Predictors of Suicidal Ideation and Preparatory Behaviors in Individuals With Bipolar Disorder:

The Contribution of Chronobiological Dysrhythmicity and Its Association With Hopelessness

Laura Palagini, MD, PhD[a,*]; Mario Miniati, MD, PhD[a]; Danila Caruso, MD[a]; Andrea Cappelli, MD[a]; Lucia Massa, MD[a]; Francesco Pardini, MD[a]; Alessandra Petrucci, MD[a]; Francesca Romeo, MD[a]; Gianluca Salarpi, MD[a]; Bruno Etain, MD, PhD[b]; and Pierre Alexis Geoffroy, MD, PhD[c,d]

ABSTRACT

Objective: To examine the role of chronobiological dysrhythmicity in suicidal ideation and behaviors and its relation with hopelessness.

Methods: One hundred twenty-seven patients (77 females, mean age of 47.4 ± 12.5 years) with a major depressive episode and bipolar disorder (BD) type I or II (according to Structured Clinical Interview for *DSM-5* assessment) were recruited in 2019 and assessed for depressive and manic symptoms (Beck Depression Inventory-II, Young Mania Rating Scale) and with the Biological Rhythms Interview of Assessment in Neuropsychiatry, Beck Hopelessness Scale, and Scale for Suicide Ideation. Univariate regression and mediation analyses were performed.

Results: Forty-one patients (32.3%) showed clinically significant suicidal ideation and were more frequently affected by BD type I ($P = .029$) with mixed features ($P = .022$). Compared to nonsuicidal individuals, they had significantly more depressive symptoms ($P = .019$), higher emotional component of hopelessness ($P = .037$), and higher dysrhythmicity of sleep ($P = .009$), activities ($P = .048$), and social life ($P = .019$). Passive and active suicidal ideation and suicidal plans were best predicted by dysrhythmicity of sleep and social life. Dysrhythmicity of sleep and social life mediated the direct effect of depressive symptoms on passive and active suicidal ideation and also of active ideation on suicidal plans. The emotional component of hopelessness was related to dysrhythmicity of social life and mediated its effect on suicidal plans ($P = .010$).

Conclusions: Chronobiological alterations directly contributed to passive and active suicidal ideation and to suicidal preparation, with a key role of dysrhythmicity of sleep, activities, and social life. Chronobiological alterations also impacted the emotional component of hopelessness, hence indirectly contributing to suicidal ideations and plans. These findings call for the systematic screening of these dysrhythmicity dimensions when considering suicidal risk in individuals with BD.

J Clin Psychiatry 2021;82(2):20m13371

To cite: Palagini L, Miniati M, Caruso D, et al. Predictors of suicidal ideation and preparatory behaviors in individuals with bipolar disorder: the contribution of chronobiological dysrhythmicity and its association with hopelessness. *J Clin Psychiatry*. 2021;82(2):20m13371.

To share: https://doi.org/10.4088/JCP.20m13371

[a]Department of Clinical and Experimental Medicine, Psychiatric Section, University of Pisa; Azienda Ospedaliera Universitaria Pisana (AUOP), Pisa, Italy

[b]Department of Psychiatry and Addiction Medicine, Assistance Publique-Hôpitaux de Paris (AP-HP), DMU Neurosciences, GH Saint-Louis—Lariboisière—F. Widal; Université de Paris; INSERM UMRS1144, Paris, France

[c]Université de Paris, NeuroDiderot, Inserm, Paris, France

[d]Department of Psychiatry and Addiction Medicine, Assistance Publique-Hôpitaux de Paris (AP-HP), University Hospital Bichat-Claude Bernard, Paris, France

**Corresponding author:* Laura Palagini, MD, Psychiatric Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy, Via Roma 67, 56100, Pisa, Italy (lpalagini@tiscali.it, l.palagini@ao-pisa.toscana.it).

Bipolar disorder (BD) is a severe and chronic psychiatric disorder affecting 1%–4% of the population worldwide and characterized by recurrences of mood episodes.[1–3] BD is the sixth leading cause of disability among all illnesses worldwide.[1–3] Therefore, the impact of BD on public health represents a major concern, as it increases global burdens of disease in terms of disability, morbidity, and premature mortality.[4–6] With regard to causes of premature mortality, patients with BD are at very high risk of suicide, which is considered a major public health issue by the World Health Organization.[6–8] Indeed, the rate of suicide among individuals with BD is approximately 20–30 times higher than in the general population; up to 20% of individuals will commit suicide, and 20%–40% will attempt suicide.[7–10] Hence, increasing the understanding of the mechanisms involved in suicidal behaviors in BD should be considered an urgent priority to better prevent suicide and to identify potential modifiable markers with personalized interventions.

Whereas risk factors for suicidal behaviors are multiple and complex, hopelessness appears to be a major independent risk factor for suicidality in BD and so merits increased attention.[11–13] Recently, the World Health Organization[10] recognized hopelessness as an important risk factor for suicide and recommended its assessment in the context of suicidal behaviors.

Hopelessness was first formulated by Beck[14–16] as a "system of negative beliefs and expectancies concerning one's future" and was a cornerstone of Beck's cognitive triad of depression.[14–17] After 30 years of research, Beck and his colleagues established that hopelessness is more strongly related to suicidality than to depression itself.[17,18] The hopelessness theory of suicide states that hopelessness—with negative emotional, motivational, and cognitive prospects for the future—leads depressed individuals to view suicide as the only way out of insoluble problems.[17,18] Hopelessness has consistently been shown to be one of the best independent predictors of suicidal behaviors in all phases of bipolar disorder, being both a trait and a state marker and predicting mortality by suicide.[11,12,17–21]

Clinical Points

- Suicidal risk is a major concern in bipolar disorder, but not all potential causes are considered in "real world" psychiatric settings.
- Clinicians should assess and treat alterations in sleep and circadian rhythms in patients with bipolar disorder, as they could be a potential cause of suicidal ideation and behaviors.

