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ORIGINAL ARTICLE

WILEY BIPOLAR DISORDERS

Total sleep time and kynurenine metabolism associated with mood symptom severity in bipolar disorder

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Objective: Chronic, low-level inflammation is associated with symptomatic bipolar disorder (BD) and with chronic insomnia. Disrupted sleep is a feature of episodes of both mania and depression. We examined the effect of neopterin, a marker of cellular immune activation, and kynurenine (KYN), an inflammatory byproduct of the serotonin pathway, on the association between total sleep time and depression severity in BD.

Method: Twenty-one symptomatic BD participants and 28 healthy controls (HC) were recruited and followed during usual clinical care. At baseline and after symptomatic recovery, total sleep time was objectively measured with actigraphy for 1 week and blood plasma was collected to measure the serotonin precursor tryptophan (TRP), KYN, the KYN/TRP ratio, and neopterin levels. Statistical analyses were conducted using chi-square, independent *t* tests and hierarchical linear multiple regression models.

Results: Total sleep time was correlated positively with depressive severity and negatively with manic severity. TRP was significantly reduced in BD participants compared to HC. KYN, TRP, and the KYN/TRP ratio were associated with depressive severity when total sleep time and body mass index (BMI) were included in the model. The KYN/TRP ratio trended towards a negative association with mania symptoms, controlling for BMI and total sleep time, in acutely symptomatic BD participants. Neopterin was not associated with sleep or mood severity. After usual clinical care, BD participants showed significantly decreased clinical symptoms but no significant differences in sleep phenotype or biomarkers.

Conclusion: Inflammation, sleep, and mood are closely intertwined. Future research into the effect of inflammation on sleep in BD may lead to clinical markers of outcome.

KEYWORDS
inflammation, kynurenine pathway, sleep

1 | INTRODUCTION

Bipolar disorder (BD) is a severe psychiatric disorder, with a complex and sometimes heterogeneous range of symptoms.[1] BD is one of the leading causes of disability, demonstrating, on average, a less favorable prognosis than major depressive disorder (MDD).[2] As a clinically heterogeneous syndromic disorder, the biological changes in BD have been reported in depressive and manic episodes, and any unifying biological underpinnings of this disorder have remained elusive.[3-5] Research shows that BD presents with numerous immune-inflammatory and

sleep abnormalities.[6-8] Activation of the kynurenine (KYN) pathway has been supported in a number of psychiatric disorders, including BD[9,10].While many studies have independently explored sleep,[11-13] inflammation,[7,14] and the KYN[9,15] pathway in BD, there is increasing evidence that inflammation is an important factor in mood, stress, and sleep disturbance[16,17] and needs to be examined simultaneously for a better understanding of the underlying biological mechanisms. Additionally, there is a dearth of research exploring inflammation, metabolites of the KYN pathway, or sleep in acutely ill BD patients.[4]

Mood spectrum disorders (BD, recurrent depressive disorder, and seasonal affective disorder) are accompanied by sleep dysregulations that are particularly common among bipolar participants.[8,12,13,18] Sleep dysregulations in mood disorders commonly occur in acute manic or depressive states but are also prevalent during remission.[8,19-21] A meta-analysis focusing on sleep in remitted BD participants highlights disturbances in several sleep parameters: longer sleep latency, longer sleep duration, and poorer sleep efficiency.[21] Sleep is a remarkably sensitive, but not specific, indicator of distress, and dysregulated sleep can occur for a variety of reasons. Inflammation has been shown to be associated with sleep disturbance and objective short sleep in primary insomnia and obstructive sleep apnea, and may mediate the association between sleep apnea and adeposity.[22-24] By examining the association of sleep dysregulation with inflammatory biomarkers in BD, we may gain an understanding of the sleep, mood, and inflammation connection.

