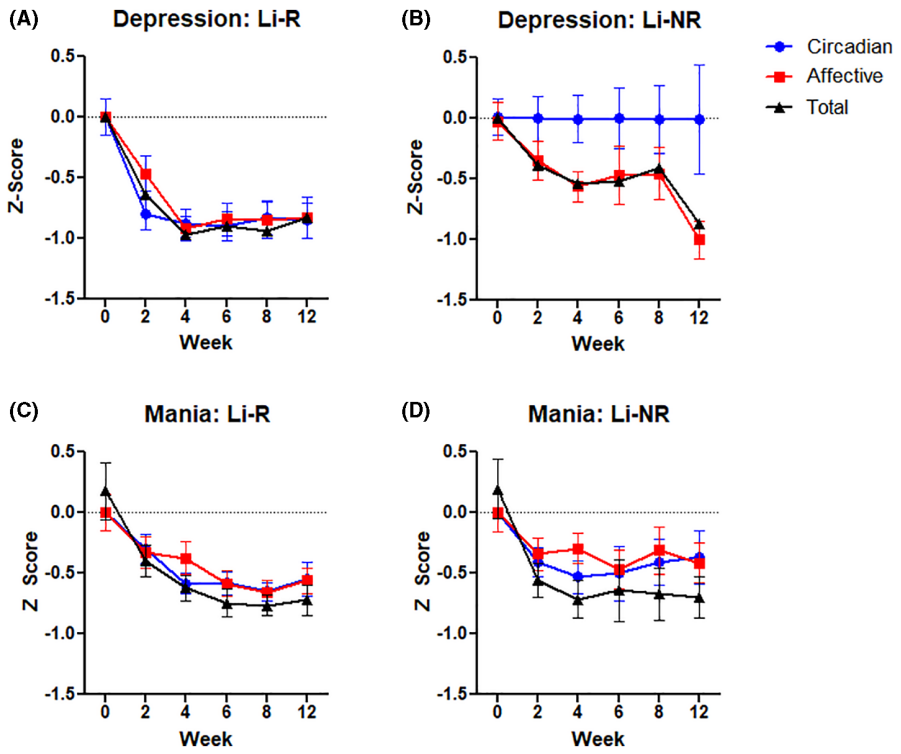

FIGURE 2 Circadian symptoms of depression are selectively associated with lithium response. Change in circadian, affective, and total symptoms differ between lithium responder (Li-R) and lithium nonresponder (Li-NR) cohorts over 12-week follow-up. Both (A) Li-R and (B) Li-NR subjects demonstrated a significant reduction in total and affective symptoms of depression. However, only Li-R patients showed improvement in circadian symptoms of depression. ANCOVA controlling for age, sex, and race revealed significant differences in depressive symptoms with main effects of time ($p < 0.001$) and lithium response group ($p < 0.02$). Post-hoc analyses reveal significant differences in circadian depressive symptoms between Li-R and Li-NR ($p < 0.01$) and trend-level differences in the reduction of affective symptoms of depression ($p = 0.058$). For manic symptoms, (C) Li-R and D) Li-NR improved to a similar extent in all three symptom categories. ANCOVA revealed significant reduction in all three categories of manic symptoms over time for both Li-R and Li-NR ($p < 0.001$). None of the demographic variables were significantly associated with response. Sample size by visit, Li-R: $N = 44/39/40/32/34/27$, Li-NR: $N = 44/30/27/18/15/8$

lithium treatment to identify changes in circadian rhythm-related mood symptoms. In this portion of the study, we demonstrated that reduction of circadian depressive symptoms was required to achieve Li-R status, defined in our study as the initial resolution of mood symptoms within 12 weeks. In Li-R, resolution of affective symptoms and total depression scores closely paralleled improvements in sleep and energy. Among Li-NR, affective symptoms and total depression scores improved significantly among subjects who remained in the study, but circadian symptoms failed to resolve, and these subjects ultimately failed treatment in subsequent study visits. Important caveats apply to the results of the Li-NR. Over the course of the trial, Li-NR subjects remained stable for varying times, but ultimately all failed to stabilize and/or relapsed. As increasing numbers of Li-NR subjects failed treatment, the size of the Li-NR group gradually diminished. Mood symptoms were not measured from subjects after leaving the study and therefore, in the Li-NR group survival bias that likely overstates the degree of overall improvement in mania and depression. Accordingly, the failure of circadian depressive symptoms to improve predicted the subsequent mood instability but not necessarily current mood instability. Taken together, these results suggest a correction of circadian depressive symptoms is essential for a patient to progress early in treatment and distinguishes Li-R and Li-NR. To the best of our knowledge, this is the first suggestion in a prospective clinical trial that the resolution of circadian disruption is essential to the therapeutic action of lithium.