Compelling evidence has also demonstrated that BD is frequently associated with circadian rhythms alteration, contributing to its vulnerability, pathogenesis, and manifestations (for an overview, see references 22–25). According to the "circadian hypothesis of mood disorders," the desynchronization of the master biological clock of the hypothalamus, the suprachiasmatic nuclei, constitutes a hallmark and a key feature of mood disorders.[22–27] Moreover, it has been shown that individuals with BD present alterations in circadian rhythms, with abnormalities in physiological and behavioral timekeeping processes including social life, activities, eating, and sleep/wake patterns, prior to and during acute phases, but also during remitted phases.[22,26–29] Biological rhythms dysregulation, in particular in the desynchronization of sleep and social life, has been associated with the severity of mood symptoms, insomnia symptoms, emotional dysregulation, and, interestingly, the risk of suicidal behaviors in BD.[26,30–39] Finally, for the first time, international chronotherapeutics guidelines were recently published specifically in BD,[39] with promising efficacy in BD observed during all phases of the disorder.[26,27,32,39] Therefore, these circadian dysrhythmicities may be directly targeted by chronotherapeutics, with direct clinical implications. Moreover, these alterations appear as potential modifiable early markers in BD and suicidal behaviors.[26,27,32,39]

Although hopelessness and circadian rhythm alterations contribute to both BD and suicidal risk, a paucity of research has examined how these factors are interrelated and how they are collectively associated with mood features and suicidal ideation and behaviors in BD. Some previous studies have suggested that actual or preferred circadian phases, such as chronotype, were associated with hopelessness in both nonclinical and clinical populations; in particular, evening chronotype has been associated with hopelessness.[40,41] A further study[42] has shown that a polymorphism in the *CLOCK* gene was related to hopelessness, to suicidal ideation history, and to attempted suicide in individuals with BD.

In this context of encouraging preliminary findings but also a paucity of research regarding hopelessness as a major independent risk factor for suicidality, we decided to specifically examine the relationships among chronobiological dysrhythmicity and the emotional, motivational, and cognitive components of hopelessness and suicidal risk in a population of patients with BD I and II during acute depressive phases.

We aimed to specifically investigate hopelessness and chronobiological dysrhythmicity in relation to suicidal ideation and behaviors in individuals with BD. We hypothesized that the chronobiological desynchronization would predict suicidal behaviors by contributing to hopelessness, and therefore we explored the potential processes underlying the relationship between these variables by conducting mediation analyses.

METHODS

Selection of Patients and Clinical Assessment

The current study included a consecutive series of patients from January 2019 to December 2019 who were hospitalized at the Azienda Ospedaliero-Universitaria Pisana (AUOP) (protocol number: 12390), University of Pisa, Italy, with a diagnosis of bipolar disorder type I or II according to *DSM-5*.[3] The current study was a cross-sectional observational study approved by the local ethical committee as part of an ongoing main research project aimed at characterizing insomnia and chronobiological rhythms in several types of mood disorders.

Inclusion criteria were (1) a current diagnosis of major depressive episode with or without mixed features in bipolar disorder type I or II according to *DSM-5* criteria,[3] (2) age between 18 and 65 years, and (3) the willingness and ability to provide signed informed consent to the study.

Exclusion criteria were (1) a current and lifetime diagnosis of substance abuse, (2) a current depressive episode with psychotic features, (3) other subtypes of bipolar disorders (ie, not other specified), and (4) cognitive impairment (Mini-Mental State Examination[43]).

All participants were clinically assessed with a set of questionnaires that included the Structured Clinical Interview for *DSM-5* Axis I Disorders,[44] the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN),[45,46] the Beck Hopelessness Scale (BHS),[16,47] and the Scale for Suicide Ideation (SSI).[48,49] At baseline, all patients also completed clinical report forms, which included current pharmacologic therapy.

The study conformed to the Declaration of Helsinki, and all participants provided written informed consent prior to being enrolled in the study.

Psychiatric diagnosis. The assessment of previous and current psychiatric diagnoses according to *DSM-5* criteria was performed using the Structured Clinical Interview for *DSM-5* Axis I Disorders.[44]

Hopelessness. The BHS is a self-report scale consisting of 20 items. Total score and emotional, motivational, and cognitive factors of hopelessness were computed.[16] We used the validated Italian version.[47]

Chronobiological rhythms. Chronobiological rhythms were assessed with the BRIAN.[45] The BRIAN contains 21 items and assesses 5 domains related to biological rhythms: (1) sleep, (2) activities, (3) social life, (4) eating pattern based on the last 15 days, and (5) predominant rhythm (chronotype) based on the last year. In accordance with

Table 1. Demographic and Psychometric Variables[a]