The essential amino acid tryptophan (TRP) is a substrate for two important biosynthetic pathways: the serotonin (5-hydroxytryptamine [5-HT]) pathway and the KYN pathway (Figure 1). During stress, proinflammatory cytokines activate the KYN pathway and deprive the serotonin pathway of TRP, thereby reducing serotonin synthesis. The dynamics of this process are characterized best by the kynurenine-to-TRP (KYN/TRP) ratio. One of the inflammatory drivers of this diversion of serotonin to KYN is neopterin, a catabolic product of guanosine triphosphate that is a marker of cellular immune system activation produced by macrophages upon stimulation by interferon-gamma.[25-28] Increased peripheral KYN results in increased central KYN. KYN is further broken down into quinolinic acid, which is a potent agonist at the N-methyl-D-aspartate (NMDA) receptor, causing excitotoxic effects through receptor overactivation[29,30] and inhibiting glutamate uptake, causing elevated extracellular glutamate concentrations.[31]

In the current study, we investigated the relationship between markers of the KYN pathway, neopterin, sleep, and clinical symptoms in acutely ill BD participants. We were also interested in exploring biomarkers and sleep patterns after symptom remission, to determine whether these biomarkers were potentially state vs trait characteristics independent of mood state. We hypothesized that:

1. Patients with acute BD would have significantly lower total TRP and a higher KYN/TRP ratio and neopterin levels than healthy controls (HC).
2. The KYN/TRP ratio and neopterin would be associated with severity of depressive and manic symptoms in acutely symptomatic participants with BD.
3. Sleep duration and biomarkers including kynurenine pathway metabolites (TRP, KYN/TRP) and the proinflammatory cytokine neopterin would be associated with depressive and manic symptom severity.

Finally, we were interested in whether these markers changed with symptom remission in asymptomatic patients, and explored differences in clinical symptoms, sleep, and biomarkers between baseline and follow up.

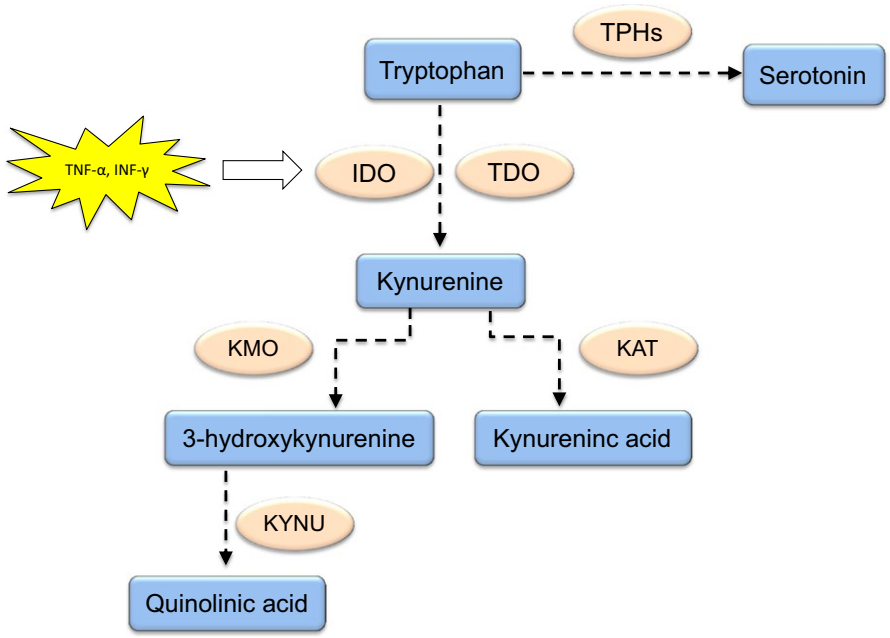

FIGURE 1 The kynurenine pathway. INF-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; TPH IDO, indolamine-2,3-dioxygenase; KAT, kynurenine aminotransferase; KMO, kynurenine 3-monooxygenase; KYNU, kynureninase; TDO, tryptophan-2,3-dioxygenase; TPH, tryptophan hydroxylase

