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ABSTRACT

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PROGNOSTIC VALUES OF CIRCADIAN RHYTHM AND SLEEP PARAMETERS IN ASSESSMENT OF STATE ANXIETY IN PARKINSON'S DISEASE WITH REGARD TO MOTOR SUBTYPE

Introduction. Parkinson's disease is characterized by motor and non-motor symptoms, the connection between which has recently attracted much attention from researchers. Sleep disturbances and anxiety can be non-motor signs of Parkinson's disease. The specificity of non-motor symptoms in different motor subtypes is being actively studied, with the PIGD (postural instability and gait difficulty) subtype being associated with more severe non-motor symptoms.

Methods. We conducted a clinical monocentric cross-sectional study that included 64 patients with Parkinson's disease. Patients were assessed according to the Unified Parkinson's Disease Rating Scale, and their motor subtype was determined by calculations using the method of Jankovich and Stebbins. We assessed circadian rhythm using the Ukrainian version of the Munich Chronotype Questionnaire, sleep quality – using the Pittsburgh Sleep Quality Index, excessive daytime sleepiness – using the Epworth Sleepiness Scale, and state anxiety – using the first block of the State-Trait Anxiety Inventory.

Results. Our sample consisted of approximately equal numbers of men and women with a mean age of 63.80 ± 9.30 years. All patients were approximately equally distributed by motor subtype and sleep quality. At the same time, our sample was dominated by patients with a high level of state anxiety, morning chronotype, and the absence of excessive daytime sleepiness. State anxiety demonstrated a moderate direct correlation with sleep latency, mid-sleep, subjective sleep quality, subjective sleep latency, sleep disturbance, and total score of Pittsburgh Sleep Quality Index and a moderate indirect association with average weekly light exposure. It was found that an increased mid-sleep time, a decreased average weekly light exposure during the day, poor sleep

quality, and PIGD subtype elevated the odds of more severe situational anxiety.

Conclusions. Our study demonstrates the relationship between the level of situational anxiety and parameters of sleep and circadian rhythm in patients with Parkinson's disease, considering their motor subtype. It was found that a later mid-sleep, lower average weekly light exposure, poor sleep quality, and PIGD subtype of Parkinson's disease had a prognostic role regarding the increase in state anxiety.

Keywords: Parkinson Disease, Prognosis, Circadian Rhythm, Sleep, Sleep Quality, Anxiety.

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ПРОГНОСТИЧНЕ ЗНАЧЕННЯ ПОКАЗНИКІВ ЦИРКАДНОГО РИТМУ ТА СНУ ДЛЯ ОЦІНКИ СИТУАТИВНОЇ ТРИВОЖНОСТІ ПРИ ХВОРОБІ ПАРКІНСОНА З УРАХУВАННЯМ МОТОРНОГО ПІДТИПУ

Вступ. Хвороба Паркінсона характеризується моторними та немоторними симптомами, зв'язок між якими останнім часом привертає велику увагу дослідників. Порушення сну і тривожність можуть бути немоторними ознаками хвороби Паркінсона. Специфіка немоторних симптомів при різних моторних підтипах активно вивчається, причому підтип PIGD (порушення ходи та постуральна нестійкість) асоціюється з більш вираженими немоторними симптомами.

Методи. Ми провели клінічне моноцентрове перехресне дослідження, яке включало 64 пацієнтів з хворобою Паркінсона. Пацієнтів оцінювали за Уніфікованою шкалою оцінки хвороби Паркінсона, а їх моторний підтип визначали шляхом розрахунків за методом Янковича і Стеббіна. Оцінювали циркадний ритм за допомогою української версії Мюнхенського хронотипового опитувальника, якість сну – за Піттсбурзьким індексом якості сну, надмірну денну сонливість – за шкалою сонливості Епворта, ситуативну тривожність – за першим блоком опитувальника Спілберга–Ханіна.

