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Sleep disorders in Parkinson's disease

SUMMARY

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Contents

Abbreviation list

ADL	activities of daily living
AHI	Apnea-Hypopnea Index
AIS	Athens Insomnia Scale
BMI	body mass index
CISI	Clinical Impression of Severity Index
DA	dopamine agonists
EDS	excessive daytime sleepiness
EMG	electromyography
ESS	Epworth Sleepiness Scale
FIS	Fatigue Impact Scale
H&Y	Hoehn & Yahr
HADS	Hospital Anxiety and Depression Scale
ICD	Impulse-control disorder
iRBD	idiopathic REM Sleep Behavior Disorder
IRLS	International Restless Legs Scale
ISCS	Inappropriate Sleep Composite Scale
ISI	Insomnia Severity Index
KPPQ	King's Parkinson's disease Pain Questionnaire
KPPS	King's Parkinson's Disease Pain Scale
LCIG	Levodopa-carbidopa intestinal gel
LEDD	Levodopa equivalent daily dose
MDS	Movement Disorder Society
MDS-NMS	The International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS)
MDS-UPDRS	MDS-Unified Parkinson's Disease Rating Scale
MMSE	The Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NMSQ	Non-Motor Symptoms Questionnaire
NMSS	Non-Motor Symptoms Scale
OABq	Overactive Bladder Questionnaire
OHQ	Oxford Happiness Questionnaire
OSA	Obstructive sleep apnea

PAS	Parkinson Anxiety Scale
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire-39
PDSS	Parkinson's Disease Sleep Scale
PFS-16	Parkinson's Disease Fatigue Scale
PLMS	Periodic Limb Movements of Sleep
pOSA	probable Obstructive sleep apnea
pRBD	probable REM Sleep Behavior Disorder
PSQI	Pittsburgh Sleep Quality Index
PSWQ	Penn State Worry Questionnaire
RBD	REM Sleep Behavior Disorder
RBDQ-HK	REM sleep Behavior Disorder Questionnaire Hong Kong
RBDSQ	REM Sleep Behavior Disorder Screening Questionnaire
REM	Rapid Eye Movement
SCOPA	Scales for Outcomes in Parkinson's Disease
SCS	Self-Compassion Scale
SHS	Subjective Happiness Scale
TIPI	Ten Item Personality Inventory
UDI-6	Urinary Distress Inventory
VAS	Visual Analogue Scale
VIP	Visual Impairment Questionnaire

Brief summary

Background: Sleep disorders represent common non-motor features of Parkinson's disease (PD) and are known to negatively impair the patients' quality of life.

Aims: The main objectives were to assess the prevalence and the main characteristics of sleep disorders in patients with PD in comparison with controls. The quality of sleep and the associations between sleep disorders and other motor and non-motor symptoms (such as pain, depression, anxiety, cognition, etc.) were also explored. The efficacy of the levodopa-carbidopa intestinal gel (LCIG) on sleep were assessed. Secondary objectives were to evaluate the prevalence and characteristics of fatigue and nocturia and their main correlations with sleep and other non-motor features. Another secondary objective was to assess the association between sleep impairments and self-compassion, worry, happiness, and personality.

Methods: Two studies were conducted in order to evaluate sleep and its correlations. Fist study: observational case-control study, in which 131 PD patients and 131 age and sex matching controls were included. Second study: open-label observational study in patients with advanced PD undergoing LCIG treatment. The participants at these studies were evaluated using validated scales and questionnaires, some examples being: Parkinson's Disease Sleep Scale version 2 (PDSS-2),

Pittsburgh Sleep Quality Index (PSQI), Parkinson's Disease Questionnaire (PDQ-39), Non-Motor Symptoms Questionnaire (NMSQ), International Parkinson and Movement Disorder Society Non-Motor Rating Scale (MDS-NMS), the International Restless Legs Syndrome Study Group rating scale (IRLS), Athens Insomnia Scale (AIS), Hospital Anxiety and Depression Scale, etc.

