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ORIGINAL ARTICLE

Impact of sleep on clinical outcomes in a cohort of patients with bipolar disorder

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Abstract
Background and Objectives: Sleep disturbances are part of the diagnostic criteria for bipolar disorder (BD). They are prodromal symptoms of the disorder and are present during relapse and euthymia. We aimed to identify the impact of sleep, as an endophenotype, on BD patients in terms of clinical features including suicidality, severity of the disorder, somatic comorbidities, and functionality.
Methods: This is a secondary analysis of a cross-sectional study including 291 outpatients during follow-up at four sites in Spain. The score on the sleep domain of the Hamilton Depression Rating Scale (HDRS_sleep) was used to evaluate current sleep disturbances. Other psychometric tests, such as the Young Mania Rating Scale or the Hamilton Anxiety Rating Scale, were used to assess clinical status. Sociodemographic and other clinical variables were collected. Statistical analysis was performed using IBM SPSS Statistics, Version 27.0. Non-parametric tests and multiple linear regression were used.
Results: Of the 291 patients included in the study, 64.3 % (n = 187) were women. Mean age was 47.86 (SD=12.693). The sample was segmented into two groups: euthymia and non-euthymia, and the analysis was carried out separately in each. We observed no differences in either of these groups in HDRS_sleep with regard to sex, age, metabolic syndrome, coffee intake, or

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smoking. After adjusting for covariates, anxiety and functionality were significantly related to sleep in the non-euthymia group.
Conclusions: Sleep disturbances are frequent in BD, even during euthymia. Its impact on functionality and anxiety levels highlights the importance of targeting sleep in clinical practice to improve the outcome of the disorder.

Introduction

Bipolar disorder (BD) is a chronic, progressive, and episodic disorder that affects more than 1 % of the population worldwide.[1]

Sleep disturbances are included in the diagnostic criteria for BD in both DSM-5 and ICD-11[2,3] and are related to higher risk of suicide, worse functionality, and worse outcome.[4-6] These disturbances are not only present during manic/hypomanic and depressive episodes but persist during euthymia.[7,8] They are robust prodromal symptoms that can be used to predict relapse. In fact, they have been found to be the most common prodromal symptoms for mania and the sixth most common for depression in BD.[9]

Sleep impairment is not only a symptom of BD but can also be considered a common comorbidity.[10] Moreover, disturbed sleep may be present since puberty, conferring a higher risk of developing BD,[11,12] even among patients with no family history of the disorder.[13] It has also been associated with a younger onset of BD.[10]

The sleep/wake cycle is a circadian rhythm, and as such, is regulated by the suprachiasmatic nucleus. Circadian rhythms are influenced by zeitgebers (environmental cues that entrain the 24-hour light/dark cycle).[14] Some of the most important zeitgebers are ones that are especially relevant to the peripheral clocks (circadian pacemakers located in peripheral tissues, which are connected through different pathways to the central clock: the suprachiasmatic nucleus).[15,16] These include not only light, but also habits related to functionality, such as social interaction. Findings on the association of circadian rhythm biomarkers and sleep disturbances in bipolar disorder are heterogenous and inconclusive.[17] However, sleep disturbances, as a symptom, have proven the most robust marker of circadian rhythm disruption in mood disorders.[6]

This study aimed to identify the impact of sleep on the outcomes of patients with BD (euthymic and no-euthymic separately) in terms of clinical features including suicidality, severity of the disorder, comorbidities, and functionality. We hypothesized a lower impact in terms of severity and dimensions affected on clinical outcomes in euthymic patients.

We chose sleep as an endophenotype since it has been found to be a strong predictor of relapse, impaired even during euthymia, and easily approached in a cost-effective and non-invasive way in daily clinical practice.

Material and methods

This is a secondary analysis of a multi-centre cross-sectional cohort study (Ref. PI11/02,493) of a sample of 291 outpatients diagnosed with BD according to DSM-IV-TR criteria, during follow-up and treatment. The study was conducted at four sites in Spain [Oviedo, Valencia, and two sites in Barcelona].