Результати. Вибірка складалася з приблизно рівної кількості чоловіків і жінок із середнім віком 63,80 ± 9,30 років. Всі пацієнти були приблизно однаково розподілені за моторним підтипом та якістю сну. Водночас у вибірці переважали пацієнти з високим рівнем тривожності, ранковим хронотипом та відсутністю надмірної денної сонливості. Стан тривожності продемонстрував помірну пряму кореляцію з латентністю сну, тривалістю середини сну, суб'єктивною якістю сну, суб'єктивною латентністю сну, порушеннями сну та загальним балом Піттсбурзького індексу якості сну, а також помірну зворотну кореляцію з середньотижневою експозицією світла. Було виявлено, що збільшення часу середини сну, зменшення середньотижневої експозиції світла, погана якість сну та підтип PIGD підвищували ймовірність більш вираженої ситуативної тривоги.

Висновки. Наше дослідження демонструє взаємозв'язок між рівнем ситуативної тривожності та показниками сну і циркадного ритму у пацієнтів з хворобою Паркінсона з урахуванням їх моторного підтипу. Виявлено, що більш пізня середина сну, нижча середньотижнева експозиція світла, погана якість сну та PIGD-підтип

хвороби Паркінсона мають прогностичну роль щодо підвищення рівня ситуативної тривоги.

Ключові слова: Хвороба Паркінсона, прогноз, циркадний ритм, сон, якість сну, тривога.

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Abbreviation
PD – Parkinson's disease
PIGD – Motor subtype with a predominance of postural instability and gait disorders
MCTQ – Munich Chronotype Questionnaire
PSQI – Pittsburgh Sleep Quality Index
ESS – Epworth Sleepiness Scale

INTRODUCTION / ВСТУП

Age-related diseases are on the rise worldwide and are driven by sociodemographic and environmental factors. Among them, neurodegenerative diseases, especially Alzheimer's disease and Parkinson's disease (PD), hold a leading position [1,2]. PD is characterized by a typical parkinsonism syndrome, numerous non-motor symptoms, and a long prodromal period. Some non-motor symptoms, including sleep and circadian rhythm disorders, develop precisely during the prodromal period [3].

Parkinsonism syndrome, which is pivotal in the diagnosis of PD, includes bradykinesia, tremor, and muscle rigidity. The motor subtype or clinical form of the disease is determined by the predominance of one of these signs. This influences the choice of treatment strategy and prognosis of the patient. The most common classification of PD is clinical form with a predominance of muscle rigidity (akinetic-rigid form) and tremor-dominant subtype and its variations. However, postural instability and gait disorders and their role in determining motor subtypes have recently been attracting increasing attention. Depending on the severity of this clinical sign, there is a motor subtype with a predominance of postural instability and gait disorders (PIGD), an intermediate subtype, and a motor subtype with a predominance of tremor. This classification is considered more specific when assessing the non-motor symptoms of PD [4, 5].

The PIGD subtype is known to have more frequent non-motor symptoms both in the prodromal period and at the stage of clinical manifestations, which leads to a more severe deterioration in quality of life [6, 7]. The association between sleep disorders and the PIHD subtype has been reported in many studies [8, 9], but the reasons for this association are not yet clear. At the same time, a link between gait disorders with poor sleep quality and anxiety in patients with PD has been identified [10]. The bidirectional relationship between sleep and anxiety disorders is also well known [11].

Sleep disturbances and psychiatric symptoms play an important role in the structure of non-motor symptoms and are characterized by a complex network of interconnections, which causes variability in the clinical course [12]. Today, anxiety attracts special attention because, against the background of the ongoing war in Ukraine, this symptom may not be a manifestation of the underlying disease but a stress-related mental disorder caused by circumstances [13, 14]**.** The Russian-Ukrainian war has caused many challenges for healthcare in general, including mental health, and has worsened the quality of sleep [15]. In such conditions, a relevant issue for patients with PD is identifying the direction of the connections between various motor and non-motor signs and developing ways to predict their course.

Sleep-targeted treatment has been shown to improve mental health. For example, the use of cognitive behavioral therapy for insomnia led to a reduction in anxiety [16]. Acceptance and commitment therapy has also been shown to be effective for insomnia with a subsequent reduction in anxiety [17]. Thus, we hypothesized that both the motor subtype and sleep and circadian rhythm disorders can affect anxiety levels in patients with PD.