	Subjects With Bipolar Disorder Depressive Episode (n = 127)	Subjects With Clinically Significant Suicidal Ideation—SSI ≥ 6 (n = 41)	Subjects With Non–Clinically Significant Suicidal Ideation—SSI < 6 (n = 86)	*t* or χ^2 (*df* = 2)	*P*[b]
Age, mean ± SD, y	47.4 ± 12.5	47.6 ± 12.0	48.6 ± 12.8	0.24	.723
Gender, female, n (%)	77 (60.6)	24 (58.5)	53 (61.6)	0.60[c]	.080
Previous suicide attempt, n (%)	39 (30.7)	19 (46.3)	20 (23.2)	3.92[c]	**.038**
Family history of suicide attempt, n (%)	38 (29.9)	14 (34.1)	24 (27.9)	0.21[c]	.395
Living alone, n (%)	25 (19.6)	11 (26.8)	14 (16.2)	1.43[c]	.168
Divorced, n (%)	9 (7.1)	2 (4.8)	7 (8.1)	0.79[c]	.721
Unemployed, n (%)	23 (18.1)	7 (17.0)	16 (18.6)	0.14[c]	.425
Illness duration, mean ± SD, y	18.2 ± 11.7	18.2 ± 11.6	17.9 ± 11.6	0.98	.754
Bipolar disorder I vs II, n (%)	53 (41.7)	23 (43.3) vs 18 (24.3)*	30 (56.7) vs 54 (75.7)	*4.38[c]	**.029**
Mixed features, n (%)	56 (44.1)	31 (75.6)	25 (29.0)	4.89[c]	**.022**
Anxiety comorbidity, n (%)	32 (25.2)	8 (19.5)	24 (27.9)	0.49[c]	.320
Chronobiological rhythms, mean ± SD					
BRIAN total	42.9 ± 17.6	44 ± 17.2	41.7 ± 17.4	0.45	.499
BRIAN Sleep	11.9 ± 3.1	12.9 ± 2.4	11.5 ± 3.3	7.03	**.009**
BRIAN Activities	13.5 ± 3.9	14 ± 3.0	13.3 ± 3.4	3.38	**.048**
BRIAN Social	9.1 ± 1.9	10.7 ± 2.2	8.4 ± 2.9	5.67	**.019**
BRIAN Alimentation	8.7 ± 3.0	9.6 ± 3.0	8.4 ± 2.9	0.24	.877
BRIAN chronotype	5.8 ± 1.6	6.3 ± 1.7	5.06 ± 1.5	0.99	.284
Hopelessness-BHS total	10.5 ± 5.5	12.7 ± 5.4	9.6 ± 5.4	0.12	.728
Feelings about the future	2.6 ± 1.7	3.0 ± 1.4	2.4 ± 1.7	4.42	**.037**
Loss of motivation	3.6 ± 2.5	4.5 ± 2.6	3.2 ± 2.3	1.04	.233
Future expectations	3.2 ± 1.5	2.7 ± 2.7	2.3 ± 2.3	0.83	.492
SSI, mean ± SD					
Total	0.45 ± 0.65	11.4 ± 5.2	1.9 ± 1.8	49.5	**< .001**
Passive suicidal desire	2.4 ± 3.1	4.8 ± 2.7	1.3 ± 1.3	33.3	**< .001**
Active suicidal desire	2.5 ± 2.5	5.2 ± 3.7	0.52 ± 0.87	41.9	**< .001**
Plans for suicide	0.45 ± 0.65	1.1 ± 1.3	0.12 ± 0.36	56.3	**< .001**
Psychiatric scales, mean ± SD					
BDI-II total score	24.3 ± 10.4	27.6 ± 11.2	22.3 ± 9.9	2.07	**.019**
YMRS total score	6.6 ± 4.2	7.5 ± 3.9	6.2 ± 4.4	1.03	.250
Current drug treatments, n (%)					
Antidepressants	80 (62.9)	26 (63.4)	54 (62.7)	1.03[c]	.145
Mood stabilizers	102 (80.3)	33 (80.4)	69 (80.2)	1.04[c]	.168
Lithium	70 (55.6)	21 (51.2)	49 (56.3)	0.0.3[c]	.225
Benzodiazepines	49 (39.2)	15 (36.5)	34 (39.0)	0.02[c]	.560
Neuroleptics	47 (37.0)	10 (24.3)	37 (42.5)	2.75[c]	.075

[a]Description of the total sample of subjects with bipolar disorder types I and II depressive episode with and without mixed features and comparison between subjects with clinically significant suicidal ideation (SSI ≥ 6) vs subjects without clinically significant suicidal ideation (SSI < 6).
[b]Boldface indicates statistical significance.
[c]χ^2 test.
*Difference between bipolar disorder I and bipolar disorder II groups is significant in subjects with clinically significant suicidal ideation.
Abbreviations: BDI-II = Beck Depression Inventory-II, BHS = Beck Hopelessness Scale, BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry, SD = standard deviation, SSI = Scale for Suicide Ideation, YMRS = Young Mania Rating Scale.

previous works,[45,46] a total score and subscores for each domain of biological rhythms were computed. The BRIAN has shown validity compared to objective parameters of circadian rhythmicity.[50] We used the validated Italian version.[45,46]

Suicidal ideation and behaviors. Suicidal ideation and behaviors were evaluated using the SSI.[48] A total score ≥ 6 has been used as a cutoff threshold for clinically significant suicidal ideation according to literature.[48,49] The SSI consists of 19 items that evaluate 3 dimensions of suicide ideation: passive suicidal desire, active suicidal desire, and specific plans for suicide. The first 5 items were used to screen for attitudes toward suicidal thoughts, and on this basis patients were rated on items 6–19. Each item is rated on a 3-point scale from 0 to 2. We evaluated the total SSI score and each of its dimensions according to literature.[48,49]

Mood symptoms scales. Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II): a BDI-II total score > 13 is indicative of clinically significant depressive symptoms.[15,49]

Manic symptoms were assessed with the Young Mania Rating Scale (YMRS).[50] A YMRS total score > 7 is indicative of clinically significant manic symptoms.[49,51]

Statistical Analysis

The statistical analysis was performed using SPSS 22.0 for Windows (IBM Corp, 2018). Descriptive statistics were expressed as mean ± standard deviation (SD) and/or percentage. The Shapiro-Wilk test was used to check the normality of the continuous variables. Differences in means between patients with clinically significant suicidal ideation (SSI total score ≥ 6) and patients with non–clinically significant suicidal ideation (SSI total score < 6) were assessed using *t* tests for normally distributed variables and the Mann-Whitney *U*/Wilcoxon test for non-normally distributed variables. Categorical variables were analyzed via the χ^2 test.

Table 2. Correlations Among Variables in Subjects With Bipolar Disorder Types I and II[a,b]

