CNS Spectrums (2020), **25**, 32–37. © Cambridge University Press 2019
doi:10.1017/S1092852918001700

ORIGINAL RESEARCH

Can sleep disturbance be a cue of mood spectrum comorbidity? A preliminary study in panic disorder

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Objective. To investigate if sleep disturbances may affect treatment outcomes of patients with panic disorder (PD).

Methods. Eighty-five PD outpatients with no Axis I comorbidity for mood disorders completed a baseline assessment (T1) and were evaluated after 3 (T2), 6 (T3) and 12 months (T4), with the Panic Disorder Severity Scale (PDSS) total score as outcome measure during a 12-month naturalistic follow-up. Patients were assessed with the Mood Spectrum Self-Report (MOODS-SR, Lifetime Version), and the PDSS.

Results. Forty-three patients (50.5%) met criteria for remission (PDSS<5) and 42 (49.5%) for no remission. In a logistic regression model with *remission* as the dependent variable, MOODS-SR *sleep disturbances* was the only determinant for a lower likelihood of PD remission. The items accounting for this result were the following: *Repeated difficulty falling asleep* (chi-square = 4.4; df = 1; $p = 0.036$), and *Repeatedly waking up in the middle of the night* (chi-square = 5.2; df = 1; $p = 0.022$).

Conclusion. Lifetime sleep disturbances would represent a cue of mood spectrum (in absence of overt affective comorbidity) that may impair remission in PD.

Received 20 August 2018; Accepted 30 November 2018

Key words: Mood spectrum, panic disorder, sleep disturbances, treatment outcome, comorbidity.

Introduction

Sleep disturbances are quite common in both mood and anxiety disorders that on the other side frequently co-occur.[1] Furthermore, any impairment of sleep quality and continuity predisposes subjects to the development or to the exacerbation of mood and anxiety disorders and vice versa, as well as to poorer treatment outcomes and to an increased risk for relapses/recurrences in depressed patients.[2] Data on the relationship between sleep disturbances and mood disorders are consistent[3–6]; conversely, the information on sleep disturbances in panic disorder (PD) is limited. The occurrence of nocturnal panic attacks is traditionally considered around 18% of all panic attacks, but may be present in 44–71% of PD patients.[7,8] Mellman and Uhde (1990)[9] suggest that 67% of PD patients report insomnia as a relevant problem. However, there is no agreement regarding the objective severity of sleep disturbances in this population, and on their impact on course/treatment response. Most of the reports are based on subjective statements of the patients, and polysomnographic studies are inconsistent. According to Ferini-Strambi et al.,[10] there is no difference between control subjects and PD patients in sleep induction and maintenance parameters, but the percentage of non-Rapid Eye Movements (REM) sleep stage 1 is increased in PD patients when compared with healthy controls. A significant improvement of PD is not usually accompanied by a corresponding improvement of major sleep variables.[11] A recent study shows that PD patients experience sleep disturbances even after PD symptomatic remission while suggesting that they are not simply consequent to nocturnal panic attacks, or to the severity of PD core manifestations.[12]

According to a different perspective, as postulated by the spectrum model proposed by Cassano et al.,[13] sleep disturbances may be considered a dimension crossing and/or underlying both Axis I categories and

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sub-threshold syndromes: indeed sleep disturbances have been considered as a transdiagnostic process in psychiatric disorders, by contributing to their onset and course.[3-6,14] In this framework, the mood spectrum model refers to a dimensional view of mood disorders that encompasses their most typical symptoms, including sleep disturbances, and also a range of more subtle features less easily detectable which may include sleep disturbances as well.[13,14] The mood spectrum manifestations might be present in patients who never suffered from a full-blown mood disorder, but who may be affected by other psychiatric disorders, such as PD,[15] obsessive-compulsive disorder (OCD), social phobia (SP),[16] or eating disorders (EDs),[17] thus determining a clinical condition of *sub-threshold* (or spectrum) mood comorbidity.

The aim of this study was to evaluate the impact of sleep disturbances, as assessed by the Mood Spectrum Self-Report Questionnaire (MOODS-SR)[18] on clinical features and treatment response of PD patients without a full-blown comorbidity for mood disorders.

Material and Methods

Study sample

Outpatients referred by primary care physicians underwent a psychiatric screening at the Section of Psychiatry of the University of Pisa, Italy. Those who met DSM-IV-TR criteria for current PD with or without agoraphobia,[19] and volunteered in participating in a naturalistic follow-up, were provided with a complete description of the study and gave written informed consent for participation. We included patients who met the following criteria at baseline: Panic Disorder Severity Scale (PDSS)[20] total score > 7; no current major depression; no past or current Bipolar Disorder (BP).