Results: For the first study: 131 PD patients and 131 controls were enrolled. Mean age of the patients was 74.41 years old; there were 65 females in each group. Mean LEDD for the PD patients was 497.2 ± 385.2 mg and the mean duration of PD was 5.06 ± 4.21 years. Low sleep quality was identified in 74.80% PD patients, compared to 43.51% controls. In PD patients, a reduced quality of sleep was correlated with the severity of the motor symptoms and with reduced quality of life. PD patients who were considered "bad sleepers" presented more non-motor symptoms (especially depression, orthostatic hypotension, and gastrointestinal symptoms) compared to "good sleepers". Insomnia was identified in 65.64% of the PD patients, compared to 30.53% of the controls. PD patients with insomnia had worse motor symptoms and lower quality of life than those without insomnia. Among PD patients, 42.74% presented excessive daytime sleepiness (EDS); PD patients + EDS presented more insomnia, fatigue, pain, anxiety/depression, visual impairments, and a broader spectrum of non-motor symptoms in comparison to PD patients - EDS. Probable REM sleep behavior disorder (pRBD) was identified in 49 PD patients; these patients presented worse motor symptoms, a worse quality of sleep/quality of life and more insomnia, pain, anxiety/depression and visual disturbances than PD patients without pRBD. Thirty-five PD patients were diagnosed with restless legs syndrome (RLS). Worse sleep quality was observed in these patients ($p<0.001$). RLS was significantly associated with physical fatigue, nocturnal pain and probable sleep-disordered breathing. Nocturia was identified in 113 patients (86.25%). Quality of life and sleep in PD patients + nocturia was worse than in PD patients - nocturia ($p < 0.001$). Fatigue was identified with a higher prevalence among PD patients. PD patients with fatigue presented significantly more EDS, insomnia, pRBD, pain, probable sleep apnoea, anxiety and depression compared to the PD patients without fatigue. PD patients with high worry reported more sleep disturbances compared to those with moderate or low worry. Happiness was low in PD patients with sleep disturbances ($p < 0.001$). Sleep problems were negatively correlated with the following personality traits: extroversion, emotional stability, agreeability, and consciousness. For the second study: Significant improvement following LCIG was observed in total scores of several scales applied for sleep assessment (PSQI, SCOPA sleep, AIS) at 6 months and 1 year, compared to the baseline.
Conclusions: The prevalence of sleep disturbances was higher in PD patients compared to controls. PD patients with sleep disorders ("bad sleepers") presented more non-motor symptoms than "good sleepers". There were significant correlations between sleep impairments and other symptoms, such as depression, anxiety, and pain. Low sleep quality and sleep disturbances have negative consequences on quality of life. LCIG infusion demonstrated sustained beneficial effects on sleep characteristics and sleep quality.

Introduction

Parkinson's Disease (PD) represents the second most common neurodegenerative disorder, with continuously increasing prevalence and a significant impact on the quality of life for patients, as well as on the healthcare system. PD is characterized by motor symptoms that are essential for the

diagnosis (bradykinesia, tremor, extrapyramidal rigidity, gait disturbances) and non-motor symptoms, which can sometimes be the most troublesome complaints for patients. Furthermore, certain symptoms such as hyposmia REM sleep behavior disorder with vivid dreams may occur as early as the prodromal stage of PD and may serve as biomarkers for this condition.

Among the non-motor symptoms, sleep disorders play a distinct role. The broad spectrum of sleep dysfunctions (insomnia, excessive daytime sleepiness, respiratory disturbances, restless legs syndrome, REM sleep behavior disorder), their high prevalence (ranging from 60 to 98% depending on the assessment methods), and the negative impact on quality of life are just some of the reasons why the evaluation of the sleep characteristics should be included in neurological practice in order to implement a personalized and comprehensive management as early as possible. Sleep disorders can occur at any stage of PD progression (including the premotor stage) and tend to worsen as the disease advances.

Considering the increased frequency of sleep disorders, their association with other non-motor symptoms and their impact on quality of life, sleep assessment is essential in current neurological practice. A thorough history of sleep habits and patterns, along with the use of standardized scales and questionnaires, represent quick and easily integrable methods into regular medical practice. Early identification of sleep disorders and related non-motor symptoms and the establishment of a multidisciplinary therapeutic plan contribute to the alleviation of these symptoms and the improvement of patients' quality of life. However, further research is needed in the field in order to establish new therapeutic strategies that could also be effective in delaying or halting the neurodegenerative processes underlying these symptoms.

The present study aims to establish the prevalence and characteristics of sleep disorders and fatigue in patients with PD in comparison to the general population, within a group of participants from Romania. Through the various scales applied in this research, the correlations between sleep disorders and other non-motor symptoms (particularly anxiety, depression, pain, urinary disturbances, cognitive disorders, etc.) were investigated, along with the impact they may have on quality of life. Less-known aspects regarding the role of sleep disorders in happiness and trait of worry, as well as their association with personality types, were also addressed. Additionally, a group of PD patients was followed over one year in order to determine the effectiveness of LCIG therapy on sleep quality. Through a detailed understanding of the various facets of sleep dysfunctions, personalized therapeutic decisions can be established; therefore, the research directions initiated in this study will not only be confined to these findings but will continue to be explored and developed in the future.

Study 1: Characterization of Sleep Disorders

Objectives:

The main objectives of this study were to evaluate the prevalence and the main sleep characteristics, as well as the quality of sleep in PD patients, in comparison to the control group. Another primary objective was to establish correlations between sleep disorders and various parameters, such as the severity of motor symptoms, pain, or other non-motor symptoms.

