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EFFECTS OF VARIOUS FACTORS ON SLEEP DISORDERS AND QUALITY OF LIFE IN PARKINSON'S DISEASE

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease [1, 2]. Despite intensive investigations conducted in previous decades, the etiology of PD is not completely resolved. Today, it is considered that multifactorial genesis, probably an interaction of genetic and environmental factors, is the most likely progenitor of the disease [3]. This chronic progressive neurodegenerative disease is mainly caused by the degeneration of nigrostriatal dopaminergic neurons [1]

PD occurs in all age groups, but more often in patients over the age of 60, and in this population its frequency is approximately 1% [3]. PD is characterized by progressive motor symptoms (MS) and non-motor symptoms (NMS), such as disorders of the gastrointestinal, urinary, circulatory, autonomic system etc.[4, 5]. In addition to MS (e.g., tremor, rigidity, bradykinesia, and postural instability), NMS (e.g., constipation, urinary disorders, sleep disturbances, sweating, depression, pain etc.) are often present and may occur much earlier than MS do.

The results of previous studies have shown that different kinds of sleep disorders are present in the majority of patients with PD, regardless of age, gender, disease duration or the stage of disease progression, and that they are more pronounced in the advanced stages of the disease. These results were obtained using questionnaires concerning sleep quality, quality of life (QoL) and assessing difficulties in performing daily activities in PD patients.

It is known that sleep disturbances (SD) in PD result from the interaction of neurochemical changes in the regulatory sleep centres in the thalamus and frontal regions of the brain and neurodegenerative changes in the dopaminergic neurons of the basal ganglia. These changes affect most patients with PD [6, 7, 8]. SD are also caused by other factors, such as depression, pain and other co-morbidities. Common SD in patients with PD include excessive daytime sleepiness (EDS), "sudden involuntary sleep" episodes, insomnia, fragmented sleep, nightmares, periodic leg movement, restless legs syndrome and frequent night-time urination - nocturia [9, 10].

The aim of this study was to compare quality of sleep, as a factor that greatly impacts quality of life in general, between PD patients and a control group and to further examine sleep disorders in the PD group with focus on incidence and types of disorders as well as on effects various factors (age, sex, PD characteristics, medication usage) have on these disorders.

METHODS

The study included 220 participants, 110 of whom fulfilled the diagnostic criteria for PD (i.e., United Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria) [1] and presented with different stages and different duration of the disease. This group was age-matched with 110 healthy controls.

All persons involved in the study gave their informed consent prior to their inclusion in the study. The study was carried out in accordance with The Code of Ethics of the World Medical Association.

We used the Pittsburgh Sleep Quality Index (PSQI) in both groups, and the Parkinson's Disease Sleep Scale (PDSS), the Epworth Sleepiness Scale (ESS), the Parkinson's Disease Quality of Life Questionnaire - 8 (PDQ-8), and items 30 and 33 of the Parkinson's Disease Quality of Life Questionnaire - 39 (PDQ-39) in the group of patients with PD. Mean values of the PSQI scores were compared between the two groups of patients.

The PD group was analysed according to the duration of the disease, the stage of disease based on the Hoehn and Yahr (H&Y) scale, medication usage and their impact on SD types (i.e., insomnia, EDS, nightmares, fragmented sleep, nocturia, PLM and RLS).

In the statistical analysis, we used descriptive statistics and the following tests: Kolmogorov–Smirnov's test for the normal distribution of certain quantitative values, the Mann-Whitney U test, Spearman's Rho test and Pearson's Chi-squared test. P value of $< 0,05$ was considered statistically significant.