Methods and Materials. We conducted a clinical monocentric cross-sectional study at the Center for Patients with PD and Other Neurodegenerative Diseases of the Department of Neurological Diseases of Poltava State Medical University. This research was approved by the Commission on Biomedical Ethics of Poltava State Medical University (protocol №219; 29 September, 2023). This study was conducted in accordance with the requirements of the Declaration of Helsinki. All participants provided written informed consent for participation in the study.

The study included 64 patients with PD. The diagnosis of PD was determined based on the statement of the International Movement Disorders and Parkinson's Disease Society in the presence of parkinsonism, absence of absolute exclusion criteria, presence of at least 2 auxiliary criteria, and absence of red flags. Parkinsonism was confirmed by bradykinesia, resting tremor, and/or muscle rigidity.

The inclusion criteria for this study were as follows:

- Clinically confirmed PD with Hoen and Yahr stage < 4,
- Disease duration of more than 1 year,
- Age from 18 to 89 years,
- Permanent treatment with levodopa during the last year.

Exclusion criteria:

- Concomitant severe somatic diseases,
- Age over 90 years,
- Secondary Parkinsonism due to medications, vascular lesions, tumors , and trauma
- Atypical parkinsonism.

Patients were assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS), and their motor subtype was determined by calculations using the method of Jankovich and Stebbins [18].

We assessed circadian rhythm using the Ukrainian version of the Munich Chronotype Questionnaire (MCTQ). We used the main module and an additional module that deals with the effects of light. Given that the patients included in the study did not work, the difference between workdays and work-free days during the week was additionally explained to the patients. Based on the results of this questionnaire, the basic and computed variables were calculated. Because all variables are time-based data, they were transformed into decimals of one for statistical analysis [19].

The assessment of daily functioning included an analysis of sleep quality, sleep disturbances, and the degree of daytime sleepiness. The Pittsburgh Sleep Quality Index (PSQI) was used to determine the quality of sleep and contains 19 questions. The answers are ranked from 0 to 3 and are composed of 7 components: C1: subjective sleep quality, C2: sleep latency, C3: sleep duration, C4: sleep efficiency, C5: sleep disturbance, C6: use of sleeping pills, and C7: daytime dysfunction. The total PSQI score was calculated as the sum of the scores of all components, which ranged from 0 to 21 points, where a score of more than 5 points corresponded to poor sleep quality. At the same time, higher values indicated poorer sleep quality and vice versa [20].

The Epworth Sleepiness Scale (ESS) provides an opportunity to assess the level of daytime sleepiness and consists of 8 statements that describe situations in which the patient falls asleep. The patient has to estimate the probability of sleeping in such conditions from 0 to 3, where 0 means never sleeping and 3 means a high probability of sleeping. The range of possible values is from 0 to 24 points and corresponds to a more pronounced level of daytime sleepiness with a higher score. Pathologic daytime sleepiness was diagnosed in patients with a score of more than 10 [21].

We used the State-Trait Anxiety Inventory (STAI) to assess state anxiety. For this study, we used the first block of the questionnaire, which contains 20 questions and characterizes reactive anxiety. The total score according to the questionnaire ranges from 20 to 80, where a higher value corresponds to a more severe level [22]. The level of state anxiety was interpreted as follows: low with a score less than 30, moderate with a score of 31 to 45, and high with a score of more than 45 [23].

We conducted a statistical analysis using Jamovi 2.3.28. To characterize the study sample, we calculated the mean (arithmetic mean with standard deviation - M±SD) and relative (absolute and percentage - abs., (%) values. $\chi 2$ goodness of fit was used to test differences with expected values. We used Spearman's rank correlation test to determine the relationships between the quantitative variables. The prognostic value of the variables was assessed using ordinal logistic regression and the extent of variance of the dependent variable Nagelkerke R2. To assess the prognostic role, we calculated the estimates and their standard error (B±m) and odd ratios with 95% confidence intervals.