Patients

Individuals were included in the study based on the following criteria: a SCID-I-confirmed diagnosis of BD according to DSM-IV-TR; age $\geq$ 18 years; and written informed consent to participate in the study. Exclusion criteria consisted only of refusal to participate in the study.

Assessments

Sociodemographic and clinical variables were collected, along with data related to the course of the disorder, such as history of suicide attempts, number of manic and depressive episodes, age of onset of BD, and psychoactive drugs (Table 1).

Current status of the illness was measured using the validated Spanish version of both the Hamilton Depression Rating Scale[18] (HDRS), the Young Mania Rating Scale[19] (YMRS), and the Hamilton Anxiety Rating Scale[20] (HARS). To evaluate cognitive status, we used the Spanish version of the Screen for Cognitive Impairment in Psychiatry[21] (SCIP). Functionality was evaluated using the Functioning Assessment Short Test[22] (FAST). The sleep domain of the HDRS (HDRS_sleep) was used to evaluate current sleep disturbances. This domain is obtained by adding up items 4 (early insomnia), 5 (middle insomnia), and 6 (late insomnia) of the HDRS. All items score from 0 to 2. The total score varies from 0 (no difficulties in any phase of sleep) to 6 (difficulties in all phases of sleep). The HDRS is not a specific test to measure sleep, but it has been found to be consistent with results obtained in polysomnography, especially in early and late insomnia.[23] Moreover, in a previous study, the sleep item of the Montgomery Asberg Depression Rating Scale (MDRS) was used as well to evaluate sleep.[8]

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics, Version 27.0. The significance level was set at $p < 0.05$. Means and standard deviations (SD) and frequencies and percentages were used to describe sociodemographic and clinical characteristics.

Since the HDRS_sleep variable did not follow a normal distribution, non-parametric tests were used. A Mann-Whitney U test was performed to identify associations between HDRS_sleep and sex, history of suicide attempts, metabolic

Table 1 Sociodemographic and clinical variables.

Sample characteristics	Euthymia (*n* = 137)	Non-euthymia (*n* = 154)
Sociodemographic characteristics		
Mean age [mean (SD)]	47.45 (12.83)	48.23 (12.61)
Sex, females [*n* (%)]	86 (62.8)	101 (65.6)
Clinical features		
Age of onset [mean (SD)]	27.52 (9.77)	27.16 (10.82)
Age of diagnosis [mean (SD)]	35.58 (12.67)	36.06 (11.93)
Hospitalisations [mean (SD)]	2.23 (2.37)	2.19 (2.98)
Manic episodes [mean (SD)]	2.20 (2.34)	2.45 (4.74)
Hypomanic episodes [mean (SD)]	1.95 (3.43)	3.50 (8.68)
Depressive episodes [mean (SD)]	2.79 (3.71)	5.17 (6.90)
Mixed episodes [mean (SD)]	0.87 (2.93)	2.04 (7.05)
Number of suicide attempts [mean (SD)]	0.41 (1.45)	0.92 (1.47)
History of suicide attempts [*n* (%)]	29 (21.3)	66 (42.9)
Metabolic syndrome [*n* (%)]	27 (19.7)	44 (28.6)
Cups of coffee per day* [mean (SD)]	2.34 (1.44)	2.25 (2.47)
Cigarettes per day** [mean (SD)]	15.77 (9.22)	16.27 (10.62)
BMI [mean (SD)]	27.66 (4.79)	29.74 (6.26)
Psychometric tests		
CGI [mean (SD)]	3.19 (1.38)	4.18 (1.11)
HDRS [mean (SD)]	3.02 (1.92)	12.60 (5.95)
HDRS_Sleep [mean (SD)]	0.31 (0.70)	1.47 (1.63)
HDRS_Melancholy [mean(SD)]	1.69 (1.79)	6.77 (3.54)
HDRS_Anxiety [mean(SD)]	0.74 (1.073)	3.24 (1.79)
HDRS_Vitality [mean(SD)]	1.36 (1.57)	5.01 (2.94)
HARS [mean (SD)]	4.84 (3.78)	16.04 (8.13)
YMRS [mean (SD)]	1.28 (1.72)	4.45 (4.89)
SCIP [mean (SD)]	63.89 (16.56)	60.95 (18.05)
FAST_Autonomy [mean (SD)]	2.26 (2.71)	5.06 (3.57)
FAST_Work [mean (SD)]	6.98 (5.92)	10.66 (5.18)
FAST_Cognition [mean (SD)]	4.97 (3.83)	7.46 (4.08)
FAST_Economics [mean (SD)]	0.83 (1.57)	1.91 (2.10)
FAST_Personal relations [mean (SD)]	3.86 (3.55)	6.84 (4.11)
FAST_Leisure [mean (SD)]	1.96 (1.80)	3.34 (1.93)
FAST_T [mean (SD)]	21.14 (14.07)	35.27 (15.32)
Psychoactive drugs (yes/no)		
Lithium [*n* (%)]	83 (62.4)	71 (49)
Benzodiazepines [*n* (%)]	58 (45.7)	103 (75.2)
Antidepressants [*n* (%)]	55 (40.1)	97 (63.0)
Antipsychotics [*n* (%)]	136 (99.3)	153 (99.4)
Mood Stabilizers [*n* (%)]	54 (39.4)	87 (56.5)