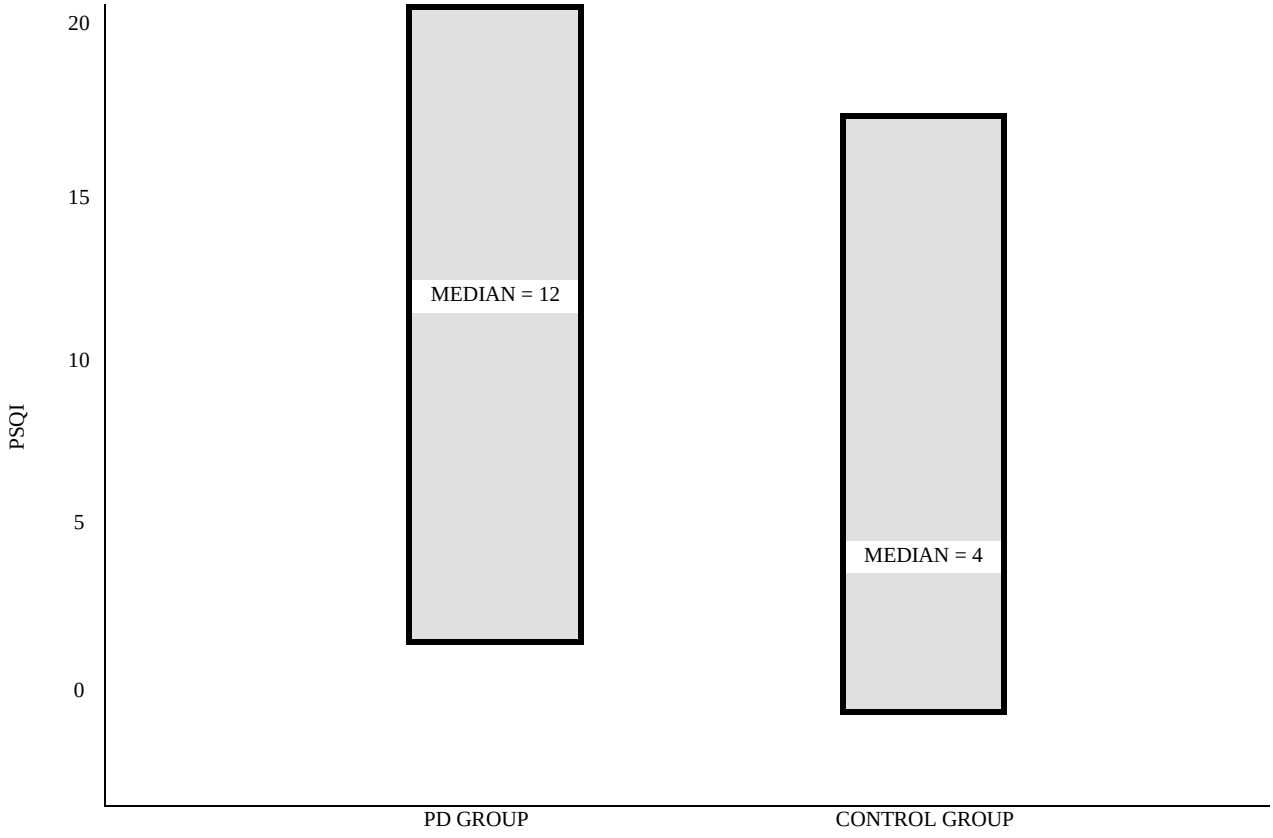
RESULTS

In the PD group of 110 patients, 56 were female and 54 were male. In the control group of 110 healthy participants, 64 were female and 46 were male. The average age of the females in the PD group was 58 years (± 11.49), and the average age of the males was 58.5 years (±10.68). The average age of the females in the control group was 57 years (±13.08), and the average age of the males was 56.5 years (±13.67)

The Kolmogorov–Smirnov test for normality of distribution was used to evaluate our data set and showed that all variables except age were significantly different from the normal distribution. Based on these data, we used non-parametric tests in further analysis.