Pharmacological treatments were guided by published international standards (American Psychiatric Association Guidelines, APA, 2000)[21] and provided by clinical physicians within the framework of a naturalistic follow-up. Structured psychotherapy was not included as a treatment option. Patients with full-blown BPs were excluded for three reasons: (a) the hierarchical position of BP on PD; (b) the potential implications of treatment with mood stabilizers or neuroleptics; and (c) the heterogeneity of clinical presentation of PD, when a BP has been diagnosed even in the past. According to international standards for PD (APA Guidelines, 2000; National Institute for Health and Care Guidelines, NICE, 2011),[21,22] treatment goals were the following: reducing frequency and intensity of panic attacks, reducing anticipatory anxiety and agoraphobic avoidance, and achieving symptomatic remission. Participants were asked to complete a baseline assessment (T0) with the Structured Clinical Interview for DSM-IV Disorders (SCID-I) administered by a rater trained and certified in its use,[23] the PDSS,[20] and the MOODS-SR,[18] and to participate in follow-up evaluations after 1 month (T1), 3 (T2), 6 (T3) and 12 months (T4), with the PDSS as outcome measure.

Follow-up procedures were approved by the Ethical Committee of the Azienda Ospedaliero-Universitaria of Pisa (Italy), according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the authors' institutional review board.

Instruments

Panic Disorder Severity Scale (PDSS)[20]

The PDSS is a 7-item scale each with a 5-point rating system, ranging from 0 to 4. Adding the scores for all seven items makes the overall assessment. The total score ranges from 0 to 28. The seven items assess the overall severity of PD, including the frequency and severity of panic and limited symptom episodes, such as severity of anticipatory anxiety, phobic avoidance and functional impairment.[21] Remission was defined as a PDSS score <5, according to published guidelines for the interpretation of the PDSS scores.[24,25]

Mood Spectrum Self-Report questionnaire lifetime version (MOODS-SR)[18]

MOODS-SR assesses lifetime symptoms, traits and lifestyles that characterize threshold and sub-threshold mood episodes as well as "temperamental" features related to mood dysregulations. It consists of 161 symptoms coded as *present* or *absent* for one or more periods of at least 3–5 days throughout the subject's lifetime. For some questions, such as exploring temperamental features or the occurrence of specific events the duration is not specified because not applicable for a limited timeframe. Summing the scores for the dichotomous items makes the overall assessment, but seven impairment items are not scored (total score ranging between 0 and 154). Items with multiple responses are coded "1"if at least one of the responses is scored positively, and "0"elsewhere. Items are organized into manic/hypomanic, depressive and rhythmicity/vegetative domains. Manic and depressive domains are sub-typed in three sub-domains, each exploring *mood, energy, and cognition*. The sum of mood, energy, and cognition manic items made the overall manic component score (range: 0–62); the sum of mood, energy, and cognition depressive items made the overall depressive component score (range: 0–63). Twenty-nine items compose the rhythmicity/vegetative function domain (range: 0–29): It explores alterations in circadian rhythms and vegetative functions, including sleep dysregulations. The sleep items are 12 out of 29 and explore in a lifetime perspective the presence/absence of sleep disturbances related to sub-threshold mood dysregulations. For the purposes of this study, we extracted the MOODS-SR sleep items that are

https://doi.org/10.1017/S1092852918001700 Published online by Cambridge University Press

TABLE 1. Panic Disorder Severity Scale scores at baseline and at each follow-up

	T0 Baseline Mean/SD	T1 1 month Mean/SD	T2 3 months Mean/SD	T3 6 months Mean/SD	T4 1 year Mean/SD
PDSS					
Total score	14.6 ± 4.9	10.4 ± 5.7	7.9 ± 5.2	5.8 ± 4.6	4.9 ± 4.4
Panic attacks	4.3 ± 1.6	2.8 ± 1.6	1.4 ± 0.9	1.3 ± 1.4	1.0 ± 1.4
Anticipatory anxiety	2.2 ± 1.0	1.7 ± 0.9	2.0 ± 1.6	1.1 ± 0.8	0.9 ± 0.8
Agoraphobia	4.1 ± 1.9	3.1 ± 2.2	2.5 ± 2.0	1.7 ± 1.7	1.8 ± 1.8
Impairment	3.9 ± 2.0	2.5 ± 2.1	1.9 ± 1.9	1.4 ± 1.7	1.0 ± 1.3

Note. PDSS, Panic Disorder Severity Scale.

