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Abstract:	Background: Little research has been conducted regarding the relationship between sleep disorders and different pain types in Parkinson's disease (PD). Objective: To explore the influence of the various pain subtypes experienced by PD patients on sleep. Methods: Three-hundred consecutive PD patients were assessed with the PD Sleep Scale-Version 2 (PDSS-2), King's PD Pain Scale (KPPS), King's PD Pain Questionnaire (KPPQ), Visual Analog Scales for Pain (VAS-Pain), and Hospital Anxiety and Depression Scale. Results: According to the PDSS-2, 99.3% of our sample suffered from at

	least one sleep issue. Those who reported experiencing any modality of pain suffered significantly more from sleep disorders than those who did not (all, $p<0.003$). The PDSS-2 showed moderate-to-high correlations with the KPPS ($rS=0.57$), KPPQ (0.57), and VAS-Pain (0.35). When PDSS-2 items 10-12 (pain-related) were excluded, the correlation values decreased to 0.50, 0.51, and 0.28, respectively, while these items showed moderate-to-high correlations with KPPS (0.56), KPPQ (0.54), and VAS-Pain (0.42). Among the variables analyzed, multiple linear regression models suggested that KPPS and KPPQ were the most relevant predictors of sleep disorders (as per the PDSS-2), although following exclusion of PDSS-2 pain items depression was the relevant predictor. Depression and anxiety were the most relevant predictors in the analysis involving the VAS-Pain. Regression analysis considering only the KPPS domains showed that nocturnal and musculoskeletal pain were the best predictors of overall nocturnal sleep disorder. Conclusions: Pain showed a moderate association with nocturnal sleep dysfunction in PD. Some pain subtypes had a greater effect on sleep than others.

Relationship of nocturnal sleep dysfunction and pain subtypes in Parkinson's disease

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Abstract

Background: Little research has been conducted regarding the relationship between sleep disorders and different pain types in Parkinson's disease (PD).

Objective: To explore the influence of the various pain subtypes experienced by PD patients on sleep.

Methods: Three-hundred consecutive PD patients were assessed with the PD Sleep Scale-Version 2 (PDSS-2), King's PD Pain Scale (KPPS), King's PD Pain Questionnaire (KPPQ), Visual Analog Scales for Pain (VAS-Pain), and Hospital Anxiety and Depression Scale.

Results: According to the PDSS-2, 99.3% of our sample suffered from at least one sleep issue. Those who reported experiencing any modality of pain suffered significantly more from sleep disorders than those who did not (all, $p<0.003$). The PDSS-2 showed moderate-to-high correlations with the KPPS ($r_S=0.57$), KPPQ (0.57), and VAS-Pain (0.35). When PDSS-2 items 10-12 (pain-related) were excluded, the correlation values decreased to 0.50., 0.51, and 0.28, respectively, while these items showed moderate-to-high correlations with KPPS (0.56), KPPQ (0.54), and VAS-Pain (0.42). Among the variables analyzed, multiple linear regression models suggested that KPPS and KPPQ were the most relevant predictors of sleep disorders (as per the PDSS-2), although following exclusion of PDSS-2 pain items depression was the relevant predictor. Depression and anxiety were the most relevant predictors in the analysis involving the VAS-Pain. Regression analysis considering only the KPPS domains showed that nocturnal and musculoskeletal pain were the best predictors of overall nocturnal sleep disorder.

Conclusions: Pain showed a moderate association with nocturnal sleep dysfunction in PD. Some pain subtypes had a greater effect on sleep than others.

Introduction

A range of sleep disorders and subtypes of pain, are very prevalent non-motor symptoms of Parkinson's disease (PD) that occur from the prodromal to the palliative stages of PD (1-5). Sleep dysfunction, which affects 60-98% of PD patients, may be manifested as insomnia, sleep disruption, sudden onset of sleep, rapid-eye-movement (REM) sleep behavior disorder, non-REM parasomnias, and restless legs syndrome (6-8). Surveys suggest that insomnia affects 46% of PD patients, vivid dreams 34%, acting out while dreaming 36%, and restless legs syndrome 42% (1). Depression, anxiety, cognitive problems, stress, and daytime sleepiness have been found to result from these conditions, and sleep disorders in PD have a negative impact on patients' quality of life (QoL) (9,10).