Equations for the probabilities of different levels of the dependent variable based on ordinal regression data were constructed according to the following formula:

$$P\% = \frac{1}{1+e^{a_1x_1 \ldots + a_nx_n - Z}} * 100\% \quad (1)$$

where a_1-a_n – predictor coefficients,
x_1-x_n – predictor value,
Z – threshold score.

The adequacy of the constructed model was assessed using the tau-b-Kendall rank correlation between observed and expected frequencies and by calculating the specificity for each level of the dependent variable. The critical level of significance in testing the statistical hypotheses in this study was taken to be 0.05.

Results. The characteristics of the demographic and clinical parameters of the patients are presented in Table 1.

Our sample consisted of approximately equal numbers of men and women with a mean age of 63.80±9.30 years. All patients were approximately equally distributed by motor subtype and sleep quality.

Table 1 – General characteristic of the studied population

Feature	Category	Values	χ^2 goodness of fit	p-value
Sex, abs., (%)	Male	33 (51.6%)	0.250	0.617
	Female	31 (48.4%)		
Motor subtype, abs., (%)	PIGD	38 (59.4%)	2.25	0.134
	non-PIGD	26 (40.6%)		
State anxiety, abs., (%)	Low	9 (14.1%)	14.70	<0.001*
	Moderate	21 (32.8%)		
	High	34 (53.1%)		
Chronotype, abs. (%)	Early	54 (84.4%)	76.5	<0.001*
	Intermediate	9 (14.1%)		
	Late	1 (1.5%)		
Sleep quality, abs., (%)	Poor	34 (53.1%)	0.250	0.617
	Good	30 (46.9%)		
Excessive daytime sleepiness, abs., (%)	Presence	23 (36.0%)	5.06	0.024*
	Absence	41 (64.0%)		

Note: * – statistically significant differences from expected values by χ^2 goodness of fit test

At the same time, our sample was dominated by patients with a high level of state anxiety, morning chronotype, and the absence of excessive daytime sleepiness.

We performed a correlation analysis between the state anxiety subscale score and the subjective assessment of sleep and circadian rhythm to determine potential predictors of anxiety syndrome severity in patients with PD. The associations between the level of state anxiety and the chronotypic features of patients with PD are presented in Table 2.

Table 2 – Correlation analysis between the level of state anxiety with circadian rhythm parameters in patients with Parkinson's disease, n=64

Parameter	SAI	
	r-value	p-value
Local time of going to bed	0,135	0,286
Local time of preparing to sleep	-0,048	0,707
Sleep onset	0,182	0,150
Sleep latency	0,356	0,031*
Sleep end	0,140	0,270
Local time of getting out of bed	0,185	0,144
Sleep inertia	0,197	0,119
Sleep duration	-0,031	0,807
Total time in bed	0,053	0,677
Mid-Sleep	0,381	0,025*
Average weekly light exposure	-0,401	0,016*

Note. * - statistically significant correlation according to Spearman's criterion

State anxiety demonstrated a moderate direct correlation with sleep latency and mid-sleep and a moderate indirect association with average weekly light exposure.

Table 3 shows the results of the correlation analysis between the level of state anxiety and indicators of sleep quality and daytime functioning in patients with PD.

We found a moderate direct correlation between the level of state anxiety and subjective sleep quality, sleep latency, sleep disturbance, and total PSQI score.

Using ordinal logistic regression, we developed a model that demonstrates the dependence of the severity of situational anxiety in PD on chronotypic and somnolgic features, considering the motor subtype.

Table 3 – Correlation analysis between the level of state anxiety with indicators of sleep quality and daytime functioning in patients with Parkinson's disease, n=64

Indicator	SAI	
	r-value	p-value
Subjective sleep quality	0,359	0,004*
Sleep latency	0,274	0,028*
Sleep duration	-0,089	0,483
Sleep efficiency	-0,058	0,648
Sleep disturbance	0,319	0,010*
Use of sleep medication	0,145	0,252
Daytime dysfunction	0,193	0,126
Total PSQI score	0,262	0,037*
ESS score	0,232	0,065

Note. * - statistically significant correlation according to Spearman's criterion

The regression analysis included the indicators that demonstrated statistical significance in the correlation analysis, namely sleep latency, mid-sleep, and average weekly light exposure during the day according to the MCTQ scale, sleep quality according to the PSQI scale as an integrating variable, and motor subtype. The results are presented in Table 4.