Secondary objectives included assessing the prevalence and characteristics of fatigue, nocturia, and pain in PD patients and exploring possible links with sleep disorders and other motor/non-motor

symptoms. The possible associations between sleep disorders and cognitive impairments and between sleep disorders and certain psychological factors such as personality, self-compassion, worry, or happiness were also assessed.

Material, method

Design

This observational case-control study was conducted between 01.02.2019 – 01.03.2023, at the Emergency County Clinical Hospital of Brașov. A total of 131 PD patients and 131 controls were enrolled. The study protocol was approved by the Ethics Committee of Transilvania University in Brașov (1.11/01/2019).

Inclusion criteria

For participants in the study group:

- Patients diagnosed with Parkinson's disease (PD), according to the criteria proposed by the Movement Disorders Society (MDS), regardless of the severity or duration of the disease.
- Age ≥ 18 years.
- Voluntary participation agreement, with the signing of the informed consent.

For participants in the control group:

- Patients without a diagnosis of Parkinson's Disease (PD), age- (± 2 years) and sex-matched with subjects from the study group
- Age ≥ 18 years
- Voluntary participation agreement, with the signing of the informed consent.

Exclusion criteria

For participants in the study group:

- Atypical or secondary forms of parkinsonism
- Diagnosis of schizophrenia or bipolar disorder
- Severe bladder or prostate disease; other neurological causes for urinary disorders
- Severe speech disorders or cognitive impairments that could interfere with the quality of the clinical examination and the ability to complete the administered questionnaires.

For participants in the control group:

- Diagnosis of PD
- Atypical or secondary forms of parkinsonism
- Diagnosis of schizophrenia or bipolar disorder
- Severe bladder or prostate disease; other neurological causes for urinary disorders
- Severe speech disorders or cognitive impairments that could interfere with the quality of the clinical examination and the ability to complete the administered questionnaires.

Assessment

All participants completed a standardized questionnaire that included questions on demographics (e.g., age, sex, place of birth, educational level, etc.), personal pathological history, family history, pre-existing medication (including medication for sleep disorders), sleep habits (e.g., usual bedtime, estimated number of hours of sleep/night, presence of certain sleep disorders). For PD patients, additional data collected included age at PD onset, disease duration, Hoehn & Yahr stage (in both ON and OFF states), and Levodopa Equivalent Daily Dose (LEDD). Subsequently, validated scales and questionnaires were completed by the patient or the examiner in order to assess various symptoms.

Sleep was characterized using the following scales: PDSS-2, PSQI, ISI, AIS, ESS, RBDSQ, RBDQ-HK, and IRLS. Quality of life for PD patients was assessed using The Parkinson's Disease Questionnaire (PDQ-39). To evaluate fatigue, the following scales were used: Fatigue Impact Scale (FIS) and Chalder for the control group, and FIS, Chalder, and Parkinson Fatigue Scale (PFS-16) for the PD patients.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), the latter being recommended as a more specific tool for evaluating the cognitive ability in patients with neurodegenerative diseases. Motor characteristics of PD patients were assessed using the MDS-UPDRS (MDS Unified Parkinson's Disease Rating Scale) part III, SCOPA-motor (Scales for Outcomes in Parkinson's disease), The Clinical Impression of Severity Index (CISI), and by determining the Hoehn & Yahr stage (H&Y).

Non-motor symptoms of PD patients were evaluated using the Non-Motor Symptoms Questionnaire (NMSQ), the Non-Motor Symptoms Scale, and The International Parkinson and Movement Disorder Society – Non-Motor Rating Scale (MDS-NMS). Pain was assessed using the visual analog scale (VAS) (from 0 to 10), the King's Parkinson's Disease Pain Questionnaire (KPPQ) and King's Parkinson's disease Pain Scale (KPPS) scales.

Urinary function was investigated using the Urogenital Distress Inventory (UDI-6) and the Overactive Bladder Questionnaire (OABq) – short form.

Several scales were used to determine the levels of anxiety and depression in patients and their psychological characteristics.

Patients' personality was assessed using the Ten-Item Personality Inventory (TIPI). The level of happiness of patients was assessed using the Subjective Happiness Scale (SHS). Another instrument used in this study to evaluate happiness is the Oxford Happiness Questionnaire (OHQ).

Finally, in order to determine if there are correlations between sleep disorders and visual impairments, the visual function was evaluated using the Visual Impairment Questionnaire in PD (VIP).