	Passive Ideation SSI	Active Ideation SSI	Preparatory Behaviors SSI	BDI-II	BRIAN Total	BRIAN Sleep	BRIAN Activity	BRIAN Social	BRIAN Alimentation	BRIAN Rhythms	BHS	BHS Feelings	BHS Motivation	BHS Expectation
Passive SSI	1													
Active SSI	**0.78****	1												
Plans SSI	**0.52****	**0.57****	1											
BDI-II	**0.39****	**0.32****	**0.39****	1										
BRIAN total	**0.32****	**0.35****	**0.20***	**0.60****	1									
BRIAN Sleep	**0.32***	**0.24****	0.15	**0.18***	**0.41****	1								
BRIAN Activity	0.16	**0.23***	0.10	**0.41****	**0.72****	**0.51****	1							
BRIAN Social	**0.30***	**0.35****	**0.24***	**0.38****	**0.73****	**0.34****	**0.40****	1						
BRIAN Alimentation	0.14	**0.24****	0.02	**0.29****	**0.67****	0.08	0.11	**0.33****	1					
BRIAN Rhythms	0.01	0.03	0.08	0.04	**0.22***	**0.35****	–0.18	0.13	**0.35****	1				
BHS total	**0.25***	0.17	0.05	**0.47****	**0.40****	**0.27****	**0.29****	**0.17***	0.13	0.08	1			
BHS Feelings	**0.35****	**0.32****	**0.27****	**0.43****	**0.41****	**0.27****	**0.31****	**0.30****	0.12	0.01	**0.85****	1		
BHS Motivation	**0.25****	0.28	0.07	**0.40****	**0.35****	**0.23****	**0.28****	0.16	0.11	0.02	**0.82****	**0.73****	1	
BHS Expectation	0.12	0.06	0.01	**0.47****	**0.36****	0.14	0.86	0.83	0.12	0.04	**0.91****	**0.70****	**0.60****	1
YMRS	0.12	0.06	0.01	0.08	**0.20***	0.14	0.13	0.03	0.02	0.11	0.03	0.01	0.04	0.05

[a]Results of Spearman correlation for non-normally distributed variables and Pearson correlation for normally distributed variables. BHS Expectation = expectation about the future, BHS Feelings = feelings about the future, BHS Motivation = loss of motivation about the future.
[b]Boldface indicates statistical significance.
*$P < .05$.
**$P < .001$.
Abbreviations: BDI-II = Beck Depression Inventory-II, BHS = Beck Hopelessness Scale, BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry, SSI = Scale for Suicide Ideation, YMRS = Young Mania Rating Scale.

Correlations between continuous variables were tested using the Spearman ρ correlation for non-normally distributed variables and the Pearson correlations index for normally distributed variables. Linear and multiple regression models were then built with active/passive suicidal ideation and suicidal plans as dependent variables. A mediation analysis using the Sobel test[52] was performed in order to study the potential processes that may underlie the relationships between these variables. All pathways of the mediation were tested.

RESULTS

Sample Description

Of the 155 potential participants evaluated, 127 patients (females, n = 77 [60.6%], mean age 47.4 ± 12.5 years) met the inclusion/exclusion criteria for bipolar disorder type I (n = 53 [41.7%]) or type II (n = 74 [58.3%]). Fifty-five patients (43.3%) showed mixed features.

Among the 155 potential participants, 16 were excluded according to exclusion criteria for having a diagnosis of substance use disorder or for psychotic features, and 12 participants were excluded because their questionnaires were incomplete. Thus, 127 individuals were included in further analyses.

Forty-one participants showed clinically significant suicidal ideation (SSI ≥ 6) (females: n = 24 [58.5%], mean age 47.6 ± 12 years), and 86 participants had non–clinically significant suicidal ideation (females: n = 53 [61.6%], mean age 48.6 ± 12.8 years).

Participants with clinically significant suicidal ideation were more frequently individuals with BD type I with mixed features (Table 1) and with a higher frequency of previous suicide attempts.

Individuals with clinically significant suicidal ideation showed greater severity of depressive symptoms and greater chronobiological rhythms dysregulation of sleep, activities, and social life. They also showed higher scores in the emotional component of hopelessness (BHS feelings) (Table 1).

Correlations Among Variables

Results of Spearman correlation for non-normally distributed variables and Pearson correlation for normally distributed variables are shown in Table 2.

Passive suicidal ideation was related to dysrhythmicity of sleep and social life, to depressive symptoms, and to all the components of hopelessness (BHS total score). Active suicidal ideation was related to dysrhythmicity of social life, sleep, and activities; to depressive symptoms; and to the emotional part of hopelessness (BHS feelings). Suicidal plans were related to chronobiological dysrhythmicity, in total and in particular of social life; to depressive symptoms; and to the emotional part of hopelessness. Hopelessness and chronobiological dysrhythmicity (BRIAN total score) were correlated, and in particular the emotional component of hopelessness was related to the majority of chronobiological alterations including domains of sleep, social life, and activities.

Table 3. Linear and Multiple Regression Analyses on Passive Suicidal Ideation, Active Suicidal Ideation, and Suicidal Preparatory Behaviors in Subjects With Bipolar Disorder Types I and II[a]

	Univariate B (SE)	*P*	Multivariate B (SE)	*P*
Passive suicidal ideation SSI				
Previous suicide attempts	**1.15 (0.59)**	**.011**	**1.36 (0.58)**	**.022**
BDI-II	**0.09 (0.01)**	**<.001**	**0.06 (0.02)**	**.004**
BHS total	**0.10 (0.03)**	**.005**	0.03 (0.04)	.445
BRIAN total	**0.06 (0.01)**	**<.001**	0.07 (0.05)	.121
BRIAN Sleep	**0.17 (0.06)**	**.012**	0.14 (0.10)	.172
BRIAN Social	**0.29 (0.08)**	**.001**	**0.27 (0.12)**	**.024**
Active suicidal ideation SSI				
Previous suicide attempts	**2.04 (0.65)**	**<.001**	**2.12 (0.68)**	**.002**
BDI-II	**0.08 (0.02)**	**<.001**	**0.04 (0.02)**	**.118**
BHS Feelings[b]	**0.08 (0.05)**	**.005**	0.03 (0.04)	.445
BRIAN total	**0.08 (0.02)**	**<.001**	0.08 (0.07)	.244
BRIAN Sleep	**0.21 (0.02)**	**.008**	0.11 (0.13)	.385
BRIAN Activity	**0.18 (0.07)**	**.011**	0.006 (0.01)	.883
BRIAN Social	**0.40 (0.09)**	**<.001**	**0.23 (0.15)**	**.223**
Preparatory behaviors SSI				
Previous suicide attempts	**0.30 (0.10)**	**.005**	0.07 (0.09)	.543
BDI-II	**0.01 (0.003)**	**.002**	0.006 (0.004)	.126
BHS Feelings[b]	**0.07 (0.02)**	**.005**	0.006 (0.09)	.522
BRIAN total	**0.01 (0.003)**	**<.001**	0.01 (0.006)	.052
BRIAN Social	**0.05 (0.01)**	**<.001**	**0.03 (0.01)**	**.045**
Active suicidal ideation	**0.10 (0.01)**	**<.001**	**0.10 (0.01)**	**<.001**
Passive suicidal ideation	**0.10 (0.01)**	**<.001**	0.02 (0.102)	.328

[a]Boldface indicates statistical significance.
[b]Feelings about the future.
Abbreviations: B = unstandardized regression coefficient, BDI-II = Beck Depression Inventory-II, BHS = Beck Hopelessness Scale, BRIAN = Biological Rhythms Interview of Assessment in Neuropsychiatry, SE = standard error, SSI = Scale for Suicide Ideation.