12 out of 29 and explore, in a lifetime perspective, the presence/absence of sleep disturbances related to sub-threshold mood dysregulations. However, for this preliminary study, no psychometric validation of this sleep domain/dimension has been carried out.

The reliability of the interview proved to be excellent: the inter-rater reliability of domains ranged between 0.93 and 0.94, and the internal consistency of domains ranged between 0.79 and 0.92. There was a high correlation between the SCI for the Mood Spectrum (SCI-MOODS) and the questionnaire of the MOODS assessment (Intra Class Correlation = 0.97), whose reliability and validity have been successively confirmed.[18]

Statistical analyses

Statistical analyses were performed using the SPSS statistic version 17.0. Results were expressed as mean ± standard deviation (SD) or percentages. The Shapiro–Wilk test was used to check the normality of the variables. Differences in means between "remitters" and "non-remitters" were assessed using *t*-tests for normally distributed variables, or the Mann–Whitney *U*/Wilcoxon test for not-normally distributed variables. Mean *p*-values were adjusted for the number of tests using the Bonferroni correction with a significance of $p < 0.05$. Univariate linear and/or logistic regression analyses were performed to test the correlates of lifetime mood spectrum and of its domains, such as depressive, manic/hypomanic, rhythmicity, sleep disturbances, and PD non-remission or remission.

Results

The study sample included 85 outpatients suffering from PD (55 women and 30 men, mean age + SD: 34.5 ± 12.5 years). Seventy-five patients (88.2%) met SCID-I criteria for PD with agoraphobia, 10 (11.8%) for PD without agoraphobia (11.8%).

The most prescribed drugs were SSRIs (63.2%), specifically in decreasing order, paroxetine and citalopram ($n = 87$, 21%), sertraline ($n = 70$, 16.9%), fluvoxamine ($n = 13$, 3.1%), and fluoxetine ($n = 5$, 1.2%). Tricyclics were also administered ($n = 98$, 23.6%), namely trimipramine ($n = 57$, 13.8%), imipramine ($n = 27$, 6.5%), clomipramine ($n = 11$, 2.6%), desipramine ($n = 2$, 0.4%), and amitriptyline ($n = 1$, 0.2). Venlafaxine was prescribed in seven (1.6%), and trazodone in three (0.7%) cases. Delorazepam was the most frequently prescribed benzodiazepines ($n = 26$, 6.2%), followed by alprazolam ($n = 12$; 2.9%), and diazepam ($n = 3$, 0.7%). Zolpidem was prescribed only in two cases (0.4%).

Effect of lifetime MOODS-SR domains on PD severity at baseline

The mean total PDSS scores at the different time points were 14.6 ± 4.9 at baseline, 10.4 ± 5.7 at T1, 7.9 ± 5.2 at T2, 5.8 ± 4.6 at T3, and 4.9 ± 4.4 at T4. The scores of the PDSS single items (panic attacks, anticipatory anxiety, phobic avoidance, and impairment) at baseline and at each time point are reported in Table 1. Lifetime mood spectrum total scores at baseline were, respectively, 50.2 ± 21.4 (range: 0–154), 22.4 ± 11.8 for the depressive domain (range: 0–62), 17.5 ± 9.4 for the manic/hypomanic domain (range: 0–63), and 10.3 ± 4.9 for the rhythmicity/vegetative function domain (range: 0–29). No correlation was found between total baseline PDSS score and lifetime mood spectrum total score or depressive, manic or rhythmicity domain scores (respectively, coeff. = 0.12, $p = 0.15$, coeff. = 0.09, $p = 0.45$, coeff = 0.10, $p = 0.32$), using a univariate regression analysis.