The average duration of PD was six years (standard deviation – SD = 4.72); the mean H&Y stage of the disease was 2.44 (SD = 0.95). The average value of the PDSS was 82.05 (SD = 36.92), ESS 6.29 (SD = 4.86), PDQ-8 6.88 (SD = 6.50), PDQ39, point 30 0,88 (SD = 1.28) and PDQ39, point 33 0.40 (SD = 0.89)

Figure 1: Comparison of Pittsburgh Sleep Quality Index (PSQI) in the PD group and the control group



Median value of the PSQI score in the PD group was 12.00, which was three times higher than in the control group (median value 4.00) (Fig. 1).

Table 1: Spearman's Rho correlation test between duration of PD and PSQI, ESS, PDQ-8, PDQ-39, between H&Y stage and PSQI, ESS, PDQ-8, PDQ-39 and between age and PSQI, ESS, PDQ-8, PDQ-39

N = 110			PSQI	PDSS	ESS	PDQ - 8	PDQ-39, I30	PDQ-39, I33
SPEARMAN'S RHO	PD DURATION	Correlation Coefficient	0.641	-0.713	0.627	0.660	0.582	0.469
		P	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
	H&Y	Correlation Coefficient	0.584	-0.573	0.480	0.606	0.376	0.488
		P	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
	AGE	Correlation Coefficient	0.394	-0.390	0.354	0.369	0.288	0.406
		P	<0.001*	<0.001*	<0.001*	<0.001*	0.002*	<0.001*

*p < 0,05

N - number of participants, H&Y - Hoehn and Yahr stage, PD- Parkinson's disease, PSQI - Pittsburgh Sleep Quality Index, PDSS - Parkinson's Disease Sleep Scale, ESS - Epworth Sleepiness Scale, PDQ-8 - Parkinson's Disease Quality of Life Questionnaire - 8, PDQ-39, I30 - Parkinson's Disease Quality of Life Questionnaire 39, item 30, PDQ-39, I33 - Parkinson's Disease Quality of Life Questionnaire 39, item 33

All correlations (Spearman's Rho coefficient) were statistically significant, and all correlation coefficients with an absolute value above 0.6 denoted strong correlation. The duration of disease was significantly positively correlated with the PSQI, ESS and PDQ-8

scores, but negatively correlated with the PDSS score, therefore longer duration of the disease caused significantly higher PSQI, ESS and PDQ-8 scores, but lower PDSS scores. The H&Y stage of the disease had the highest association with the PDQ-8 (Table 1).

Age also showed a significant correlation with tested scores but age was significantly positively correlated with PSQI scores in both the PD and control groups. The control group even showed a slightly higher correlation coefficient, which was not significant.

Table 2: Frequency of sleep disorders (insomnia, excessive daytime sleepiness, nightmares, fragmenting sleep, nocturia, PLM and RLS) and medication usage (DA agonist, levodopa, MAO-B inhibitors, COMT inhibitors, NMDA antagonists and atypical neuroleptics) in all patients and according to gender

	TOTAL	%	MALE	%	FEMALE	%
INSOMNIA	37	33.6	11	19.6	26	48.1
EDS	23	20.9	11	19.6	12	22.2
NIGHTMARES	15	13.6	9	16.1	6	11.1
FS	42	38.2	27	48.2.	15	27.8
NICTURIA	42	38.2	34	60.7	8	14.8
PLM	8	7.3	8	14.3	0	0.0
RLS	13	11.8	4	7.1	9	16.7
DA AGONIST	86	78.2	44	78.6	42	77.8
LEVODOPA	51	46.4	29	51.8	22	40.7
MAO-B INH	50	45.5	24	42.9	26	48.1
COMT INH	14	12.7	8	14.3	6	11.1
NMDA ANT	29	26.4	11	19.6	18	33.3
ATYPICAL NL	20	18.2	12	21.4	8	14.8

EDS - excessive daytime sleepiness, FS - fragmented sleep, PLM - periodic leg movements, RLS - restless legs syndrome, DA agonist - dopamine agonist, MAO-B INH - monoamine oxidase inhibitors, COMT INH - catechol-O-methyl transferase inhibitor, NMDA ANT - N-methyl-D-aspartate antgonist, ATYPICAL NL - atypical neuroleptic

The most common SD were fragmented sleep and nocturia. The least common was PLM. The most commonly used medications were DA agonists, followed by levodopa and MAO-B inhibitors. The least frequently used were COMT inhibitors. The numbers obtained according to gender showed that women were significantly more likely to have insomnia, while men experienced significantly more fragmented sleep, nicturia and PLM (Table 2).