Predictors of passive suicidal ideation. Linear regression analyses showed that significant predictors of passive suicidal ideation were previous suicide attempts, depressive symptoms, all components of hopelessness, and alterations in biological rhythms, in total and in particular of sleep and social life. In the multiple regression model, previous suicide attempts, depressive symptoms, and alterations in biological rhythms of social life remained significantly associated with passive suicidal ideation (Table 3).

Predictors of active suicidal ideation. The linear regression analyses showed that predictors of active suicidal ideation were previous suicide attempts, depressive symptoms, negative feelings about the future, and alterations in biological rhythms, in total and in particular of sleep, social life, and activities. In the multiple regression model, previous suicide attempts, depressive symptoms, and alterations in biological rhythms of social life remained significantly associated with active suicidal ideation (Table 3).

Predictors of suicidal plans. Linear regression analyses showed that significant predictors of suicidal plans were previous suicide attempts, depressive symptoms, negative feelings about the future, alterations in biological rhythms in total and in particular of social life, and passive and active ideation. In the multiple regression model, alterations in biological rhythms of social life and active suicidal ideation remained significantly associated with suicidal plans (Table 3).

Mediation Analyses

Results of the mediation analyses for passive ideation showed that BRIAN total, BRIAN social, BRIAN sleep, and hopelessness (BHS total) acted as mediators between depressive symptoms and passive suicidal ideation (mediator BRIAN total: $Z = 2.63$, SE = 0.007, $P = .0008$; mediator BRIAN social $Z = 2.12$, SE = 0.001, $P = .0003$; mediator BRIAN sleep $Z = 2.27$, SE = 0.001, $P = .0022$; mediator hopelessness [BHS total]: $Z = 2.12$, SE = 0.003, $P = .003$).

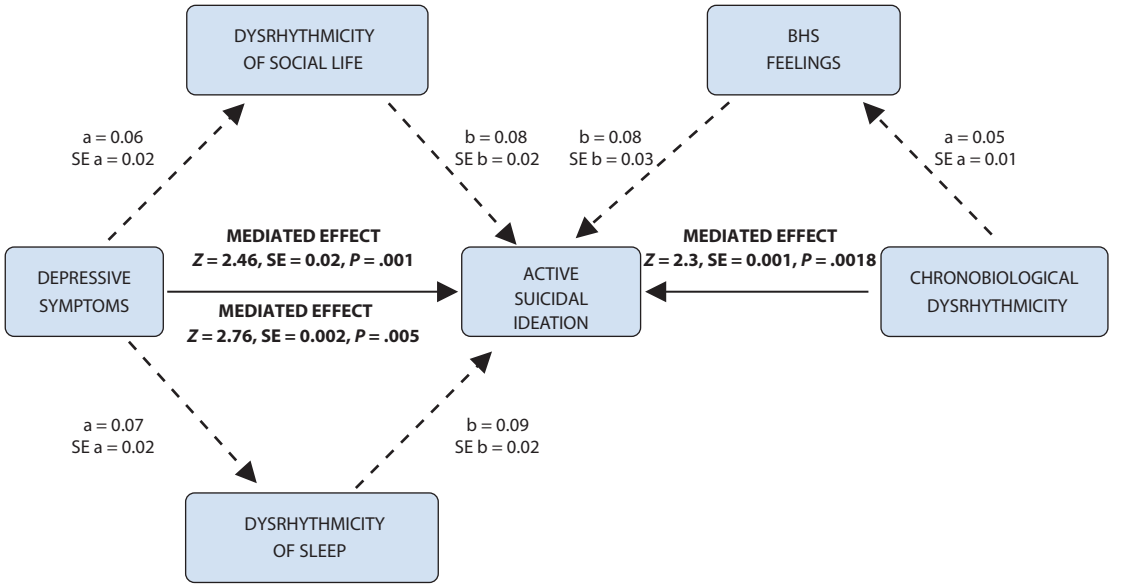
Results of the mediation analyses for active suicidal ideation found that the BRIAN social and BRIAN sleep domains acted as mediators between depressive symptoms and active suicidal ideation (mediator BRIAN social: $Z = 2.46$, SE = 0.02, $P = .001$; mediator BRIAN sleep: $Z = 2.76$, SE = 0.002, $P = .005$) (Figure 1). The emotional part of hopelessness (BHS feelings) acted as a mediator between BRIAN social and active suicidal ideation ($Z = 2.14$, SE = 0.0014, $P = .004$) and between BRIAN total and active suicidal ideation BRIAN total ($Z = 2.3$, SE = 0.001, $P = .0018$) (Figure 1).

Results of the mediation analyses for suicidal plans found that the emotional part of hopelessness (BHS feelings) acted as a mediator between BRIAN social and suicidal plans ($Z = 2.55$, SE = 0.04, $P = .010$; Figure 2) and between active suicidal ideations and suicidal plans ($Z = 3.0$, SE = 0.002, $P = .0002$).