2 | PARTICIPANTS AND METHODS

2.1 | Participants

Thirty BD participants with current mood symptoms participated in the study, and 21 completed all measures for this analysis. Participants were recruited when presenting for inpatient or partial hospital care at the Pennsylvania Psychiatric Institute, under Institutional Review Board Protocol No. 39164EP and NIH Office of Human Subject Research Exemption #11509 (7/16/2012). Participants were screened and consented for the study, and assessments including sleep and biomarkers were administered while they were receiving inpatient or partial hospital care. Inclusion criteria for BD participants included adults with a primary diagnosis of BD I or II. Exclusion criteria included use of nonsteroidal anti-inflammatory drugs (NSAIDs) on a daily basis, active substance intoxication or withdrawal, major endocrinological or rheumatological illness, or pregnancy. Twenty-eight HC participants were recruited via advertisement, based on the inclusion criteria that they had no personal or family history of mental illness, rheumatological or endocrinological illness, pregnancy, or daily NSAID use. HCs provided actigraphy data in their home environment, while clinical and blood measures were collected at the research site.

2.2 | Measures

Structured clinical interview based on the Mini Neuropsychiatric Interview[32] were conducted and current mood state was assessed using the Hamilton Depression Rating Scale-21 plus atypical items (HDRS-21+AT),[33] and the Clinician-Administered Rating Scale for Mania (CARS-M).[34] A combination of clinically significant manic and depressed symptoms defined a mixed-manic phenotype. HDRS-21+AT scores between 0 and 6 indicated no depression; scores between 7 and 17 indicated mild depression; scores between 18 and 24 indicated moderate depression; and scores over 24 indicated severe depression. CARS-M scores below 7 were considered non-manic. Scores between 7 and 12 were mild, and above 12 were severe manic phenotypes. The body mass index (BMI) for each participant was calculated by measuring height and weight. Participants received usual clinical care and were discharged from the program. After discharge from the hospital or partial hospital program, participants were followed each week by telephone and assessed for clinical improvement. A return visit was scheduled to collect a second blood sample when the subject was asymptomatic, or after 3 months had elapsed. Additional measures were collected but not used for this analysis. Saunders et al[35] provided a more detailed report on the methods and results of analysis of fatty acid concentrations.

2.3 | Objective measure of total sleep time

During the period of initial evaluation, participants wore an actigraph (Sleepwatch-O, Ambulatory Monitoring, Inc., Ardsley, NY, USA), a watch-like device that measures acceleration, on the nondominant hand for 7 days. They also maintained a sleep log, which, combined with the actigraphy recording, provides an accurate assessment of objective sleep measures. ActiLife V.6.4.5 software (ActiGraph Software Department, Pensacola, FL, USA) was used to compute the actigraphy sleep variables, including total sleep time, bedtime variability, sleep latency, sleep duration, and sleep efficiency. BD participants completed the actigraph during hospitalization, and HCs completed it at home. Owing to the small sample size, we limited the analysis of sleep variables to the investigation of total sleep time only, which allowed us to conserve statistical power. However, an additional exploratory analysis of mean lag (variability in bedtime from night to night) was also made.

2.4 | Sample collection and biochemical analysis

Participants fasted for at least 6 hours, and blood was drawn in vacutainers containing ethylenediaminetetraacetic acid (EDTA) in the morning. BD participants had blood drawn between 07:15 and 10:30 (average time 08:24) and HC participants had blood drawn between 08:00 and 14:00 (average time 09:19). After centrifugation for 10 minutes at 654.03 *g*, the plasma supernatant was transferred to plastic tubes and maintained at −80°C until processed. Total TRP (micromoles per liter) and KYN (micromoles per liter) were measured by reverse-phase high-performance liquid chromatography, as previously described[36,37], using 3-nitro-L-tyrosine as an internal standard. The KYN/TRP ratio was calculated (expressed as micromoles of KYN per millimoles of TRP). Neopterin was measured by enzyme-linked immunosorbent assay (BRAHMS, Hennigsdorf, Germany) according to the manufacturer's instructions, with a detection limit of 2 nmol/L.