Thus, it was found that an increased mid-sleep time (OR=4.49, 95% CI 1.38-16.59, p=0.029), a decreased average weekly light exposure during the day (OR=0, 72, 95% CI 0.52-0.98, p=0.043), poor sleep quality (OR=3.93, 95% CI 1.30-13.94, p=0.022), and PIGD subtype (OR=2.26, 95% CI 1.13-4.86, p=0.026) elevated the odds of more severe situational anxiety. However, there was no statistically significant effect of sleep latency in this model.

Table 4 – Estimates for the pedictors of the state anxiety severity in Parkinson's disease

№	Factor	Category	Estimate, B±m	Odds ratio	95% confidence interval	p-value
1	Mid-sleep		1,50±0,63	4,49	1,38-16,59	0,029
2	Sleep latency		0,47±0,60	1,29	0,55-3,13	0,565
3	Average weekly light exposure		-0,32±0,16	0,72	0,52-0,98	0,043
4	Sleep quality	Poor	1,37±0,60	3,93	1,30-13,94	0,022
		Good	0	-	-	-
5	Motor subtype	PIGD	0,81±0,37	2,26	1,13-4,86	0,026
		non-PIGD	0	-	-	-

The threshold scores of the regression parameters for the severity of the low–moderate state anxiety was Z=-1.87 (p=0.021) and for moderate–high state anxiety was Z=3.01 (p=0.038).

Thus, on the basis of the obtained estimates of the regression parameters, an algorithm was developed to calculate the probability of different levels of state anxiety. The probability of moderate situational anxiety in patients with PD based on circadian and sleep indicators can be calculated using the following equation:

$$P\% = \frac{1}{1+e^{1,87+1,50*mid-sleep-0,32*light\ exposure+1,37*sleep\ quality+0,81*motor\ subtype}} * 100\% \quad (2)$$

The following equation can be used to calculate the probability of severe state anxiety:

$$P\% = \frac{1}{1+e^{1,50*mid-sleep-0,32*light\ exposure+1,37*sleep\ quality+0,81*motor\ subtype-3,01}} * 100\% \quad (3)$$

The constructed model explains almost a third of the variation in the dependent variable, which indicates a significant contribution of the identified factors (R^2_N=0.352).

The distribution of the expected and observed levels of state anxiety in patients with PD is shown in Table 5.

A direct strong correlation was established between the expected and observed values of the level of severity of state anxiety in PD (τ=0,702, p<0,001) that is shown adequacy of the proposed model. The sensitivity of the developed model in predicting low state anxiety was 66.7%, moderate anxiety was 61.9%, and high anxiety was 85.3%.

Table 5 – Frequencies of observed and expected levels of state anxiety in PD by the proposed model

Levels		Expected		
		Low	**Moderate**	**High**
Observed	Low	6 (66,7%)	2 (22,2%)	1 (11,1%)
	Moderate	0 (0,0%)	13 (61,9%)	8 (38,1%)
	High	0 (0,0%)	5 (14,7%)	29 (85,3%)

Discussion. Usually, PD develops preferentially in old age, which is also accompanied by the development of several diseases, including cognitive impairment and cardiovascular and metabolic disorders [24,25]. Patients with PD have various non-motor symptoms that significantly impair their quality of life.

In our study, we found a supreme frequency of high situational anxiety, which is consistent with other studies. At the same time, anxiety has been reported to be associated with poor sleep quality [26]. Excessive daytime sleepiness in our sample was observed in 36% of the patients and poor sleep quality in 53%. Similar findings were reported in a recent meta-analysis, which showed that the overall prevalence of excessive daytime sleepiness in patients with PD was 35% and that of insomnia was 44%, which is associated with more severe neuropsychiatric symptoms and longer disease duration. Despite the high prevalence of insomnia in patients with PD and its association with mental health, this symptom is often overlooked by clinicians [27]. The predominance of the morning chronotype in the population of patients with PD found in our study is supported by another study. This study also reported that chronotype was associated with age but not with excessive daytime sleepiness or medications [28].