There was no difference in the resolution of circadian manic symptoms in Li-R versus Li-NR, and both BD groups improved to a similar extent in each manic symptom category. Therefore, the changes in depressive circadian symptoms contribute specifically to overall lithium responsiveness. However, given that this was an outpatient study, the burden of manic symptoms among the BD subjects was low and may not have been sufficiently high to detect reductions in circadian disruption associated with severe mania. Previous work in BD patients equipped with accelerometers has demonstrated the relationships among mood, sleep, and activity states, and that loss of rhythm is correlated with the severity of manic symptoms.[4,36] Lithium is an effective treatment for acute mania, therefore, there is good reason to expect in instances of severe mania, lithium may also have corrective effects on circadian disruption. Future studies of circadian rhythms and lithium in acute mania may be justified to study this question in detail.

Our work adds to a substantial body of literature revealing overlap in the therapeutic mechanisms of lithium and circadian rhythms. In a previous study of this population, chronotype predicted lithium-responsiveness: Higher morningness was associated with lower baseline depressive and manic symptoms and fewer suicide attempts.

BD patients undergoing chronotherapeutic interventions for bipolar depression (partial sleep deprivation, bright light therapy, and phase advance) show a more durable recovery when the interventions are paired with lithium, implying overlapping mechanisms.[37] Genetic factors have been shown to contribute to lithium response.[38-40] While to date only a limited set of genome-wide significant loci have been identified, aggregate polygenic risk for schizophrenia and major depression negatively influence lithium response,[39,40] and genetic risk for these disorders overlaps with genetic determinants of chronotype and circadian amplitude.[17,35,41] Clinically, this is relevant as it suggests that residual symptoms of insomnia, energy disturbance, or diurnal mood variation paired with depression may portend an unsuccessful treatment course and necessitate additional steps to stabilize BD patients on lithium. In the context of previous studies, our work supports the notion that the biological correlates of lithium response overlap meaningfully with neurobiological factors supporting circadian rhythms. Future work to target circadian disruption as an augmentation strategy for lithium and explore the mechanisms in more detail is warranted.

Our study design has some inherent limitations. Subjects were enrolled for a 2-year study, making it unethical to withhold treatment. Therefore, we did not have a control group and factors unrelated to lithium may have influenced treatment outcomes. Additionally, there are some symptoms of both depression and mania that did not fit neatly into our circadian versus affective dichotomy. For instance, appetite and concentration both correlate strongly with wakefulness and therefore have circadian components but are also strongly altered by affective state and other variables. Given this ambiguity, we decided to consider some mood symptoms only in aggregate in the total QIDS-SR/CARS-M scores but not distinctly in the circadian versus affective scheme. Another limitation of this exploratory analysis was that the study was not optimally designed to measure circadian disruption, and we were only able to measure circadian disruption indirectly. CDI score is subject to various artifacts that limit our ability to measure the circadian contribution to symptoms with precision. Moreover, we did not reassess CDI at the end of the prospective study and cannot determine the extent of improvement or differences in Li-R and Li-NR. Future studies making use of accelerometry and other wearable devices may be able to more precisely capture changes in circadian disruption as primary outcome measures in more precise terms of behavioral/physiological variables and allow for more comprehensive analyses of rhythms as they relate to mood symptoms. While others have previously examined the relationship of the TEMPS-A to chronotype to reveal significant associations,[42] our use of the CDI is novel and has not yet been validated in other populations. In the cross-sectional portion, LiM patients are likely overrepresented in Li-Rs. It is therefore difficult to discern the long-term effects of lithium treatment from the inherent circadian factors that may predispose a patient to be lithium responsive prior to treatment. The prospective portion of the study addresses this issue to some extent but the sample was relatively small and after dropout, became even smaller, especially at later times. For this reason, our results should be viewed as preliminary.

In conclusion, stabilization of sleep and energy rhythms in BD may be an important goal of lithium pharmacotherapy and perhaps with other mood-stabilizing treatments. Among Li-R, improvement of depression-associated rhythm disruption may be critical to a good therapeutic outcome. Future studies will expand upon these findings and determine in more detail precisely how lithium acts upon neurobiological systems affecting sleep and energy to promote mood stability.

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DATA AVAILABILITY STATEMENT

Deidentified data will be made available to qualified researchers upon written request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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