2.5 | Data and statistical analysis

SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for all statistical calculations. Values of continuous variables were compared between the BD and HC groups using independent-samples *t* tests, and categorical variables were compared using the Pearson chi-square test. Paired *t* tests were used for baseline and follow-up measurements. In an exploratory analysis, Pearson's *r* was used for separate bivariate correlations on demographics and clinical symptoms, sleep, and inflammation variables in the BD and HC samples. Baseline depression was predicted using linear regression models based on a priori variables, controlling for BMI due to the known association between inflammation and obesity.[38] Model 1 included total sleep time and KYN/TRY, model 2 included total sleep time and KYN, model 3 included total sleep time and TRP, and model 4 had total sleep time and neopterin as predictor variables. The same models were implemented to predict baseline manic symptoms controlling for BMI. Paired *t* tests were conducted to compare symptoms, total sleep time, and inflammatory variables from baseline to follow-up. However, follow-up data were available for considerably fewer participants. This was the result of an inability to maintain regular contact with some participants owing to a number of issues (e.g., unstable housing conditions). The maximum number of days to follow-up was 187; the median was 22 days and the average was 52 days. However,

an analysis of dropouts vs those who continued to be a part of the study did not show any significant differences based on baseline clinical symptoms and demographics, including age and gender (*P* values >.16). Dependent variables were compared between BD smokers and nonsmokers using independent *t* tests.

3 | RESULTS

3.1 | Demographic and clinical description of the sample

A cohort of 30 participants with BD was recruited while in a symptomatic mood episode. Six participants did not have sleep assessment data, and three did not have biomarker data; therefore, 21 BD participants were included in the final analysis. A parallel HC group of 31 participants was recruited for the study, of which three participants did not have sleep data (n = 28). Participants with BD did not differ from the HC group in age, gender, or race (Table 1). A significantly higher proportion of participants with BD were unemployed, not married, and smokers than in the HC group (Table 1). Independent *t* tests were run between the smokers and nonsmokers within the BD group, to detect any differences based on age, BMI, HDRS, CARS-M, TRP, KYN, KYN/TRP, and sleep variables. No differences were detected, with all *P* values above .10.

Clinically, BD individuals had a significantly higher BMI, and when evaluated for the study exhibited, on average, severe depressive symptoms and moderate manic symptoms (Table 1).

TABLE 1 Demographics, clinical symptoms, and differences in sleep and biomarkers between healthy controls and bipolar disorder individuals

	Healthy control	Bipolar disorder	
	N (%)	N (%)	*P*
Total sample size	28	21	
Gender (F)	16 (57%)	10 (48%)	.57
Race			
Asian	3 (11%)	0	.19
Black	1 (4%)	0	
White	24 (86%)	21 (100%)	
Marital status			.02
Married	14 (50%)	4 (18.2%)	
Not married	14 (50%)	17 (81.8%)	
Employment			<.001
Unemployed	2 (7%)	11 (55%)	
Disabled	0	4 (20%)	
Employed	16 (57%)	4 (20%)	
Student	10 (36%)	1 (5%)	
Smoking status	1 (4%/)	11 (52%)	<.001
	Mean (SD)	Mean (SD)	
Age (y)	31.57 (10.33)	36.10 (11.33)	.16
Body mass index(kg/m^2)	25.01 (4.91)	30.32 (5.49)	.001
Mania (CARS-M)	0	16.52 (13.87)	<.001
Depression (H-21)	0.32 (.61)	33.62 (15.37)	<.001
Total sleep time (min)	414.68 (70.98)	392.56 (117.23)	.45
Bedtime variability (min)	−3.67 (58.31)	−22.62 (61.17)	.26
KYN (μmol/L)	1.98 (.55)	1.79 (.50)	.22
TRP (μmol/L)	68.74 (11.62)	60.25 (14.30)	.03
KYN/TRP	28.93 (7.26)	29.88 (6.21)	.63
Neopterin (nmol/L)	5.45 (1.39)	5.80 (1.66)	.46

KYN, kynurenine; Kyn/Trp, kynurenine/tryptophan ratio; SD, standard deviation; TRP, tryptophan.