On the other hand, using the King's Parkinson's Disease Pain Scale (KPPS) (11), the syndromic nature of pain has been formally subdivided into several patterns. Prior research has shown that the prevalence of pain is 68-81% in PD patients (12-14) and that it can be manifested in several modalities, such as musculoskeletal (41-89%), dystonic (15-17%), radicular-neuropathic (27-32%), and central pain (4-22%) (2,12,14-18). Furthermore, 35% of PD patients are affected by two types of pain, 10% by three, and 2% by four (14). Pain can become crippling in a subset of PD patients, affect their ability to conduct activities of daily living (ADL) (13,19), and negatively impact their QoL (20-22). Yet, despite the impact of this non-motor symptom, pain often remains underdiagnosed and undeclared (23).

PD patients with pain have been found to experience poorer sleep quality and more sleep disorders than patients without pain (24). Using the Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) (25) and the KPPS (11), the present study seeks both to explore the influence of the various modalities of pain experienced by PD patients on sleep disorders and to examine the

relationship between sleep disorders and other factors, such as anxiety and depression, motor complications, and QoL.

Methods

Design

International, multicenter, observational, cross-sectional study.

Patients

Consecutive PD patients were included in this study if they were diagnosed with PD according to the UK PD Brain Bank criteria (26) and if they declared unexplained pains on item 10 of the Non-Motor Symptoms Questionnaire (27). However, if patients had an alternative or uncertain diagnosis of PD or drug-induced PD, were unable to consent, had dementia as diagnosed by international criteria, or were diagnosed with known conditions that cause pain unrelated to PD (e.g. arthritis, malignancy, etc.), they were excluded from this study (28).

Patients were recruited from nine different movement disorder centers across the United Kingdom (eight) and Romania (one) from August 2013 to February 2016. This study was conducted under the UK's National Institute of Health Research's portfolio of studies (UKCRN No. 13344) (28).

Ethical issues

The study was approved by the respective hospital ethical committees/institutional review boards. All participants provided informed consent before inclusion in the study.

Assessments

Socio-demographic data and disease history (i.e. sex, age, ethnicity, PD duration, current treatment, and surgery) were collected from all patients. According to Tomlinson et al., levodopa equivalent daily dose (LEDD) was also calculated (29).

The following instruments were used to assess each patient:

1. Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) (25), a 15-item, patient-completed clinical tool used to assess the frequency of sleep disturbances during the past week in PD patients. Items 10, 11, and 12 of the PDSS-2 directly assess pain while sleeping or when waking up.

2. Hoehn-Yahr classification (HY) (30), a five-stage system that classifies PD on a continuum from unilateral expression of the disease to the most severe.

3. Scales for Outcomes in Parkinson's Disease-Motor (SCOPA-Motor) (31), a 21-item scale that measures motor impairment, difficulty with ADL, and motor complications.

4. Non-Motor Symptoms Scale (NMSS) (32), a 30-item scale that considers the frequency and severity of the non-motor symptoms of PD grouped into nine domains: cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary function, sexual function, and miscellaneous. Item 27 of the NMSS directly inquires about unexplained pains.

5. Clinical Impression of Severity Index for PD (CISI-PD) (33), an overall estimate of PD based on motor signs, disability, motor complications, and cognitive status.

6. King's Parkinson's Pain Scale (KPPS) (11), a 14-item scale that evaluates the types of pain suffered by PD patients: musculoskeletal, chronic, fluctuation-related, nocturnal, oro-facial, discoloration and oedema/swelling, and radicular pain. Each item is rated by the clinician according to its severity (from 0 to 3) and frequency (from 0 to 4). An item's score is then

calculated as the product of each pain type's frequency and severity, and a total score is calculated by summing the scores of each item. KPPS time frame is "the past month".

7. King's Parkinson's Pain Questionnaire (KPPQ) (28), a patient-completed derivative of the KPPS, asks about the same pain modalities as the KPPS, and only provides information regarding the presence or absence of 14 specific types of pain in a given patient. The time framework is "past month".

8. Visual Analog Scales for Pain Severity and Frequency (VAS-Pain) (34). A VAS-Pain total score was calculated by multiplying both scales, whose time framework was "past month".

9 Hospital Anxiety and Depression Scale (HADS) (35), which is a 14-item, patient-completed scale with subscales for anxiety and depression.

10. EQ-5D-3L (36), which contains five items that inquire about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that assesses current health status.

11. Parkinson's Disease Questionnaire-8 items (PDQ-8) (37), a PD-specific health-related QoL measure. Item 8 of the PDQ-8 specifically asks about painful muscle cramps or spasms.

<u>Data Analysis</u>

Data were anonymized and sent to the National Center of Epidemiology, Carlos III Institute of Health, in Madrid, Spain for analysis.