Effect of lifetime MOODS-SR domains on PD severity at follow-up

Lifetime spectrum scores had a significant effect, but scarce, on PDSS outcome. Only the MOODS-SR depressive and rhythmicity/vegetative functions domains were associated with outcomes (anticipatory anxiety), with low/moderate statistical correlations. Thus, results of the univariate analyses showed a positive correlation between higher scores at the rhythmicity/vegetative functions domain and higher PDSS scores (coeff. = 0.233; $p = 0.03$), and PDSS *panic frequency* and *severity* (coeff. = 0.25; $p = 0.02$) at T1. Higher scores in MOODS-SR

https://doi.org/10.1017/S1092852918001700 Published online by Cambridge University Press

TABLE 2. Mood spectrum components in panic disorder "remitters" and "non-remitters"

MOODS-SR lifetime scores	PDSS "non-remitters" ($n = 42$) mean/SD	PDSS "remitters" ($n = 43$) mean/SD	Coeff.	p
Depressive score	24.8 ± 11.0	19.9 ± 12.0	1.9	0.056
Manic score	18.8 ± 10.3	16.2 ± 8.3	1.2	0.214
Rhythmicity score	11.2 ± 4.7	9.3 ± 4.8	1.7	0.085
Sleep disturbances total score	4.8 ± 2.4	3.4 ± 2.4	2.6	**0.011**
MOODS-SR total score	54.9 ± 21.3	45.6 ± 20.7	2.0	**0.045**

Note. MOODS-SR Lifetime, Mood Spectrum Self-Report Questionnaire Lifetime Version; PDSS, Panic Disorder Severity Scale. Significance $p < 0.05$ in bold.

depressive and rhythmicity/vegetative functions domains were positively correlated with higher anticipatory anxiety scores at T1 (coeff. = 0.21; $p = 0.049$; coeff. = 0.27; $p = 0.01$, respectively) and at T4 (coeff. = 0.28; $p = 0.035$; coeff. = 0.28; $p = 0.038$, respectively).

Determinants of PD outcome: non-remission

We categorized each patient as a *remitter* or *non-remitter* at each time point. Forty-three patients (50.5%) met criteria for remission during the follow-up period. Twenty out of 43 patients (46.5%) firstly met remission criteria at T1, nine (20.9%) at T2, 11 (25.5%) at T3, and 3 (6.9%) at T4. Compared to non-remitters patients ($n = 42$), those who achieve remission ($n = 43$) had significantly lower scores on the *mood spectrum total score* (45.6 ± 20.7 vs 55.0 ± 21.5; $t = 2.0$, $p = 0.045$) and on the *sleep disturbances* dimension, namely on the sum of the items from 138 to 149 (3.4 ± 2.4 vs 4.8 ± 2.4, respectively; $t = 2.6$, $p = 0.011$; range: 0–9) (Table 2).

In a logistic regression model with *remission* (yes/no) as the dependent variable and the mood spectrum scores as the independent variables, *sleep disturbances* was the only component associated with a lower likelihood of remission (Odd Ratio = 0.79; $p = 0.045$). The items accounting for this result were as follows: *repeated difficulty falling asleep* (chi-square = 4.4; df = 1; $p = 0.036$) and *repeatedly waking up in the middle of the night* (chi-square = 5.2; df = 1; $p = 0.022$) (Table 3).

Discussion

The study evaluated the impact of lifetime sleep dysregulations, as assessed by a specific instrument for mood assessment called MOODS-SR, on PD treatment response. The main finding was that two items of the MOODS-SR *sleep disturbances* component, namely *trouble falling asleep* (item 139) and *waking in the middle of the night* (item 140), resulted associated with less likelihood of remission of PD. Several data showed that the comorbidity between panic and mood disorders might occur frequently and have important prognostic and therapeutic implications, such as higher suicide risk, higher rates of chronicity, greater social impairment, and poorer outcome in comorbid compared with non-comorbid illnesses.[26] However, to our knowledge, this is the first study considering *sleep disturbances* as a symptoms' dimension belonging to the sub-threshold mood spectrum realm, able to interfere with treatment response and clinical course of PD. Two previous studies[27,28] explored a converse question, namely if panic-agoraphobic spectrum symptoms could influence treatment response and course of unipolar and bipolar depression. The presence of panic-agoraphobic spectrum, as assessed by the Panic-Agoraphobic Spectrum Questionnaire Self-Report Version (PAS-SR)[29] in the absence of a full-blown comorbidity for PD, was related to a poorer response to interpersonal psychotherapy (IPT) in a sample of women with recurrent major depressive episodes (MDE).[27] Moreover, a sample of patients with Bipolar I Disorder (BP-I) was reported to achieve remission 27 weeks later when PAS-SR scores were >45.[28]

In our study, we observed no correlation between the total number of MOODS-SR symptoms and treatment response. However, in our opinion, lifetime MOODS-SR was helpful to identify a clinical phenotype of PD characterized by a comorbidity for sleep disturbances belonging to the realm of (sub-threshold) mood spectrum signs that would represent a cue of mood liability.