3.2 | Sleep and inflammation variables

The HC group slept an average of 6.9 hours a night, with a standard deviation of about 1 hour; and the mean lag (variability in bedtime from night to night) was 4 minutes, with a standard deviation of 1 hour. The BD group slept an average of 6.5 hours, with a standard deviation of almost 2 hours, and the mean lag was 23 minutes, with a standard deviation of 60 minutes. Total sleep time was correlated positively with depressive symptom severity and negatively with the severity of manic symptoms (Table 2).

3.2.1 | Group comparisons of TRP, KYN/TRP, and neopterin

As hypothesized, the BD group had significantly lower levels of TRP than the HC group ($P < .03$) (Table 1). The BD group did not differ significantly from the HC group in mean levels of KYN, KYN/TRP, and neopterin (Table 1).

3.2.2 | TRP, KYN/TRP, and neopterin, and severity of depressive and manic symptoms

Based on Pearson's correlation test, KYN, KYN/TRP, and neopterin did not correlate significantly with depressive and manic symptoms, as measured by the HDRS and CARS-M clinical measures or sleep measures, including total sleep time and bedtime variability. None of the kynurenine pathway markers were associated with total sleep time in either the BD or HC group. Neopterin levels correlated positively with KYN/TRP ($r = .53$, $P < .01$) but were not correlated with clinical severity, TRP, or KYN (Table 3).

3.2.3 | Association of biomarkers and sleep with depressive and manic severity

The association of depressive severity was tested with four hierarchical regression models, using depressive severity as the dependent variable and total sleep time, KYN, TRP, and KYN/TRP as the predictor variables controlling for BMI (Table 4). Depressive severity was

TABLE 2 Bivariate correlations among clinical symptoms of depression, mania, inflammation, and sleep variables in bipolar participants only (n = 21)

	HDRS21	CARS-M	BMI	Total sleep time	Mean lag	TRP	KYN	Kyn/Trp	Neopterin
HDRS21		−0.62**	0.11	0.72**	−0.32	0.36	0.44	0.14	−0.11
CARS-M			−0.05	−0.52*	0.32	−0.04	−0.25	−0.25	0.36
BMI				−0.03	0.21	−0.46*	−0.04	0.38	0.24
Total sleep time					−0.25	0.21	0.03	−0.26	−0.34
Mean lag						−0.05	0.21	0.33	0.25
TRP							0.67**	−0.22	−0.19
KYN								0.56*	0.24
Kyn/Trp									0.53*

BMI, body mass index; CARS-M, Clinician-Administered Rating Scale for Mania; HDRS21, Hamilton Depression Rating Scale-21; KYN, kynurenine; Kyn/TrP, kynurenine/tryptophan ratio; TrP, tryptophan.
*$P < .05$
**$P < .01$

TABLE 3 Bivariate correlations among inflammation and sleep variables in healthy control participants only (n = 28)

	BMI	Total sleep time	Mean lag	TRP	KYN	Kyn/Trp	Neopterin
BMI		−0.25	0.04	−0.12	−0.08	0.01	−0.010
Total sleep time			−0.12	−0.07	−0.19	−0.14	0.01
Mean lag				−0.23	0.12	0.31	0.32
TRP					0.479**	−0.12	0.18
KYN						0.81**	0.40*
Kyn/Trp							0.60**

BMI, body mass index; KYN, kynurenine; Kyn/TrP, kynurenine/tryptophan ratio; TrP, tryptophan.
*$P < .05$
**$P < .01$

significantly associated with KYN (model 3) and TRP (model 4), when total sleep time and BMI were accounted for. Models 3 and 4 (Table 4) accounted for 71% and 60% of the variance, respectively. Model 1, consisting of KYN/TRP and total sleep time, trended toward significance, accounting for 60% of the variance (Table 4). Although total sleep time was significantly associated with manic severity in all four models, only the KYN/TRP biomarker trended towards significance (Table 5). This model explained 35% of the variance (Table 5).

3.3 | Follow-up data

Exploratory analysis of the follow-up data showed that although the BD participants reported significantly decreased clinical symptoms of depression and mania,[35] no significant differences were detected in total sleep time, TRP, KYN/TRP. Total sleep time appears to have increased at follow-up but was not significantly different from baseline scores. This may have been the result of the high variability in total sleep time score for BD participants (Table 6).