Socio-demographic, historical data, and rating scales scores were examined using descriptive statistics (i.e. mean, median, and, standard deviation). Main data showed non-normal distribution (Shapiro-Francia test); therefore non-parametric statistical tests were used.

The prevalence of each sleep symptom assessed by the PDSS-2 was calculated by considering an item score ≥1 to be the presence of that symptom and an item score of 0 to be its absence. Furthermore, patients were divided into groups using the prevalence of each of the seven pain modalities (domains) assessed by the KPPS, which were calculated using the same method described above (15). Then, after excluding the PDSS-2 pain-related items (items 10-12: "PDSS-2 Pain"), the effect of each type of pain on non-pain-related PDSS-2 score was determined by comparing the means of the two groups (with and without that specific pain) and by applying the Mann-Whitney test.

The association of the PDSS-2 with the KPPS and other clinical variables evaluating pain present in the study was assessed by Spearman correlations. Partial correlations were also used to adjust these associations for age, PD duration, SCOPA motor examination, and LEDD. Coefficient values higher than 0.50 were deemed strong correlations and those from 0.30 to 0.49 moderate ones.

The influence of pain on PDSS-2 score was determined using multiple linear regression models in which the dependent variable was the PDSS-2 and the independent ones were (after checking for association, collinearity, and interaction): SCOPA-Motor ADL and complications sections, HADS-Anxiety, HADS-Depression, and the NMSS gastrointestinal and urinary domains. Each model also included one of the following pain measures as an independent variable: KPPS, KPPQ, and VAS-Pain. In order to explore the influence of each type of pain on nocturnal sleep issues, another multiple linear regression analysis was conducted using the KPPS domains as predictors of PDSS-2 total score.

To exclude the influence of the PDSS-2 pain-related items on the findings, the correlation coefficients and multiple regression models were recalculated after excluding the "PDSS-2 Pain" dimension.

For further analysis regarding the PDSS-2 total score, Kruskal-Wallis and Mann-Whitney tests were conducted to determine if there were significant differences between sexes, groups of age, PD duration, and LEDD (based on quartiles) in reference to the scale. Finally, Spearman rank correlations were calculated between PDSS-2 and the remaining assessments in the study.

Results

Three hundred PD patients, most of them males (59.7%) and predominantly Caucasians (84.8%) were included in the study. Median HY was 2 with an interquartile range of 2–3 (limits: 1–5). One hundred and fifty one patients (50.3%) had Postural instability and gait difficulty PD subtype; 93 (31.0%) showed tremor predominant subtype; and 56 (18.7%) were indeterminate (38,39). Other descriptive data of the sample are displayed in the Table 1. On the PDSS-2, the average total score was 18.57±10.89 (range: 0–51), while scores were 22.85±19.45 (0–102) on the KPPS, 3.96±2.56 (1–12) on the KPPQ, and 32.78±24.40 (0–100) on the VAS-Pain.

Table 2 shows the prevalence rates for each sleep issue assessed by the PDSS-2; 99.3% of our sample was afflicted by at least one sleep problem. Moreover, as shown in Table 3, those who reported experiencing any modality of pain suffered from significantly more severe non-pain-related sleep disorders than those who did not (all, $p<0.003$).

The PDSS-2 was moderately or highly correlated with the KPPS domains of fluctuation-related pain (r_S=0.34), nocturnal pain (0.52), discoloration and oedema/swelling related pain (0.31), and radicular pain (0.32) as well as with the KPPS total score (0.57), whereas it showed weak relationships with the remaining KPPS domains (r_S=0.20–0.28). Similarly, the correlations with KPPQ (0.57) and VAS-Pain (0.35) were moderate-to-high. These coefficients were only slightly modified in the partial correlation analysis of total scores (KPPS, 0.51; KPPQ, 0.52; and VAS-Pain, 0.31). When the “PDSS-2 Pain” component was excluded from the PDSS-2 total score, all

correlation coefficients with total scores decreased 0.06-0.07 (KPPS, 0.50; KPPQ, 0.51, VAS-Pain, 0.28), and 0.04 in average (0.01-0.08) with KPPS domains. Furthermore, the two QoL assessments showed moderate-to-high associations with the three pain measures in the study: -0.45 to -0.60 for the EQ-5D-3L and 0.42 to 0.59 for the PDQ-8.

Using "PDSS-2 Pain" (the sum of items 10-12), the following correlations were found between this pain score and other measures in the study: the KPPS domains of musculoskeletal (r_S=0.30), fluctuation-related (0.32), nocturnal (0.52), and radicular (0.37) pain as well as its total score (0.56); the KPPQ (0.54); VAS-Pain (0.42); the EQ-5D-3L's pain/discomfort question (0.37); and PDQ-8 item 8 (0.43).