BMI: body mass index; CGI: The Clinical Global Impressions Scale; HDRS: Hamilton Depression Rating Scale; HDRS_Sleep: Sleep domain of the Hamilton Depression Rating Scale; HARS: The Hamilton Anxiety Rating Scale; YMRS: The Young Mania Rating Scale; SCIP: Screen for Cognitive Impairment in Psychiatry; FAST: Functioning Assessment Short Test; MS: mood stabilizers other than lithium.

* Only for subjects who had ≥ 1 cup of coffee per day.

** Only for smokers.

syndrome, and psychoactive drugs. Spearman's R was used when analysing correlations between HDRS_sleep and sociodemographic, clinical, and psychometric variables. A multiple linear regression was used with HDRS_sleep as a dependent variable to adjust for covariates. When doing so, we discarded the HDRS total score to minimize the risk of potential bias, since HDRS_sleep results are obtained by adding up four items of the scale. However, we did include the melancholy and vitality domains of the HDRS, considering them to be of clinical importance.

Results

A total of 291 individuals were included in the study, of whom 64.3 % (*n* = 187) were women. Mean age was 47.86 (SD = 12.693). Age of onset of the disorder was 27.33 (SD = 10.328) and age of diagnosis was 35.84 (SD = 12.256). More than two-thirds of the sample were diagnosed with Type I BD (69.4 %), and only a small percentage had other types of BD like cyclothymia or substance-induced BD (0.3 %).

Almost half of the sample (137 subjects, 47.1 %) were euthymic (YMRS $\leq$ 6 and HDRS $\leq$ 7). Most of the patients in the non-euthymia group were in a sub-depressive or depressive phase (YMRS $\leq$ 6 and HDRS > 7) at the time of the assessment (n = 111, 72 %). When analysing the differences in HDRS_sleep score between euthymia and non-euthymia groups, the latter reported poorer sleep (0.31 vs 1.47, $p < 0.001$). However, when dividing the non-euthymia group into manic/mixed (n = 43) and depressive (n = 111) episodes, no differences were found in HDRS_sleep score (p = 0.630). Therefore, we decided to perform all analyses separately for the euthymia and non-euthymia groups.

Euthymia group

Sociodemographic, clinical, and psychometric characteristics of these patients are shown in Table 1. Mean HDRS_sleep score was 0.31 (SD = 0.70), and 22.6 % had a score $\geq$ 1.