4 | DISCUSSION

The current study examined the relationship between objective markers of sleep and biomarkers of TRP metabolism and inflammation in a group of acutely symptomatic BD individuals. We found significantly lower levels of TRP in BD patients compared to HC. We also found that biomarkers, in conjunction with total sleep time, were associated positively with depressive severity and negatively with manic severity in BD patients.

Our first question addressed whether there were group differences between BD and HC in total sleep time, TRP, and KYN/TRP. Our finding of lower TRP levels in acutely symptomatic BD participants was concordant with several recent reports examining TRP levels in BD and schizophrenia[10,39,40] and the theory that decreased plasma TRP levels in BD participants may potentially lead to dysfunctional brain serotonin synthesis and release. TRP depletion studies[41,42] provide a useful tool to examine the role and association of serotonin in different psychiatric disorders. Most of the TRP depletion studies have focused on unipolar depression owing to decreased serotonin as an underlying cause. For example, TRP depletion has been associated either with no effect[43] or with a slight but insignificant relapse of manic symptoms in fully recovered BD patients. No TRP depletion studies have been carried out in acutely manic BD patients.[39] The present study provides evidence for decreased TRP levels in a naturalistic occurrence of acute mood episodes. While experimental studies support the notion that decreased levels may be a precursor to a depressed mood state, in our study it was unclear whether the decreased TRP levels preceded or resulted from an acute mood state.

TABLE 4 Association between depressive symptom severity and total sleep time and KYN/TRP ratio in bipolar disorder (controlling for BMI) (n = 21)

Variable	β	*t*	*R*	Adj.R^2
Model 1			0.81	0.60
BMI	0.05	0.34		
Total sleep time	0.85	5.42**		
KYN/TRP	0.32	2.0^		
Model 2			0.54	0.24
BMI	0.50	3.85**		
Total sleep time	0.27	2.15*		
Neopterin	0.17	0.92		
Model 3			0.85	0.71
BMI	0.21	1.53		
Total sleep time	0.78	5.88**		
KYN	0.39	2.93**		
Model 4			0.81	0.60
BMI	0.30	1.83		
Total sleep time	0.66	4.53**		
TRP	0.35	2.10*		

BMI, body mass index; Kyn, kynurenine; Kyn/Trp, kynurenine/tryptophan ratio; TRP, tryptophan.
*P < .05
**P < .01
^ = 0.06

TABLE 5 Association between manic symptom severity and total sleep time and KYN/TRP in the bipolar disorder group (controlling for BMI) (n = 21)

Variable	β	*t*	*R*	Adj.R^2
Model 1			0.66	0.35
BMI	0.04	0.19		
Total sleep time	−0.69	−3.59*		
KYN/TRP	−0.39	−2.00**		
Model 2			0.40	0.10
BMI	0.17	1.21		
Total sleep time	−0.29	−2.12*		
Neopterin	0.12	0.90		
Model 3			0.60	0.25
BMI	−0.21	−0.57		
Total sleep time	−0.57	−2.97*		
KYN	−0.21	−1.07		
Model 4			0.57	0.21
BMI	−0.06	−0.28		
Total sleep time	−0.56	−2.76*		
TRP	0.05	0.20		

BMI, body mass index; Kyn, kynurenine; Kyn/TrP, kynurenine/tryptophan ratio; Trp, tryptophan.
*P <. 05
**P = .06

Secondly, we asked if TRP, KYN/TRP, and neopterin were associated with severity of depressive and manic symptoms. We did not find levels of neopterin, an inflammatory marker, to be significantly different from those in HC, and they were not associated with depression or mania severity. However, neopterin levels were found to be associated positively with the KYN/TRP ratio, which replicated earlier studies investigating depression and chronic inflammation. [44,45] Further mechanistic studies examining the role of neopterin in mood disorders are warranted. For example, one study[25] found that significantly higher levels of neopterin predicted poststroke depression in patients who had previously experienced a major depressive episode. Another cross-sectional study found a positive association between MDD with a history of suicide attempt and KYN but no association with neopterin.[44] However, similar to our findings, Sublette et al[44] found a positive correlation between the cytokine activation marker neopterin and KYN/TRP, suggesting that KYN production may be influenced by inflammatory processes. The present study supports previous studies finding an association between neopterin and the KYN/TRP ratio but does not support a direct association between neopterin and mood disorders.