Table 4 shows the results of six multiple linear regression models. In the analyses using the KPPS and KPPQ, pain was shown to be the most powerful predictor of the sleep disorders assessed by the PDSS-2 (p<0.001); however, in the analysis using the VAS-Pain, depression and then anxiety were the best predictors of these sleep problems (p<0.001). However, when the "PDSS-2 Pain" domain was excluded, depression and urinary disorders were first and second determinants in importance in the models with KPPS and KPPQ, whereas there were no changes in those of the VAS-Pain model (Table 4).

An additional multiple linear regression model using the KPPS pain modalities as predictors of the PDSS-2 was explored. In this model, only nocturnal (p<0.001; beta=0.38) and musculoskeletal (p=0.003; beta=0.15) pain were significant determinants of overall nocturnal sleep disorder, a finding that was not modified by excluding the pain-related items of the PDSS-2 (Table 5).

Patients who had longer PD duration (p=0.001) and higher LEDD (p<0.001) also reported significantly more severe sleep disturbances. Moreover, the PDSS-2 showed moderate-to-high correlations with the other clinical measures in the study: CISI total score (r_S=0.39); HADS-

Anxiety (0.50); HADS-Depression (0.54); EQ-5D summary index (-0.49); PDQ-8 summary index (0.60); SCOPA-Motor ADL (0.43), complications (0.38), and total score (0.40); the NMSS domains of sleep/fatigue (0.58), mood/apathy (0.34), gastrointestinal (0.37), urinary (0.35), and its total score (0.54).

Discussion

In line with previous findings, almost all patients in our sample (99.3%) declared having at least one nocturnal sleep dysfunction according to the PDSS-2, confirming the high prevalence of this non-motor symptom in PD (6). The most prevalent of these issues in our study were nocturia (85.0%), tiredness and sleepiness upon waking (72.0%), and poor sleep quality (71.7%). While some studies have found figures that are similar to ours, other studies did not (40-42); however, the PDSS-2 has never been used to analyze the prevalence of nocturnal sleep disorders in PD, and, therefore, our results cannot be compared at present with other studies. For example, problems related to “PDSS-2 Pain” showed prevalence rates of 44.1-54.2%, but data encompassing a similar combination of items has not been explored previously to our knowledge. Yet, a limitation of our study is that it included only patients who experience at least some form of pain, and, thus, our findings cannot be generalized.

On the other hand, it is very well known that pain can interfere with sleep. Specifically, it has been demonstrated that pain in PD is linked to poorer sleep quality (24,43). In fact, after removing the PDSS-2 pain-related items, those who reported the presence of any type of pain on the KPPS had significantly higher scores on the PDSS-2. Moreover, the PDSS-2 score was moderately or highly correlated with KPPS total score and several domains (i.e. fluctuation-related, nocturnal, discoloration and oedema/swelling, and radicular pain), the VAS-Pain, and the KPPQ. As these coefficient values were only slightly modified when adjusting for age, PD

duration, motor examination, and LEDD, our results suggest that these PD-related variables do not associate significantly with the impact of pain on nocturnal sleep. Similarly, Beiske et al. found that pain was not associated with age, disease duration, or disease severity (2).

Multiple linear regression analyses showed that, among the variables that have been analyzed, the KPPS and KPPQ were the most relevant predictors of the PDSS-2 total score in their respective models, while the predictive effect of the VAS-Pain was barely significant in its model; thus, it can be concluded that pain may have a greater impact on PD patients' sleep than other factors and that the PD-specific instruments for pain (i.e. KPPS and KPPQ) may perform better than generic pain tools (i.e. VAS-Pain). However, a limitation of this analysis is the presence of a pain-related domain ("PDSS-2 Pain") in the PDSS-2, which intensified the relationship between these instruments in such a way that urinary disorders replaced the PD-specific pain evaluations when the PDSS-2 Pain domain was kept out.

Pain and sleep in PD can be pathophysiologically linked. Noradrenergic cells of the locus coeruleus are known to modulate the cortical signal-to-noise ratio. They are also part of the medial pain system, which regulates the pain-control system that inhibits the relay nuclei for somatosensory and viscerosensory inputs (44). In Braak stage 2, stage 1-related PD pathology becomes more advanced and lesions (mainly Lewy neurites) occur in the medulla oblongata and pontine tegmentum, including the lower raphe nuclei, the magnocellular portions of the reticular formation, and the gigantocellular reticular nucleus (45). The coeruleus and raphe neurons exert an inhibitory effect on the tegmental pedunculopontine nucleus, which stimulates REM sleep. The reticular cholinergic neurons also regulate arousal mechanisms. As such, the origins of both pain and sleep dysfunction in PD, even at the premotor Braak stage 2, appear to be closely related pathophysiologically (46).