Statistical Analysis

The recorded data were analyzed using RStudio and IBM SPSS for Windows, version 26.0. Descriptive data were presented as mean ± standard deviation (SD). The distribution of the sample was determined using the Shapiro-Wilk test. Pearson correlation was employed to determine correlations between various parameters. Chi-square tests, Fisher's exact tests, and Mann-Whitney U tests were used for comparing characteristics between groups. Logistic regression models were applied to determine predictors for various analyzed parameters. The Kruskal-Wallis test was used to compare means of subscales in the examined groups.

Results

Sleep Disorders in Parkinson's Disease

PD patients, unlike controls, reported irregular sleep schedule, decreased appetite, more difficulties falling asleep, difficulties waking up in the morning, tiredness in the morning, morning confusion, and difficulties staying awake during the day.

A significantly higher percentage of PD patients exhibited lower sleep quality compared to controls, based on PSQI scores >5. More PD patients reported insomnia compared to those in the control group. Regarding excessive daytime sleepiness, quantified by an ESS score ≥ 10, it was observed that PD patients experience daytime sleepiness to a greater extent than controls (p=0.578), but without statistical significance. Two scores, Berlin and STOP-BANG, were used to assess the risk of obstructive sleep apnea (OSA) during the night. According to the Berlin assessment, 79.39% of PD patients are at risk for OSA, compared to 51.91% of subjects in the control group. As for the STOP-BANG evaluation, the risk of OSA is considered significant for a value ≥ 5. Thus, 29.77% of PD patients are at risk for OSA, compared to 22.90% of participants in the control group.

In patients with Parkinson's Disease (PD), sleep quality tends to decrease with advancing age (p=0.046). Correlations were observed between the decline in sleep quality and decreased quality of life, as patients having PSQI scores >10 showed the highest PDQ-39 scores (p≤0.001).

PD patients classified as "bad sleepers," based on a PDSS score ≥ 18, have statistically significantly higher values for the total PDQ-39 score and for all the individual components of the PDQ-39 scale compared to "good sleepers."

Hypokinesia, Dyskinesias, and Sleep Disorders

Based on the response to item 9 of the PDSS-2 ("Did you feel uncomfortable at night because you were unable to turn over in bed or move due to immobility?"), PD patients were grouped into two categories: those with nocturnal hypokinesia (PD + hypokinesia), comprising 97 (74.04%) participants, and those without nocturnal hypokinesia (PD - hypokinesia), comprising 34 (25.95%) participants. PD patients + hypokinesia had statistically significantly higher scores than PD patients - hypokinesia for the PSQI, PDSS-2, ISI, and AIS scales. Patients with PD + hypokinesia also exhibited more fatigue than those without hypokinesia, more pain, according to the mean total scores of KPPQ ($p < 0.001$) and KPPS ($p = 0.002$), and more depression. The quality of life for patients with hypokinesia is lower than those without hypokinesia, according to the higher total scores of PDQ-39 for the first category, as well as for the individual components of PDQ-39.

Insomnia in Parkinson's Disease

Insomnia, defined by an AIS score of ≥6, was identified in 86 PD patients (65.64%) and in 40 controls (30.53%). Patients with PD + insomnia exhibit a higher prevalence of significant excessive daytime sleepiness (ESS score > 15) and depression compared to controls + insomnia. Lower mean scores for MMSE and MoCA were observed in patients with PD + insomnia, along with higher mean scores for MDS-NMS, compared to the control group + insomnia. Patients with PD and insomnia reported lower

quality of life than those without insomnia, with statistical significance for all components of the PDQ-39 scale.

Excessive Daytime Sleepiness and Parkinson's Disease

An ESS score ≥ 10 was used to identify patients with PD and excessive daytime sleepiness (PD + EDS). Fifty-six patients with PD and EDS were identified, representing 42.74% of the sample. The majority of patients with EDS were male. Patients with EDS exhibited a more severe motor status, as assessed by MDS-UPDRS part III, SCOPA - motor, and CISI.
PD patients with EDS reported significantly lower scores on MMSE and MoCA evaluations compared to those without EDS. Additionally, higher scores were observed for PD patients with EDS regarding all the scales used in the analysis, statistical significance being noted for PSQI, PDSS-2, PDQ-39, SCOPA – sleep daytime and nighttime symptoms, ISI, AIS, FIS, PFS-16, Chalder, NMSQ, NMSS, MDS-NMS, KPPQ, KPPS, Stop-BANG, IRLSSG, OABQ, UDI-6, VIP, and HADS.

Obstructive Sleep Apnea Syndrome and Parkinson's Disease

According to the Berlin evaluation, 79.39% of PD patients are at risk for obstructive sleep apnea (OSA). Patients at increased risk for OSA exhibit higher scores on all scales used in the analysis, with statistical significance identified for PDSS-2, SCOPA – sleep daytime symptoms, ESS, ISI, AIS, RBDSQ, RBSQ – HK, PFS-16, and NMSQ.