The Pearson Chi-squared test was performed to determine the statistically significant differences in the frequency of SD and medication usage according to gender.

Table 3: Pearson Chi-Square Test used to determine differences in the frequency of SD and medication usage according to gender

INSOMNIA	χ^2	10.007
	P	**0.002***
EDS	χ^2	0.111
	P	0.739
NIGHTMARES	χ^2	0.574
	P	0.449
FS	χ^2	4.864
	P	**0.027***
NICTURIA	χ^2	24.538
	P	**<0.001***
PLM	χ^2	8.319
	P	**0.004***
RLS	χ^2	2.393
	P	0.122
DA AGONIST	χ^2	0.010
	P	0.920
LEVODOPA	χ^2	1.349
	P	0.246
MAO-B INH	χ^2	0.310
	P	0.577
COMT INH	χ^2	0.249

	P	0.617
NMDA ANT	χ^2	2.654
	P	0.103
ATYPICAL NL	χ^2	0.808
	P	0.369

*p < 0,05

χ^2 - Chi-square value, EDS - excessive daytime sleepiness, FS - fragmented sleep, PLM - periodic leg movements, RLS - restless legs syndrome, DA agonist - dopamine agonist, MAO-B INH - monoamine oxidase inhibitors, COMT INH - catechol-O-methyl transferase inhibitor, NMDA ANT - N-methyl-D-aspartate antgonist, ATYPICAL NL - atypical neuroleptic

The results of the Pearson's Chi-squared test showed differences according to gender. Women were significantly more likely to have insomnia, while men experienced fragmented sleep, nicturia and PLM. The analysis of the therapy showed small differences in the use of drugs, according to gender (Table 3).

An analysis was conducted to determine the influence of selected drugs on PSQI, ESS, PDQ-8, and PDQ-39. Drugs selected for analysis were DA agonists (a commonly used drug) and atypical neuroleptics (clozapine and quetiapine), both with a sedative effect and NMDA antagonists, with an excitatory effect.

The results of the Mann-Whitney U test that was performed showed that the application of DA agonists in patients with PD had a statistically significant ($p < 0.05$) effect on PSQI, PDSS and PDQ-8.

The results indicate that the use of atypical neuroleptics in patients with PD had a statistically significant effect ($p < 0.05$) in all the tests evaluated (PSQI, PDSS, ESS, PDQ-8, PDQ-39, I30 and PDQ-39, I 33).

The results indicate that the use of NMDA antagonists in patients with PD had a non-significant ($p > 0.05$) effect on PSQI, ESS, PDQ-8, PDQ-39: I and 30 and 33.

DISCUSSION

The quality of sleep significantly affects the QoL of the healthy population in general. It particularly affects the QoL of patients with various diseases, especially those with chronic and long-term diagnoses. Duration of PD and being over the age of 60 are top risk factors that influence the quality of sleep and QoL of patients [3, 6]. In this study, the average age of patients in the PD group was less than 60 years (58 years for women and 58.5 year for men), which indicates that age here was not one of the main risk factors for SD.

The H&Y scale for grading the progression of PD in five stages was originally released in 1967 [11] with later modifications and different applications [12, 13]. The mean H&Y stage of PD in the study was 2.44, indicating that the majority of patients had bilateral motor affection, a certain degree of functional disability and a number of NMS.