We observed no differences in HDRS_sleep with regard to sex, age, cigarettes and cups of coffee per day, or metabolic syndrome (Table 2). We found that the more manic or mixed episodes (p = 0.047, p = 0.017, respectively) a subject had, the milder the sleep impairment was. Individuals reported poorer sleep when depressive symptoms were more severe (p = 0.016). As for current psychoactive drugs, those who used a prescription mood stabilizer other than lithium reported better sleep than those who did not (HDRS_sleep score 0.15 vs 0.41; U = 1873.5, p = 0.026) (Table 2). Finally, when applying the multiple linear regression, no variables entered the model.

Non-euthymia group

Sociodemographic, clinical, and psychometric characteristics of these patients are shown in Table 1. Mean HDRS_sleep score was 1.47 (SD = 1.63), and 63.6 % scored $\geq$ 1.

We observed no differences in HDRS_sleep with regard to sex, age, cigarettes and cups of coffee per day, or metabolic syndrome (Table 2). As shown in Table 2, HDRS_sleep score positively and significantly correlated with longtime number of depressive episodes, history of suicidality, and depressive and anxious symptomatology, as well as functionality domains.

The multiple linear regression obtained a model that explained 15.9 % of the variance (F = 12.892, $p < 0.001$). The model retained only two variables: HARS total score ($p < 0.001$; β = 0.321) and the FAST autonomy domain (p = 0.035; β = 0.183) (Table 3).

Depressed patients in the non-euthymia group

A new analysis was conducted in the depressive subgroup to control for possible clinical bias, considering the clinical differences between mania and mixed episodes and depressive episodes. Mean HDRS_sleep score was 1.62 (SD = 1.55), and 72.5 % scored $\geq$ 1. In the bivariate analysis, the only difference from the results of the whole non-euthymia group was a lack of statistical significance between HDRS_sleep and suicidal behaviour (Supplementary Table 1).

When applying the regression, the model explained 13.4 % of the variance (F = 8.170, $p < 0.001$), and only the FAST cognitive domain entered the model (beta = 0.265, t = 2.471, $p < 0.05$).

Discussion

Our results show that sleep disturbances are frequent in patients with BD, even during euthymia, although lower than in non-euthymia patients (almost one in four patients vs two in three showed some sleep impairment, respectively). Severity of sleep disturbances is associated with severity of BD, especially in terms of comorbidity and self-care, only in non-euthymic patients after controlling for confounding factors.

Sleep disturbances and their impact in euthymic patients

Prevalence of sleep disturbances in the euthymia group is noteworthy (22 %), although it is important to note that most of these subjects reported no trouble sleeping at all. The small sample size of those with sleep disturbances could be partly responsible for these results. Previous studies have reported a wide prevalence range (15—100 %) of these disturbances in euthymia.[8,24-27] Our results are closer to those studies obtaining lower prevalences.[26,27]

We were not able to find a significant model explaining the impact of sleep impairment on the clinical outcomes of euthymic patients, but some interesting correlations were found in the partial analysis that we would like to discuss.

Past manic and depressive episodes have been related to a poorer BD outcome and worse functionality, as well as psychiatric (including sleep disturbances[28]) and medical comorbidities.[29] Mixed episodes are typically related to greater severity of BD, as has already been highlighted in previous studies,[30-32] and are unlikely in the absence of sleep disruptions.[33] In our study, surprisingly, it is mixed and manic episodes that showed a negative correlation to sleep during phases of BD remission. One possible reason for this finding is that it is more likely to be treated with mood stabilizers when presenting with more manic or mixed episodes, which can affect sleep. It has been observed that lithium influences the expression of circadian genes,[34] so when used chronically, it could modify genetic expression and influence positive changes in circadian rhythmicity. On the other hand, other mood stabilizers, especially valproic acid[35] and, to a lesser extent, lamotrigine[36] have more sedative effects. This might be why patients treated with a mood stabilizer other than lithium reported better sleep.

A previous study has found a significant association between poorer sleep quality and a higher level of state anxiety in BD patients in euthymia as measured with the State-Trait Anxiety Inventory (STAI).[37] On the contrary, our results did not show a statistically significant relationship between anxiety and sleep during euthymia.