Rapid Eye Movement Sleep Behavior Disorder (RBD) in Parkinson's Disease

Based on the RBSQ-HK score, patients with Parkinson's Disease (PD) were divided into two groups: patients with probable RBD (PD + pRBD), with a score <18, and patients without probable RBD (PD – pRBD), with a score ≥18. PD patients + pRBD exhibited greater severity of motor symptoms compared to PD - pRBD patients, according to the MDS-UPDRS part III and SCOPA-motor assessments. The mean total PSQI score in the PD + pRBD group was 11.06 ± 5.10, indicative of reduced sleep quality, and it was significantly higher than the mean score in the PD - pRBD group ($p = 0.003$). The quality of life for PD + pRBD patients was statistically significantly lower than that of PD – pRBD subjects ($p = 0.001$). In the PD + pRBD group, the following symptoms were observed, with statistical significance: insomnia (according to ISI and AIS assessments), fatigue (according to FIS, PFS-16, and Chalder scales), probable OSA (according to the Stop-BANG questionnaire), pain (according to total scores on the KKPQ and KPSS scales), anxiety (through total HADS scores), and other non-motor symptoms.

Restless Legs Syndrome (RLS) in Parkinson's Disease

The diagnosis of RLS was established based on meeting all the five criteria proposed by the International Restless Legs Syndrome Study Group (IRLSSG). In the cohort examined, 35 PD patients (26.71%) met the diagnostic criteria for RLS.
Assessing the individual components of PDQ-39 in patients with and without RLS, statistically significant differences were observed for the domain of body discomfort.

PDSS-2 and MDS-NMS total scores were higher with increasing severity of RLS, indicating poorer sleep quality and a broader spectrum of non-motor symptoms in patients with more severe RLS symptoms.

Fatigue in Parkinson's Disease and Correlations with Sleep Disorders

Fatigue (according to a score on the Chalder scale ≥ 4) is more common in PD patients (38.16%) compared to controls (26.71%). PD patients were assessed using the PFS-16 scale, and those with a total score ≥ 3.3 were considered PD patients + fatigue (61 patients, 46.54%), while those with scores < 3.3 were classified as PD patients - fatigue (70 patients, 53.43%). PD patients + fatigue show higher values for all PSQI components compared to those without fatigue, with statistically significant differences in the following domains: daytime dysfunction, sleep disturbances, sleep efficiency, sleep duration, sleep latency, and sleep quality.

Patients with PD + fatigue have higher scores than those without fatigue on the following scales: SCOPA sleep (nighttime and daytime symptoms), ESS, ISI, AIS, RBDSQ, RBSQ-HK, NMSQ, NMSS, KPPQ, KPPS, Berlin, STOP-BANG, HADS (including HADS-A and HADS-D subscales), PAS, PSWQ, OABQ, UDI-6, IRLSSG, and VIP.

Sleep disorders and cognition

As cognitive decline worsens, higher scores were observed in the following (statistically significant) assessments: PDQ-39, SCOPA sleep – component of daytime symptoms; ESS, AIS, FIS, PFS-16, Chalder, NMSQ, NMSS, MDS-NMS, HADS-A, HADS-D, HADS – total score, PAS, and PSWQ. Regarding the OHQ score, patients with more severe cognitive dysfunction have lower scores than those with moderate dysfunction or normal cognitive function.

Anxiety, Depression, and Sleep Disorders

PD patients with anxiety reported fewer estimated hours of sleep per night compared to PD patients without anxiety, $p = 0.039$. Sleep quality was lower in patients with anxiety ($p = 0.001$). The spectrum of sleep disorders was also broader in patients with anxiety, with statistically significant differences observed in the mean total scores of scales such as SCOPA (nighttime symptoms), ISI, AIS, and RBSQ-HK, which were higher in patients with anxiety compared to those without this symptom. Similarly, significantly higher scores were observed in patients with anxiety for scales such as FIS, PFS-16, Chalder, NMSQ, and NMSS.

Clinically significant depression (defined as an HADS-D score ≥ 11) was identified in 45 of the PD patients (34.35%). PD patients + depression had higher scores for all scales assessed, with statistically significant differences in the following: PSQI, PDSS-2, PDQ-39, SCOPA (nighttime symptoms), ESS, ISI, AIS, RBDSQ, RBSQ-HK, FIS, PFS-16, Chalder, NMS, MDS-NMS, KPPQ, KPPS, STOP-BANG, VAS for pain, PSWQ, OABQ, UDI-6, and VIP. Significantly lower scores in patients with depression compared to those without depression were noted for the MMSE and MoCA scales.