SD as NMS are experienced by the vast majority of the patients. They may be present in all stages of PD but are mostly found in the more advanced stages [6, 8]. The types of SD that were present in the group we studied (insomnia, EDS, nightmares, fragmented sleep, frequent night-time urination, PLM and RLS) were in accordance with previous studies [7-9]. The most common among them were fragmented sleep and nocturia, and the least common was PLM. Analysis according to gender showed that women were significantly prevalent in the group with insomnia, while men experienced fragmented sleep, nicturia and PLM significantly more often than women. The frequent presence of fragmented sleep in men may be connected with high prevalence of prostate disease in the elderly that can have a combined effect with PD on frequent night urination.

Given that previous studies showed PD significantly affects the quality of sleep [14] and QoL [15, 16], we used different scales to assess the incidence, degree and type of SD and their effect on QoL while taking into consideration various characteristics of PD [17-19]. The median PSQI score was 12, which was significantly higher in the group with PD than in the control group, where the median value was 4. These results confirmed the assumption that PD significantly affects all points related to the quality of sleep, which are more pronounced as the disease progresses. Given that one-third of the human lifespan is spent in sleep, it is clear that QoL directly depends on the quality of sleep [20, 21]. The average duration of PD in our study group was 6 years, and the longer duration significantly positively correlated with the PSQI, ESS and PDQ-8 scores, but negatively with the PDSS score. The H&Y stage of the disease was significantly positively associated with the PDQ-8, which was expected, given that the progression of the disease significantly decreases QoL. This is also in accordance

with previous studies which stated that the incidence of SD increases with the progression of PD [21, 22].

In many studies [22, 23], researchers found a correlation between REM SD and the consequent development of PD. Some investigations [23, 24] found that up to 75% of patients with REM sleep disorder developed a Parkinson-like disorder, or probable PD, which indirectly confirmed that very disturbed sleep quality may be a risk factor for the development of PD. In addition, the frequent coexistence of PD, RLS and PLM was observed in some patients, which is supported by the fact that we treat these disorders with the same or similar drugs [25]. Furthermore, the presence of either RLS or PLM significantly disturbs not only individual sleep, but also that of partners and others members of the household. Nevertheless, there is no clear evidence that RLS and PLM are risk factors for the development of PD, and much controversy surrounds this subject [10, 26].

In addition to sleep disorders, patients with PD often complain of daytime sleepiness, and studies showed that daytime sleepiness occurs in most patients with PD [9, 21]. These symptoms occur not only as consecutive daytime sleepiness after disturbed night sleeping but also because of factors related to the disease and treatment, and they have a major influence on the QoL of patients with PD, which should certainly be taken into consideration in choosing therapeutic treatment for PD [27]. According to our results, excessive daytime sleepiness was present in 19.9% men and 22.6% women. This is important to detect because of the possibility of introducing specific therapy (modafinil), if the correction of previous therapy and other methods are not effective [28].

It is well known that some antiparkinsonian drugs have a sedative effect [27-29] as do other drugs used in PD, but no previous study has investigated this issue. Therefore, in our study, we also conducted an analysis of the effect of certain drugs (used in the treatment of PD) with known sedative or excitatory effects that could possibly influence development of SD. These included primarily DA agonists (a commonly used drug), followed by atypical neuroleptics (clozapine and quetiapine) as drugs with sedative effects and NMDA antagonists, which are known to have an excitatory effect. Analysis of the effects of these drugs on PSQI, ESS, PDQ-8, PDQ-39 showed DA agonists and atypical neuroleptics to have a statistically significant sedative effect during the day, which is a possible cause of SD. These drugs were also proved to cause excessive daytime sleepiness, which indirectly indicates the need for the correction of the daily dose of some drugs in some patients. These results also show that careful consideration is needed when using multiple drugs with sedative effects in the same

patient. While creating a schedule of when a certain drug should be taken during the day, circadian rhythm of the patient shoud always be taken into consideration.

NMDA antagonists had no effect on the scores of the scales, which pointed to the fact that the patients adhered to the instructions of their doctor regarding taking the last dose of the NMDA antagonist no later than 4 p.m., given the excitation and insomnia that can this drug can cause.

As co-morbidity is very common in age groups usually affected with PD, using multiple drugs in patients with PD is not rare. This suggests the need for the analysis of other therapy as well in further studies.