We hypothesized a significant association between sleep duration and biomarkers (TRP, KYN/TRP, neopterin), and depressive and manic symptom severity. TRP degradation follows one of two main metabolic pathways, which ultimately lead to the production of either serotonin and melatonin, or kynurenine and its metabolites (Figure 1). Enhanced activation of the kynurenine pathway due to stress or an acute mood state would theoretically hinder melatonin production, thereby potentially affecting the sleep patterns of patients.[6,46,47] Thus, activation of the kynurenine pathway potentially suggests the association of sleep and the kynurenine metabolites with mood states. While we did not find a correlation between these biomarkers and severity of mood symptoms, we found an association with the severity of clinical mood symptoms when considering KYN/TRP in conjunction with objective total sleep time. Neopterin and TRP degradation, as measured by the KYN/TRP, is highly associated with immune activation, which in turn leads to the production of KYN instead of serotonin from TRP;[48] however, in our data neopterin, although correlated with KYN/TRP, was not associated with mood severity, with or without accounting for sleep. The association of KYN, TRP, and total sleep time with severity of depression and manic symptoms implies that these pathways are related but further research is necessary to delineate exactly how they influence each other.

Finally, we asked whether total sleep time, TRP, and KYN/TRP changed with symptom remission in asymptomatic BD patients. Despite subjectively reported decreased clinical symptoms, no differences were detected in the biomarkers or total sleep time. One explanation could be the short follow-up time – perhaps these markers change on a slower time scale, or they may leave a long-term residual mark of the episode, indicating a change in physiology despite remission.[49-51]

However, the results should be treated with caution owing to the small sample size of the study. Additionally, the patients were all receiving medication for an acute mood episode, which makes it difficult to parse the effects of medication. Further, in order to maximize statistical power, the study investigated only one sleep variable – total

TABLE 6 Paired sample *t* test comparing clinical symptoms of depression, mania, sleep, and inflammation variables at baseline and follow-up in bipolar disorder
Data represents mean (SD)

	Baseline	Follow-up	N	*P*-value
Mania	19.69 (15.11)	3.75 (5.47)	16	<.001
Depression	32.40 (14.32)	11.13 (10.60)	15	<.001
Total sleep time (min)	353.34 (124.68)	421.51 (125.70)	8	.24
KYN (μmol/L)	1.69 (.48)	1.70 (0.50)	13	.92
TRP (μmol/L)	61.24 (15.91)	62.04 (13.78)	13	.82
KYN/TRP	27.81 (5.65)	27.34 (5.81)	13	.82

Kyn, kynurenine; Kyn/TrP, kynurenine/tryptophan ratio; Trp, tryptophan.

sleep time. However, sleep is a complex phenomenon and consists of multiple aspects which are easily measured using actigraphic devices. Based on the results of the present study, different sleep variables, along with inflammatory markers, warrant further investigation with a larger sample size. Another important methodological factor was the use of a structured hospitalized setting compared to a home environment. It may be argued that a hospitalized setting led to patients feeling more stressed than the HC; however, we argue that the patients were already in acute distress and unable to cope with their existing resources, leading to inpatient hospitalization. The structured setting of the hospital often relieves stress through learning basic skills and teaching patients to generalize those skills to real-world naturalistic settings.[52]

5 | CONCLUSION

In conclusion, the study provides evidence supporting the association of mood severity in acutely symptomatic BD participants with metabolites of the KYN pathway, in association with objective measurements of sleep. Further understanding of the role of in BD is important for the development of potential targets for intervention, or markers of treatment response. Targeting sleep and regulation of the TRP breakdown pathway for intervention in BD participants is an area of research warranting further investigation. Targeting these areas for improvement and observing clinically significant changes may lead to more sustained improvement and remission rates.

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DISCLOSURES

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