DISCUSSION

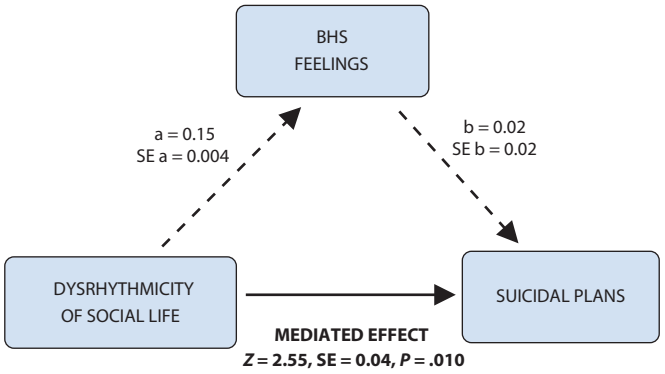
Our results suggested that individuals with clinically significant suicidal ideation more frequently had BD type I with mixed features, with dysrhythmicity of sleep, activities, and social life and a more severe emotional component of hopelessness. This dysrhythmicity of sleep and social life and the emotional component of hopelessness, in addition to a history of previous suicide attempts and greater severity of depressive symptoms, predicted passive and active suicidal ideation and suicidal plans in BD during a depressive episode. We demonstrated that not only hopelessness but also dysrhythmicity of sleep and social life acted as significant mediators in the association between depressive symptoms and passive and active suicidal ideation. Moreover, both negative feelings about the future and chronobiological dysregulation of social life mediated the association between active suicidal ideation and suicidal behaviors. Dysrhythmicity of sleep and social life directly contributed to suicidal ideation and plans, but may also contribute to suicide risk by favoring hopelessness. These findings, especially our mediation analyses, confirmed that BD is a complex disorder involving the interaction of multiple factors; circadian rhythms alterations may be a key factor contributing to the severity of mood symptoms and hopelessness, hence contributing to suicidal behaviors. In this framework, our data appear possibly useful to inform preventive strategies that act on the dysregulation of sleep and circadian rhythms with available chronotherapeutics. These can include bright light therapy, dark therapy,

Figure 1. Chronobiological Dysrhythmicity as a Mediator in the Association Between Depressive Symptoms and Suicidal Ideation[a,b]



[a]Both chronobiological dysrhythmicity of social life and of sleep acted as mediators in the association between depressive symptoms and active suicidal ideation. The emotional component of hopelessness acted as a mediator between chronobiological dysrhythmicity of social life and active suicidal ideation and between chronobiological dysrhythmicity and active suicidal ideation.
[b]Statistical notations in the figure are as follows: a = unstandardized regression coefficient for the association between the independent variable and mediator; SE a = standard error of a; b = coefficient for the association between the mediator (in presence of independent variable) and the dependent variable; SE b = standard error of b; *Z* = Sobel test value. Boldface indicates statistical significance.
Abbreviation: BHS = Beck Hopelessness Scale.

Figure 2. Hopelessness as a Mediator in the Association Between Chronobiological Dysrhythmicity and Suicidal Plans[a,b]



[a]The emotional part of hopelessness acted as a mediator between chronobiological dysrhythmicity social life and suicidal plans.
[b]Statistical notations in the figure are as follows: a = unstandardized regression coefficient for the association between the independent variable and mediator; SE a = standard error of a; b = coefficient for the association between the mediator (in presence of independent variable) and the dependent variable; SE b = standard error of b; *Z* = Sobel test value. Boldface indicates statistical significance.
Abbreviation: BHS = Beck Hopelessness Scale.

treatments utilizing sleep deprivation, melatonergic agonists, interpersonal social rhythm therapy, and cognitive behavioral therapy adapted for BD.[39]

The present study sheds some light on the existing scientific literature. First, we were able to confirm that patients with clinically significant suicidal ideation were more frequently affected by bipolar disorder type I with mixed features.[7,9,10] Patients with clinically significant suicidal ideation had more severe depressive symptoms and levels of hopelessness, confirming previous works,[19–21] but also more chronobiological alterations when compared to patients with non–clinically significant suicidal ideation. Indeed, individuals with suicidal ideation showed a high degree of desynchronization in the rhythms of sleep, activities, and social life. These new data may highlight not only that the majority of individuals with BD present with dysrhythmicity of social life and sleep during depression[28,29,33,34,36] but also that these alterations may represent a state marker for active suicidal ideation and suicidal plans. These findings are in line with recent observations reporting sleep and circadian abnormalities using actigraphy in individuals with BD who attempted suicide[52] and observations reporting the disruption of social rhythms as a key factor for BD.[30]

In our sample, the regression analyses identified that both passive and active suicidal ideation were predicted not only by previous suicide attempts, depressive symptoms, and hopelessness, but also by chronobiological rhythms disruption, in particular the alteration of the rhythmicity of sleep, activities, and social life.

Dysrhythmicity of social life appeared to predict suicidal plans. These findings extend previous work reporting an association between sleep and chronobiological alterations and increased suicidal

risk in BD.[36,42,52] In particular, alterations in social cues may modify the exposure to light, and changes in exposure to light can disrupt in turn the timing of circadian rhythms. According to the social rhythm hypothesis of mood disorders, an irregular exposure to "social zeitgebers" may lead to instability in specific biological rhythms contributing to the alteration of sleep patterns in vulnerable individuals.[30] Accordingly, circadian dysrhythmicity of sleep and social life may alter sleep regulation, hence playing a pivotal role in increasing suicidal risk.[52,53] In the end, the alteration of the "sleep machinery" may play a key role by dysregulating most of the systems involved in mood and emotion regulation, hence contributing to BD severity.[23–25,54]

In particular, dysrhythmicity of sleep, activities, and social life was correlated with the emotional/motivational component of hopelessness. These findings are in line with and clarify previous studies relating chronotype alterations to hopelessness[40,41] and associating *CLOCK* gene polymorphism with hopelessness and suicidal ideation.[42]

Our mediation analyses allowed us to clarify these relationships and revealed that dysrhythmicity of sleep, activities, and social life may act directly on suicidal behaviors but may also act through a mediation effect in the links between depressive symptoms and suicidal ideation and between suicidal ideation and suicidal plans. In addition, chronobiological dysrhythmicity may contribute to the emotional component of hopelessness, hence contributing to active suicidal behaviors. These data are in line with those showing the association between insomnia, hopelessness, and suicidal risk in the nonclinical population.[55] Accordingly, dysrhythmicity of sleep, activities, and social life may contribute to hopelessness in individuals with bipolar disorder during a depressive episode, hence contributing to suicidal risk. This effect may be linked to the alteration of sleep regulation and its effect on emotion and cognition in BD.[56,57]