As for suicidal behaviour, we did not observe poorer sleep to be associated with past suicide attempts in euthymic patients, as other authors have previously published.[8,37] Both in those studies and our own, the samples are cohorts, but different psychometric instruments were used to

Table 2 Sociodemographic and clinical variables in euthymia and non-euthymia in relation to the sleep domain of the Hamilton Depression Rating Scale (HDRS_sleep).

Sample characteristics	Euthymia (n = 137) Statistical test, p	Non-euthymia (n = 154) Statistical test, p
Sociodemographic characteristics		
Sex	2175.5[1], 0.915	2354.0[1], 0.203
Age	0.037[2], 0.668	0.069[2], 0.392
Clinical features		
Age of onset	0.117[2], 0.186	−0.035[2], 0.671
Age of diagnosis	0.043[2], 0.631	0.075[2], 0.366
Hospitalisations	0.081[2], 0.358	0.034[2], 0.680
Manic episodes	−0.176[2], 0.047	−0.008[2], 0.925
Hypomanic episodes	0.027[2], 0.763	0.070[2], 0.403
Depressive episodes	−0.025[2], 0.782	0.238[2], 0.004
Dysthymic episodes	0.121[2], 0.184	−0.022[2], 0.805
Mixed episodes	−0.216[2], 0.017	0.067[2], 0.442
Number of suicide attempts	−0.017[2], 0.842	0.203[2], 0.012
History of suicide attempts	1518.0[1], 0.808	2354.5[1], 0.037[a]
Cups of coffee per day*	−0.131[2], 0.249	−0.021[2], 0.859
Cigarettes per day**	0.085[2], 0.515	0.113[2], 0.380
BMI	0.090[2], 0.309	0.028[2], 0.736
Metabolic syndrome	1291.0[1], 0.786	1798.0[1], 0.143
Psychometric tests		
CGI	−0.029[2], 0.738	0.100[2], 0.223
HDRS_T	0.206[2], 0.016	0.478[2], 0.000
HDRS_Melancholy	0.020[2], 0.817	0.255[2], 0.001
HDRS_Anxiety	0.095[2], 0.268	0.096[2], 0.235
HDRS_Vitality	0.069[2], 0.423	0.170[2], 0.035
HARS	0.141[2], 0.100	0.374[2], 0.000
YMRS	0.085[2], 0.325	−0.062[2], 0.445
SCIP	−0.149[2], 0.087	−0.100[2], 0.222
FAST_Autonomy	0.033[2], 0.700	0.182[2], 0.025
FAST_Work	−0.111[2], 0.216	0.167[2], 0.049
FAST_Cognition	0.099[2], 0.251	0.244[2], 0.002
FAST_Economics	0.086[2], 0.319	0.190[2], 0.019
FAST_Personal relations	0.012[2], 0.888	0.172[2], 0.036
FAST_Leisure	−0.062[2], 0.471	0.195[2], 0.015
FAST_T	−0.042[2], 0.645	0.257[2], 0.002
Psychoactive drugs (yes/no)		
Lithium	1881.5[1], 0.223	2315.0[1], 0.201
Benzodiazepines	1869.5[1], 0.384	1600.5[1], 0.437
Antidepressants	2211.5[1], 0.793	2294.0[1], 0.068
Antipsychotics	52.5[1], 0.591	14.5[1], 0.148
Mood Stabilizers	1873.5[1], 0.026[b]	2595.5[1], 0.228

BMI: body mass index; CGI: The Clinical Global Impressions Scale; HDRS: Hamilton Depression Rating Scale; HDRS_Sleep: Sleep domain of the Hamilton Depression Rating Scale; HARS: The Hamilton Anxiety Rating Scale; YMRS: The Young Mania Rating Scale; SCIP: Screen for Cognitive Impairment in Psychiatry; FAST: Functioning Assessment Short Test; MS: mood stabilizers other than lithium.