Pain and sleep disorders

PD patients considered "bad sleepers" showed more significant pain than "good sleepers" for all component domains of the KPPS scale, with statistically significant differences highlighted in the following domains: musculoskeletal pain, chronic pain—central pain, nighttime pain—pain related to akinesia, and radicular pain.

Higher total scores were noted in the ESS, ISI, AIS, Chalder, NMSS, MDS-NMS, and IRSSLG scales as the severity of pain increased, with statistical significance.

Nocturia and sleep disorders

Based on a positive response to question number 9 in the NMSQ ("Getting up regularly at night to pass urine"), 113 (86.25%) PD patients with nocturia and 18 (13.74%) PD patients without nocturia were identified. Nocturia was more commonly reported by females ($p = 0.041$); no other significant differences were identified regarding demographic data.

Significant differences were recorded regarding the motor status of PD patients + nocturia, which was found to be more severe compared to PD patients - nocturia. Various scales that assessed sleep quality and sleep disorders (PSQI, PDSS-2, SCOPA sleep—components of nocturnal and diurnal symptoms, ESS, ISI, AIS, RBDSQ) showed significantly higher scores in PD patients + nocturia compared to PD patients - nocturia. Additionally, PD patients + nocturia exhibited lower quality of life (based on the PDQ-39 score), more fatigue (according to FIS, PFS-16, and Chalder scales), more non-motor symptoms (based on NMSQ, NMSS, MDS-NMS scores), more pain (according to KPPQ and KPPS scales), more anxiety/depression, and higher worry (through the assessment of HADS, HADS-A, HADS-D, PAS, and PSWQ scores) compared to PD patients - nocturia.

Worry, Self-Compassion, Happiness, Personality, and Sleep Disorders

No statistically significant differences were recorded between PD patients and controls regarding the level of self-compassion; however, a higher number of participants in the control group showed a moderate level of self-compassion compared to PD patients, while a high level of self-compassion was identified in an equal number of patients in both groups.

It was noted that, as the tendency for worry increased, PD patients estimated more minutes required to fall asleep and fewer hours of sleep per night, but these values did not reach statistical significance. Patients with a more advanced motor status, according to the SCOPA-motor and CISI evaluations, worry more than those with milder motor symptoms. PD patients with high worry exhibited statistically significantly higher scores on the PSQI, PDSS-2, PDQ-39, SCOPA sleep—nocturnal symptoms, ESS, ISI, AIS, RBDSQ, PFS-16, KPPQ, and KPPS scales than PD patients with moderate or low worry.

PD patiets self-assessed their happiness using the Oxford Happiness Questionnaire (OHQ). Patients with lower happiness levels showed statistically significantly higher scores on all evaluated scales (MDS-UPDRS part III, SCOPA-motor, CISI, PSQI, PDSS-2, PDQ-39, SCOPA sleep—nocturnal and diurnal symptoms, ESS, ISI, AIS, RBDSQ, RBSQ-HK, FIS, PFS-16, Chalder, NMSQ, NMSS, MDS-NMS).

In patients PD patients, significant but weak negative correlations were observed between the presence of sleep disorders and personality types characterized by extroversion and emotional stability, and very weak negative correlations with personality types dominated by agreeableness and conscientiousness.

Conclusions

The main conclusions of this study are as follows:

- The prevalence of sleep disorders (difficulties in falling asleep and waking up, tiredness or confusion in the morning, difficulty staying awake during the day) is higher in PD patients compared to controls.
- PD patients use more sleep-inducing medications than controls.
- The sleep disorders most frequently reported by PD patients were tiredness and morning sleepiness, and difficulty maintaining sleep.
- Sleep disorders are more prevalent in females (in the study group).
- Sleep disorders become more severe with the increasing severity of PD.
- PD patients and poor sleep quality experience more daytime sleepiness, pain, and depression, as well as more non-motor symptoms than those with good sleep quality.
- PD patientswith sleep disorders ("bad sleepers") have a lower quality of life and more non-motor disorders, especially depression, orthostatic hypotension, and gastrointestinal disorders. They also experience more visual disturbances than patients without sleep disorders.
- Difficulty falling asleep may be a predictor of poor sleep quality ("bad sleeper").
- Nocturnal hypokinesia is associated with poor sleep quality, insomnia, fatigue, pain, and anxiety/depression.
- Excessive daytime sleepiness was identified in 42.74% of PD patients, especially in male patients, and was associated with motor status, insomnia, and fatigue.
- More than half of PD patients reported insomnia, unlike approximately 30% of controls
- PD patients with insomnia had a more advanced motor status, more non-motor symptoms, and a lower quality of life than PD patients without insomnia.
- The prevalence of probable RBD (based on an RBDSQ score ≥ 5) is higher in PD patients (43.51%) compared controls (19.08%). PD patients with probable RBD have more depression, more non-motor symptoms, and lower cognitive ability than controls with the same suspicion of RBD.
- PD patients with probable RBD had a more advanced motor status, more fatigue, pain, and anxiety, but also lower sleep quality compared to PD patients without probable RBD.
- The association of probable OSA in PD patients is associated with insomnia, excessive daytime sleepiness, and fatigue.
- The association of sleep disorders in PD patients can negatively impact the quality of life.
- The prevalence of fatigue is higher in PD patients compared to controls. Patients with fatigue have fewer estimated total sleep hours/night. Also, in PD patients, fatigue is associated with advanced H&Y stages, excessive daytime sleepiness, insomnia, pain, anxiety, and depression.
- In PD patients, cognitive function tends to be lower as the quality of sleep decreases, according to the total scores of MoCA.
- Anxiety correlates with motor severity and nocturnal sleep disturbances, while depression is associated with insomnia and fatigue in patients with PD.