Taken together, these findings emphasize the need to assess not only the chronotype but also all of the aspects of circadian rhythmicity, including the patterns of sleep/wake, of daily activities, and of social life. We call for implementing the evaluation of sleep and circadian disorders in the routine clinical evaluation of patients with BD. Better screening of these circadian rhythms dimensions could provide additional preventive strategies and/or improve the treatment of mood disorders with chronotherapeutics.[26,27,39,57]

Limitations

These results should be interpreted in light of several limitations including, first, the lack of physiological measures of circadian rhythms. In particular, objective measures such as actigraphy or melatonin and cortisol levels should be used in future studies in bipolar disorder. Second, the cross-sectional design limits any causal interpretations. Consequently, longitudinal studies are needed with larger samples of patients and other types of mood disorders with psychotic symptoms, anxiety, or other features of bipolar disorder but also with individuals who attempted suicide in order to better examine the direction of risk and be able to generalize the findings.

CONCLUSION

This study suggests that (1) individuals with BD during a depressive phase with clinically significant suicidal ideation had greater severity not only of depressive symptoms and of hopelessness, but also of dysrhythmicity of sleep, social life, and activities; (2) this dysrhythmicity of sleep and social life directly predicted passive and active suicidal ideation and suicidal plans, also mediating the role of depressive symptoms on them; (3) chronobiological dysrhythmicity was related to the emotional component of hopelessness, which acted as a mediator in its relationship with suicidal ideation and behaviors; and (4) these findings may have clinical implications for systematic screening of these dysrhythmicity dimensions, for prevention and early intervention with chronotherapeutics.

The evaluation and treatment of sleep and circadian disorders should therefore be included in the routine evaluation of BD and should also encompass dysregulations or difficulties in sleep and circadian rhythms that do not meet full criteria for a specified disorder. Acting on the dysregulation of sleep and circadian rhythms in BD with available chronotherapeutics may have a preventive value for suicidal risk and may favorably impact hopelessness and its consequences with regard to suicidal ideation and behaviors.

Submitted: April 1, 2020; accepted August 3, 2020.
Published online: January 19, 2021.
Potential conflicts of interest: None.
Funding/support: None.

REFERENCES

1. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Arch Gen Psychiatry*. 2011;68(3):241–251.
2. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
3. Moreira ALR, Van Meter A, Genzlinger J, et al. Review and meta-analysis of epidemiologic studies of adult bipolar disorder. *J Clin Psychiatry*. 2017;78(9):e1259–e1269.
4. Fagiolini A, Goracci A. The effects of undertreated chronic medical illnesses in patients with severe mental disorders. *J Clin Psychiatry*. 2009;70(suppl 3):22–29.
5. Ferrari AJ, Norman RE, Freedman G, et al. The burden attributable to mental and substance use disorders as risk factors for suicide: findings from the Global Burden of Disease Study 2010. *PLoS One*. 2014;9(4):e91936.
6. Hayes JF, Miles J, Walters K, et al. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. *Acta Psychiatr Scand*. 2015;131(6):417–425.
7. Tondo L, Pompili M, Forte A, et al. Suicide attempts in bipolar disorders: comprehensive review of 101 reports. *Acta Psychiatr Scand*. 2016;133(3):174–186.
8. Preventing suicide: a global imperative. World Health Organization. 2014. http://www.who.int/mental_health/suicide-prevention/world_report_2014/en/.
9. Miller JN, Black DW. Bipolar disorder and suicide: a review. *Curr Psychiatry Rep*. 2020;22(2):6.
10. Tondo L, Vazquez GH, Baldessarini RJ. Suicidal behavior associated with mixed features in major mood disorders. *Psychiatr Clin North Am*. 2020;43(1):83–93.
11. Valtonen HM, Suominen K, Haukka J, et al. Hopelessness across phases of bipolar I or II disorder: a prospective study. *J Affect Disord*.