The clinical usefulness of the spectrum assessment in detecting signs and symptoms that can interfere with treatment, thus depicting more refined clinical phenotypes of patients, has been demonstrated in a number of studies on patients with eating disorders[17] unipolar depression and BP.[30–35] It could be argued that mood spectrum dysregulations, including sleep disturbances, could reflect some aspects of PD (e.g., nocturnal panic attacks). Unfortunately, the proposed lifetime assessment did not allow us to determine if mood spectrum symptoms might precede or follow the onset of PD. Previous studies investigated the association between sleep disturbances and the onset of depressive or anxiety disorders, and led to the hypothesis of the existence of an

https://doi.org/10.1017/S1092852918001700 Published online by Cambridge University Press

TABLE 3. Sleep disturbances component of mood spectrum in panic disorder "remitters" and "non-remitters"

MOODS-SR items	PDSS "non-remitters" ($n = 42$)	PDSS "remitters" ($n = 43$)	χ^2	df	p
In the course of your life, including when you were a child, have you ever had periods of at least 3–5 days in which . . .	% of response "yes"	% of response "yes"			
138 . . . you felt sleepy all the time?	46.3	37.2	0.72	1	0.396
139 . . . you repeatedly had difficulty falling asleep?	69.0	46.5	4.42	1	**0.036**
140 . . . you repeatedly woke up in the middle of the night and had difficulty falling asleep again?	64.3	39.5	5.21	1	**0.022**
141 . . . you repeatedly woke up much earlier than you wanted to, and were unable to go back to sleep?	47.6	32.6	2.00	1	0.156
142 . . . you needed much more sleep than usual either at night or during the day?	45.2	44.2	0.01	1	0.922
143 . . . you went for days without sleeping or with much less sleep than usual but didn't feel tired?	28.6	30.2	0.02	1	0.867
144. Do you have a lot of difficulty sleeping before or after stimulating physical, social, or professional activities?	61.9	46.5	2.02	1	0.154
145. Does the quality of your sleep or your need for sleep increase in a particular season of the year or during the change of seasons?	56.1	34.9	3.81	1	0.051
146. Does the quality of your sleep or your need for sleep increase when you travel across at least four time zones?	22.2	7.1	3.63	1	0.056
147. Does the quality of your sleep or your need for sleep decrease when you travel across more than at least four time zones?	11.8	4.8	1.26	1	0.260
148. Does the quality of your sleep or your need for sleep increase over the course of the menstrual cycle?	38.2	20.6	2.55	1	0.110
149. Does the quality of your sleep or your need for sleep decrease over the course of the menstrual cycle?	8.8	5.9	0.21	1	0.642

Note. MOODS-SR Lifetime, Mood Spectrum Self-Report Questionnaire Lifetime Version; PDSS, Panic Disorder Severity Scale. Significance $p < 0.05$ in bold.

underlying vulnerability, such as temperamental features or cognitive styles.[36] We started from a different perspective, by observing that PD patients may show a spectrum of associated clinical features, not included in the criteria set, and belonging to mood dysregulations, without meeting criteria for a comorbid Axis I mood disorder, even if we were aware that our study had a number of limitations. The sample size was limited. Moreover, the naturalistic follow-up study design did not allow any balance of the two groups of remitters and non-remitters on the use of pharmacotherapy. Thus, pharmacological treatments were decided on a clinical base by an independent clinician, blind on the study procedures. Length of treatment was a variable across patients: future studies should take into account mean and range of treatment duration.

According to this model, spectrum manifestations may occur in the absence of threshold level criteria for mood disorders. Some are *trait-like* symptoms that occur as the subtle manifestations of an illness diathesis. Early onset of such signs and symptoms can act to shape developing mental functions and change personality.[13] Mood spectrum features, including sleep disturbances, are significant also when they remain as residual symptoms or co-occur with another disorder, such as PD. Failure to recognize residual or comorbid mood spectrum features in treating PD may explain continued impairment, even when core PD symptoms have been successfully treated.[29]

Conclusions

Sleep disturbances, experienced during lifetime, seem to be a *chain* linking mood spectrum comorbidity and PD, considering that they were the only ones related with PD non-response, in a logistic regression model. As a consequence, we could speculate that the adoption of specific therapeutic strategies for sleep disturbances as part of a sub-threshold mood comorbidity could be useful to increase the remission rates of PD, or to prevent the development of a full-blown mood disorder.

Disclosures

The authors have nothing to disclose.

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