- Pain is associated with poor sleep quality and, also, with lower quality of life. As the severity of pain increases, more daytime sleepiness, insomnia, and fatigue are observed in PD patients.
- In this study, 35 patients (26.71%) met all 5 criteria necessary for the diagnosis of Restless Legs Syndrome (RLS), compared to 9 participants (6.87%) in the control group.
- Quality of life is lower in PD patients with RLS compared to PD patients without RLS. Anxiety and depression are associated with RLS in PD patients
- Worry is more pronounced in PD patients, especially in those with PD and sleep disorders ("bad sleepers").
- Nocturia is one of the most commonly reported symptoms by PD patients, especially by females. This symptom has significant consequences on the quality of life and sleep.
- Happiness is lower in patients with PD and sleep disturbances.
- Sleep disorders are negatively correlated with the personality types dominated by extraversion, emotional stability, agreeableness, and conscientiousness.

Practical applicability

Sleep disorders are highly prevalent and diverse in Parkinson's Disease (PD) and can negatively patients' quality of life. In clinical practice, screening for sleep disorders should be performed for all PD patients at all stages of progression. However, the pattern of sleep disorders may vary depending on the gender of the patients. Based on the results of this study, a structured algorithm has been proposed that can be applied for the rapid and personalized assessment of PD patients, aiming to establish a multidisciplinary therapeutic approach.

Study 2. Longitudinal Assessment of Patients with Intrajejunal Levodopa Infusion (LCIG)

Objecive:

The main objective of this study was to evaluate the efficacy of intrajejunal levodopa infusion therapy (levodopa-carbidopa intestinal gel – LCIG) on sleep disorders at 6 months and 1 year after initiating this treatment.

Material, Method

Study Design

Ten patients with advanced Parkinson's disease (PD) who were initiated on LCIG therapy were recruited for the study at the Clinical Neurology Department of the Emergency County Clinical Hospital Braşov. This was a longitudinal, observational, open-label study. Patients were evaluated clinically evaluated and by questionnaires at baseline (before the initiation of LCIG treatment), at 6 months and at 12 months of treatment. Clinical assessment of patients was performed in the "ON" state. The study was approved by the Ethics Committee of Transilvania University of Braşov (1.11/01/2019).

Inclusion criteria

Patients were included based on the following criteria:

- Diagnosis of Parkinson's disease (PD) according to the clinical diagnostic criteria proposed by the Movement Disorders Society (MDS)
- Advanced stage of PD requiring initiation of LCIG therapy
- Patients without dementia or severe cognitive decline (MMSE > 24)
- Patients who voluntarily wanted to participate in the study and signed the informed consent.

Exclusion Criteria

The exclusion criteria were as follows:

- Secondary causes of parkinsonism
- Patients with advanced stages of PD with indications for other device-assisted therapies
- Severe cognitive impairment
- Comorbidities that could have influenced sleep or sleep quality (e.g., stroke, chronic pulmonary, renal, or hepatic conditions).

Assessments

Information on age, sex, age at onset of Parkinson's disease (PD), disease duration, Hoehn and Yahr stage (in ON and OFF states), pre-existing medication (including sleep-related medications), and Levodopa Equivalent Daily Dose (LEDD) was collected. Cognition was assessed using the MMSE and MoCA scales. The standardized questionnaires used for sleep evaluation during the three monitoring visits were PDSS-2, SCOPA-sleep, PSQI, AIS, and ESS.

Satistical analysis

Data were analyzed using SPSS software, version 23.0. Descriptive statistics were used for the clinical characteristics of patients at baseline. The Wilcoxon test was used to compare scores before and after the initiation of LCIG treatment. The Friedman test was used to compare mean scores before initiation, at 6 months, and at 12 months of treatment. Associations between various parameters were analyzed using Spearman correlation. A probability value (p) <0.05 was considered statistically significant.