2009;115(1-2):11–17.
12. Undurraga J, Baldessarini RJ, Valenti M, et al. Suicidal risk factors in bipolar I and II disorder patients. *J Clin Psychiatry*. 2012;73(6):778–782.
13. Nasrallah HA. Consequences of misdiagnosis: inaccurate treatment and poor patient outcomes in bipolar disorder. *J Clin Psychiatry*. 2015;76(10):e1328.
14. Beck AT. *Depression: Clinical, Experimental, and Theoretical Aspects*. Philadelphia, PA: University of Pennsylvania Press; 1967.
15. Beck AT, Steer RA, Ball R, et al. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67(3):588–597.
16. Beck AT, Weissman A, Lester D, et al. The measurement of pessimism: the Hopelessness Scale. *J Consult Clin Psychol*. 1974;42(6):861–865.
17. Beck AT, Steer RA, Kovacs M, et al. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry*. 1985;142(5):559–563.
18. Wenzel A, Beck AT. A cognitive model of suicidal behavior: theory and treatment. *Appl Prev Psychol*. 2008;12(4):189–201.
19. Hawton K, Sutton L, Haw C, et al. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry*. 2005;66(6):693–704.
20. Latalova K, Kamaradova D, Prasko J. Suicide in bipolar disorder: a review. *Psychiatr Danub*. 2014;26(2):108–114.
21. Klonsky ED, May AM, Saffer BY. Suicide, suicide attempts, and suicidal ideation. *Annu Rev Clin Psychol*. 2016;12(1):307–330.
22. Harvey AG. Sleep and circadian functioning: critical mechanisms in the mood disorders? *Annu Rev Clin Psychol*. 2011;7(1):297–319.
23. McClung CA. How might circadian rhythms control mood? let me count the ways.... *Biol Psychiatry*. 2013;74(4):242–249.
24. Vadnie CA, McClung CA. Circadian rhythm disturbances in mood disorders: insights into the role of the suprachiasmatic nucleus. *Neural Plast*. 2017;2017:1504507.
25. Geoffroy PA. Clock genes and light signaling alterations in bipolar disorder: when the biological clock is off. *Biol Psychiatry*. 2018;84(11):775–777.
26. Dallaspezia S, Benedetti F. Chronobiology of bipolar disorder: therapeutic implication. *Curr Psychiatry Rep*. 2015;17(8):606.
27. Geoffroy PA, Scott J, Boudebesse C, et al. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatr Scand*. 2015;131(2):89–99.
28. Slyepchenko A, Allega OR, Leng X, et al. Association of functioning and quality of life with objective and subjective measures of sleep and biological rhythms in major depressive and bipolar disorder. *Aust N Z J Psychiatry*. 2019;53(7):683–696.
29. Caruso D, Meyrel M, Krane-Gartiser K, et al. Eveningness and poor sleep quality contribute to depressive residual symptoms and behavioral inhibition in patients with bipolar disorder. *Chronobiol Int*. 2020;37(1):101–110.
30. Ehlers CL, Kupfer DJ, Monk TH. Biological rhythms and depression: the role of zeitgeibers and zeitstorers. *Depression*. 1993;1(6):285–293.
31. Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry*. 2012;73(9):e1160–e1167.
32. Gonzalez R. The relationship between bipolar disorder and biological rhythms. *J Clin Psychiatry*. 2014;75(4):e323–e331.
33. Bellivier F, Geoffroy PA, Etain B, et al. Sleep- and circadian rhythm-associated pathways as therapeutic targets in bipolar disorder. *Expert Opin Ther Targets*. 2015;19(6):747–763.
34. Takaesu Y, Inoue Y, Ono K, et al. Circadian rhythm sleep-wake disorders predict shorter time to relapse of mood episodes in euthymic patients with bipolar disorder: a prospective 48-week study. *J Clin Psychiatry*. 2018;79(1):17m11565.
35. Gonzalez R, Tohen M. Circadian rhythm and the prediction of relapse in bipolar disorder. *J Clin Psychiatry*. 2018;79(1):17com11821.
36. Palagini L, Cipollone G, Moretto U, et al. Chronobiological dis-rhythmicity is related to emotion dysregulation and suicidality in depressive bipolar II disorder with mixed features. *Psychiatry Res*. 2019;271:272–278.
37. Rumble ME, Dickson D, McCall WV, et al. The relationship of person-specific eveningness chronotype, greater seasonality, and less rhythmicity to suicidal behavior: a literature review. *J Affect Disord*. 2018;227:721–730.
38. Benard V, Etain B, Vaiva G, et al. Sleep and circadian rhythms as possible trait markers of suicide attempt in bipolar disorders: an actigraphy study. *J Affect Disord*. 2019;244(244):1–8.
39. Gottlieb JF, Benedetti F, Geoffroy PA, et al. The chronotherapeutic treatment of bipolar disorders: a systematic review and practice recommendations from the ISBD Task Force on Chronotherapy and Chronobiology. *Bipolar Disord*. 2019;21(8):741–773.
40. Lester D. Morningness-eveningness, current depression, and past suicidality. *Psychol Rep*. 2015;116(2):331–336.
41. Antypa N, Verkuil B, Molendijk M, et al. Associations between chronotypes and psychological vulnerability factors of depression. *Chronobiol Int*. 2017;34(8):1125–1135.
42. Benedetti F, Riccaboni R, Dallaspezia S, et al. Effects of *CLOCK* gene variants and early stress on hopelessness and suicide in bipolar depression. *Chronobiol Int*. 2015;32(8):1156–1161.
43. Measso G, Cavarzeran F, Zappalà G. Mini-Mental State Examination: new normative values on subjects in southern Italy. *Dev Neuropsychol*. 1993;9(2):77–85.
44. First MB, Williams JBW, Karg RS, et al. *Intervista Clinica Strutturata per i Disturbi del DSM-5. Versione per il Clinico*. Fossati A, Borroni S, eds; Scalabrini A, Somma A, trans. Raffaello Cortina Editore: Milan, Italy; 2017.
45. Giglio LM, Magalhães PV, Andreazza AC, et al. Development and use of a biological rhythm interview. *J Affect Disord*. 2009;118(1-3):161–165.
46. Moro MF, Carta MG, Pintus M, et al. Validation of the Italian Version of the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN): some considerations on its screening usefulness. *Clin Pract Epidemol Ment Health*. 2014;10(10):48–52.
47. Pompili M, Rinaldi G, Lester D, et al. Hopelessness and suicide risk emerge in psychiatric nurses suffering from burnout and using specific defense mechanisms. *Arch Psychiatr Nurs*. 2006;20(3):135–143.
48. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979;47(2):343–352.
49. Conti L. *Repertorio Delle Scale di Valutazione in Psichiatria*. SEE Firenze; 1999.
50. Allega OR, Leng X, Vaccarino A, et al. Performance of the Biological Rhythms Interview for Assessment in Neuropsychiatry: an item response theory and actigraphy analysis. *J Affect Disord*. 2018;225:54–63.
51. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133(5):429–435.
52. Bernert RA, Luckenbaugh DA, Duncan WC, et al. Sleep architecture parameters as a putative biomarker of suicidal ideation in treatment-resistant depression. *J Affect Disord*. 2017;208:309–315.
53. Bernert RA, Kim JS, Iwata NG, et al. Sleep disturbances as an evidence-based suicide risk factor. *Curr Psychiatry Rep*. 2015;17(3):554.
54. Palagini L, Domschke K, Benedetti F, et al. Developmental pathways towards mood disorders in adult life: is there a role for sleep disturbances? *J Affect Disord*. 2019;243:121–132.
55. Woosley JA, Lichstein KL, Taylor DJ, et al. Hopelessness mediates the relation between insomnia and suicidal ideation. *J Clin Sleep Med*. 2014;10(11):1223–1230.
56. Palagini L, Bastien CH, Marazziti D, et al. The key role of insomnia and sleep loss in the dysregulation of multiple systems involved in mood disorders: a proposed model. *J Sleep Res*. 2019;28(6):e12841.
57. Wirz-Justice A, Benedetti F. Perspectives in affective disorders: clocks and sleep. *Eur J Neurosci*. 2020;51(1):346–365.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.