[1] Mann-Whitney U.

[2] Spearman's R.

[a] HDRS_sleep in patients with past history of suicide attempts (1.77 vs 1.25).

[b] HDRS_sleep in patients treated with MS vs not treated with MS (0.15 vs 0.41).

[*] Only for subjects who had ≥ 1 cup of coffee per day.

[**] Only for smokers.

measure sleep (Pittsburgh Sleep Quality Index, the sleep item of the Montgomery-Asberg Depression Rating Scale, and the sleep domain (three items) of the HDRS, respectively). The different results might be a consequence of this heterogeneity in methodology.

Sleep disturbances and their impact in non-euthymic patients

In non-euthymic patients, over 60 % of the patients showed some kind of sleep impairment. This is compatible with the

Table 3 Multiple linear regression model explaining HDRS_sleep score in the non-euthymia group (n = 154).

	B	Beta	t	p	Multicollinearity (VIF)
Constant	−0.106		−0.314	0.754	
HARS_T	0.069	0.321	3.733	<0.001	1.104
FAST_Autonomy	0.085	0.183	2.130	0.035	1.104

HARS: The Hamilton Anxiety Rating Scale; FAST: Functioning Assessment Short Test.

lower range of the results obtained in a review, which found that 69−100 % of patients experienced sleep disturbances during manic or depressive phases.[28]

As for anxiety, association with sleep disturbances was reported in euthymic patients.[37] In our case, this association was observed only in non-euthymic patients. In addition, in high-risk youths, both sleep disorders and anxiety have been identified as risk factors for the onset of BD.[11]

In terms of functionality, our results are consistent with previously published studies that have observed better functioning with improved sleep quality, among other variables.[38] Other authors also emphasize the relationship between sleep disturbances and worse functionality, as well as severity of depressive and manic symptoms.[5,39] Additionally, many daily activities that are part of functionality are considered zeitgebers and are of great importance to the regulation of circadian rhythms, including sleep. This suggests that improving functionality could be a way to ameliorate sleep.

When analysing the depressed subgroup in the non-euthymia group, only cognitive functionality showed a significant association with sleep disturbances. This reiterates the importance of functionality impairment in BD and its relationship with sleep disorders, as noted before. More specifically, sleep impairment is associated with worse cognitive performance in BD.[28] Likewise, in keeping with our results, sleep disturbances have been indirectly associated with functioning through residual depressive symptoms and perceived cognitive performance.[40] Nonetheless, the effects of cognitive impairment in bipolar depression are still unclear, but it seems to play an important role in the disability experienced by patients with BD.[41]

These findings should be interpreted cautiously, for this study has limitations. It is a cross-sectional study; thus, it is not possible to evaluate the causality of sleep vis-a-vis the clinical course of the sample. Furthermore, there is no control group, and no objective measures or specific sleep questionnaires were used to evaluate sleep.

One of the most important strengths of our study is the fact that sleep is evaluated in both euthymic and non-euthymic patients, whereas most previous studies have been carried out only in euthymia. Controlling for effects of psychoactive drugs in sleep is also worth mentioning, since they can affect sleep quality and architecture. Moreover, using affordable and non-invasive instruments to evaluate sleep such as the sleep domain of the HDRS, which has previously been used to assess sleep impairment and its association with biomarkers in BD,[42,43] makes the study more accessible for participants in all stages of the disorder and easier to replicate.

Conclusions

Sleep disturbances are a frequent symptom in BD, even during euthymia. Its impact on functionality and anxiety levels highlights the importance of targeting sleep in daily clinical practice in order to improve the outcome of the disorder.

Ethical considerations

The Clinical Research Ethics Committee of Hospital Universitario Central de Asturias in Oviedo approved the study protocol (refs. 36/12 and 142/15). Written informed consent was obtained from all participants prior to enrolment.

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Declaration of competing interest

The authors declare no conflict of interest related to this study.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ejpsy.2024.100264.

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