The pathogenesis of PD is quite complex and involves the interaction of genetic, metabolic, and environmental factors. The leading role belongs to the development of mitochondrial dysfunction and oxidative stress, which can act as a bridging link between PD and its non-motor symptoms [29]. The development of oxidative stress leads to damage to multiple body systems and can be caused by chronic stress [30]. Psychological stress leads to the activation of proinflammatory cytokines, which are directly related to the response of the hypothalamic-pituitary-adrenal axis to distressing experiences [31,32]**.** Therefore, melatonin is recognized as one of the newest approaches for treating PD [33]. The administration of exogenous melatonin, which has antioxidant properties, has demonstrated the ability to improve sleep quality, reduce anxiety, and affect metabolism in patients with PD [34–36], which once again demonstrates the possibility of reducing anxiety severity through sleep-focused interventions.

We found that the level of state anxiety is associated with mid-sleep, which represents the chronotype, the average weekly light exposure, which characterizes the impact of the main time cues on the circadian system of the patient, as well as sleep latency, sleep disturbance, and sleep quality, which define the main signs of insomnia and poor sleep quality in PD. In addition, prognostic significance was found for mid-sleep, average weekly light exposure, poor sleep quality, and PIGD subtype. These results indicate the importance of assessing circadian and somnological parameters in patients with PD and the ability to predict one of the most important non-motor symptoms of the disease.

The relationship between later mid-sleep and increased levels of situational anxiety is supported by the hypothesis of a link between chronotype and mental health. The chronotype indicates the rhythmicity of the circadian functioning of the sleep-wake rhythm and tends to become earlier with aging. On the other hand, it has shown a link between later chronotypes and mental disorders [29].

Light is the most powerful zeitgeber that provides delicate entrainment of the circadian system. The use of light therapy has been widely studied in patients with PD. Although depression is the most popular outcome, one report showed the effectiveness of light therapy in reducing anxiety [37].

Poor sleep quality in PD can be a feature of many sleep disorders, but the common thread is that regardless of the cause, this condition can increase nervous system arousal and lead to increased anxiety [38]. This confirms the hypothesis of an association between circadian rhythms and anxiety in PD, which makes it possible to use behavioral therapy approaches, including sleep hygiene, psychotherapy, and day scheduling, as well as chronotherapy in the form of melatonin and light therapy.

We consider the association between the PIGD subtype and state anxiety to be a significant finding. Previous studies have demonstrated a link between falls in de novo patients with PD and anxiety and the subsequent diagnosis of this particular motor subtype [39]. A higher severity of mood disorders in this subtype was also found in patients with de novo PD [40]. We hypothesize that the association of the PIGD subtype of PD with sleep and mood disorders may explain the association of this motor subtype with greater disease severity and poorer prognosis in PD found in a previous study [41].

The current study first investigated the role of circadian and somnological indicators on the severity of state anxiety in patients with PD by considering the motor subtype and exploring the relationship between these three variables. At the same time, it has certain limitations. First, a small sample of patients requires a cautious interpretation of the results. Second, we did not study the effect of severity, duration of disease, and levodopa dose on anxiety, which could have influenced our results and should be considered in future studies.

CONCLUSIONS / ВИСНОВКИ

Our study demonstrates the relationship between the level of situational anxiety and indicators of sleep and circadian rhythm in patients with PD, considering their motor subtype. It was found that a later mid-sleep, lower average weekly light exposure, poor sleep quality, and PIGD subtype of PD have a prognostic role regarding the increase in state anxiety.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Further studies should examine the effectiveness of interventions aimed at adjusting the circadian rhythm and improving sleep quality regarding anxiety in patients with PD. The limitations of our study should be addressed.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

The authors confirm their contribution to the paper as follows: study conception and design: A. Shkodina, K. Tarianyk and M. Delva; data collection: A. Shkodina and K. Tarianyk; analysis and interpretation of results: A. Shkodina and K. Tarianyk; draft manuscript preparation: A. Shkodina and M. Delva. All authors reviewed the results and approved the final version of the manuscript.

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