The analysis of sleep disorders in most patients needs to include video-polysomnographic testing [30]. The selection of additional, specific treatment of SD in PD is based on defining weather the problems are in falling asleep, sleeping or early awakening, and discussing other symptoms, especially the presence of depression, hallucinations or other psychiatric phenomena. When introducing sedatives, hypnotics, antidepressants or other psychopharmacological drugs their potential positive or negative effects on other symptoms of PD should always be taken into account. The possibility of side effects and unwanted interactions with other therapies should be expected.

Patients with PD have fragmented sleep because of night hypokinetic and akinetic crises, the inability or difficulty of turning in bed, difficult covering, autonomic disturbances (e.g., excessive cold, excessive heat, sweating), pain in the musculoskeletal system, depression, and inadequate drug regimens (the last dose of PD taken too early). In some patients, it is necessary to increase the evening dose of the drug and/or prescribe a later dose. Further reasons may include shortened effects of the drug dose, weakening effect of the drug, co-medication and co-morbidity, and the side effects of medications for PD and other therapies. All these symptoms and effects should be taken into consideration when diagnosing and solving this complex problem, which in most cases requires a polyvalent approach and consulting with experts in different fields. Therefore, the correction and adjustment of therapy for each PD patient should include a personalized, integrative approach using the principles of individualized treatment and the input of a highly specialized multidisciplinary team (i.e., neurologist, psychiatrist, somnologist, psychologist, urologist, gastroenterologist, PD nurse, physician, physiotherapist, speech therapist, occupational therapist).

It is also necessary to educate patients and family members (or caregivers) about the necessity of conducting adequate sleep hygiene, that is, adherence to times of falling asleep and waking up, avoiding stimulating beverages (e.g., coffee, tea, cola), proper diet, adequate

supply of beds, the optimum temperature of the room, darkness, silence etc. Furthermore, because the quality of the sleep disorders in PD patients directly and indirectly affects sleep of the whole family (caregiver), the problem involves more than one person and often the entire household.

It is extremely important to ask the PD patient specifically about problems related to sleep because many will not even complain about this, as they consider it an expected part of the disease that cannot be resolved. Furthermore, it is important to define accurately the type or the combination of several types of sleep disorder. It is therefore necessary to use a variety of relevant scales and questionnaires. In addition to the objectification and quantification of sleep disorders, the appropriate scales and tests allow monitoring the progression of symptoms, as well as evaluating the effects of therapy and other methods used to solve the problem. These simple, reproducible and comparable methods significantly contribute to not only better diagnoses and treatment of sleep disorders but also other NMS in PD, as well as diseases in general. Therefore, they should be an indispensable part of routine diagnostic and therapeutic algorithms of PD. Their inclusion in the PD protocol would greatly improve not only the QoL of patients with PD, but also QoL of their family. PD is a chronic and progressive disease with serious repercussions not only for the affected person, but also his or her family, caregivers, as well as the entire community.

In this study, only some patients had a video polysomnography, which is a limitation of our investigation. Given that this method is fully objective for sleep disorders (unlike patient history and questionnaires) it should be included in further investigations.

CONCLUSION

This study shows that in order to improve the QoL of PD patients, it is necessary to pay more attention to detecting and solving problems related to sleep.

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PSQI was reproduced from *Buysee DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.* with permission from Professor Buysee at the University of Pittsburgh School of Medicine.

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FINANCIAL DISCLOSURE

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CONFLICT OF INTERESTS

All of the authors named above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTORSHIP:

Telarovic S. made substantial contributions to the main idea, conception and design, acquisition of the data and analysis, supervised this study and interpretation of the data and wrote the manuscript.

Mijatovic D. made contributions to data analysis and interpretation of the data.

Telarovic I. made contributions to the acquisition of the data, statistical analysis, interpretation of the data and was involved in drafting the manuscript and provided critical revisions of the manuscript.

All authors read and approved the final manuscript.

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