Results

As part of the longitudinal follow-up, 10 patients with advanced PD requiring treatment with intrajejunal levodopa infusion (Levodopa-Carbidopa Intestinal Gel – LCIG) were evaluated before initiation of treatment, at 6 months, and at 1 year to observe the effects of LCIG on sleep.

The total self-reported sleep time increased from 5.9 ± 1.19 hours before LCIG initiation to 7 ± 0.66 hours at 6 months of treatment and 7.2 ± 0.63 hours at 12 months. Significant improvements were observed at 6 months and 12 months after the initiation of LCIG treatment for the following sleep rating scales: PSQI ($p = 0.007$), total SCOPA-sleep score ($p = 0.008$), sub-score SCOPA-sleep –

nocturnal symptoms (p = 0.007), and AIS (p = 0.001). No statistically significant differences were noted regarding the evolution of ESS and SCOPA-sleep – diurnal symptoms scores.
Regarding sleep quality, significant improvements were observed for three domains of the PSQI scale: component 1 (subjective sleep quality), p = 0.004, component 2 (sleep latency), p = 0.012, and component 4 (sleep efficiency), p = 0.003.

Study conclusions

The results of this longitudinal study suggest that LCIG therapy is effective in improving sleep disorders in patients with advanced PD. Sleep quality, insomnia, morning tiredness, as well as motor symptoms (painful morning postures, tremor, immobility and discomfort, limb pain) significantly improved with LCIG treatment, and these beneficial effects were consistent over the course of one year. However, no significant improvement in Excessive Daytime Sleepiness (EDS) was noted.

Originality and Innovative Contributions to the Field

This study confirms some literature data regarding the prevalence and impact of sleep disorders in PD patients, but applied to a newly investigated population in Romania. The current research included the analysis of over 35 validated scales for characterizing motor status, various sleep disorders (insomnia, excessive daytime sleepiness, REM sleep behavior disorder, restless legs syndrome), fatigue, non-motor symptoms, etc., as well as a standardized questionnaire for assessing demographic data and sleep characteristics. Thus, it was observed that sleep disorders are more common in PD patients compared to controls, being reported by over half of the subjects with PD. Poor sleep quality was identified in over 70% of PD patients. The most common sleep disorders identified in this group of participants were tiredness and sleepiness upon waking in the morning, and difficulties in maintaining sleep.
The study provides new insights into the multiple connections between sleep disorders and other non-motor symptoms, including gastrointestinal, urinary, pain, and visual disturbances. PD patients with poor sleep quality showed a broader spectrum of non-motor disorders, with statistically significant values recorded for depression, orthostatic hypotension, gastrointestinal disorders, sleep disorders, and pain. Similarly, PD patients with excessive daytime sleepiness associated more pain, urinary disorders, anxiety, depression, and visual disturbances compared to those without this symptom. Difficulty falling asleep is a predictor of poor sleep quality, according to the results of this study.
Other aspects evaluated in this research, unexplored until now in the literature, consist in demonstrating the association between sleep disorders and worriness, as well as highlighting the associations between sleep disorders, personality, and happiness. The results of this study attest that PD patients with sleep disorders have high worry and a low level of happiness. Sleep dysfunctions negatively correlate with the personality types characterized by extroversion, emotional stability, agreeableness, and conscientiousness.
Additionally, this research explored the associations between fatigue (a related symptom of sleep disorders) and other symptoms such as pain, visual disturbances, and nocturia—aspects that have been incompletely studied in the literature to date. Fatigue is often a neglected symptom in current clinical practice. The results of this study demonstrate a high prevalence of fatigue among PD

patients (46.54%) and its negative impact on quality of life, thus requiring attention and assessment for establishing appropriate therapeutic strategies.

The present study also included the evaluation over one year of sleep characteristics in PD patients undergoing intrajejunal levodopa infusion therapy (LCIG). Validated scales were used to characterize sleep. This therapy has been shown to improve sleep quality and other symptoms, such as insomnia, morning tiredness, and motor symptoms. The beneficial effects on sleep remained consistent throughout the follow-up period. To date, few studies have had the primary objective of examining sleep evolution following LCIG treatment.

By obtaining statistically significant results, this study provides arguments supporting the idea that sleep disorders are common in Parkinson's disease, have multiple connections with motor status and other non-motor symptoms, and can have a strong impact on the patient's quality of life. For these reasons, sleep and sleep quality should be assessed both in current medical practice and in future research, requiring new therapeutic directions and a multidisciplinary approach to these symptoms.

Publication List

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