Furthermore, when considering only “PDSS-2 Pain,” it showed moderate or high correlations with several KPPS domains (i.e. musculoskeletal, fluctuation-related, nocturnal, and radicular pain) and with the KPPS, KPPQ, and VAS-Pain total scores.

Also, another multiple linear regression analysis showed that musculoskeletal and nocturnal pain were significant predictors of PDSS-2 total score using a model that included only the domains of the KPPS. These results suggest that specific types of pain are more relevant to nocturnal sleep problems (44,46).

However, this is not to say that pain is the only predictor of sleep problems in PD. Several studies have shown that anxiety and depression are also related to poor sleep quality (7,24,47). In the multiple linear regression model involving the VAS-Pain, the HADS-Depression, followed by the HADS-Anxiety, was the most pertinent predictor of PDSS-2 total score. These two psychiatric measures were also moderately or highly correlated with the PDSS-2.

Neurotransmitter-dysfunction-based non-motor endophenotypes of PD have been recently proposed, and pain and sleep dysfunction characterize some of these phenotype clusters, which form part of the limbic- and brainstem-generated cholinergic and serotonergic subtypes of PD (48,49).

Additionally, the NMSS urinary and gastrointestinal domains as well as the SCOPA-Motor complications section were also significant predictors of PDSS-2 total score in the models explored in this study. Similarly, the NMSS domains of sleep/fatigue, mood/apathy, gastrointestinal, and urinary as well as NMSS total score were also moderately or highly associated with the PDSS-2. Fatigue, cognitive impairment, and urinary issues were also found to be significantly associated with sleep quality in another study (7).

Moderate associations were found between the PDSS-2 and the SCOPA-Motor ADL, complications section, and its total score, as well as between the PDSS-2 and the CISI-PD,

suggesting that motor problems and disability may have some effect on sleep-related issues in PD (8,50). In fact, nocturnal hypokinesia has recently been highlighted as an important factor impairing sleep quality (51).

Although PD duration and LEDD were not significant predictors of PDSS-2 total scores, patient groups with longer PD duration and higher LEDD scored significantly higher on the PDSS-2 than those with shorter PD duration and lower LEDD, suggesting that problems with sleep could worsen with disease progression (52). Additionally, there were no significant differences between groups of age and sex in reference to PDSS-2 total score, although differences related to sex were found in another study (53).

Sleep disturbances and pain are significant factors in patients' lives as demonstrated by the moderate-to-high correlations of the PDSS-2, KPPS, KPPQ, and VAS-Pain with both the EQ-5D-3L and the PDQ-8, the two measures of QoL utilized in this study. When considering only "PDSS-2 Pain," there were moderate correlations with the EQ-5D-3L's pain/discomfort question and PDQ-8 item 8, findings in line with previous studies that identified pain is a determinant factor of QoL (54).

In conclusion, our results show that (1) nocturnal sleep disorders could affect the majority of PD patients; (2) pain, as a whole, showed a moderate association with the severity of nocturnal sleep disorders; and (3) nocturnal sleep disorders could be influenced more by certain subtypes of pain than others.

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    B. Organization: PMM, AR, KRC
    C. Execution: SP, RS, CC, DM, CFP, BK, TA, DP
2) Statistical Analysis
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    B. Execution: PMM, JBW
    C. Review and Critique: AR, AA, PO, CT, KRC
3) Manuscript
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- Ethics committees that approved the study:

In United Kingdom: Institute of Psychiatry, Psychology, & Neuroscience at King's College, London; King's College Hospital NHS Foundation Trust, London; Forth Valley Royal Hospital, Larbert, Scotland; Yeovil Hospital, Somerset; Derriford Hospital, Plymouth; Princess Royal University Hospital, King's College Hospital, Kent; Guy's Hospital, London; and Neurology, St. Georges's Hospital, London. In Romania: Ethics Committee of the Transilvania University from Brasov, Romania.

- All participants provided informed consent before inclusion in the study.
- We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

References

1. Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; Study using nonmotor symptoms questionnaire in 545 patients. Mov Disord 2007; 22: 1623-1629.

2. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: Prevalence and characteristics. Pain 2009; 141: 173-177.

3. Zis P, Rizos A, Martinez-Martin P, Pal S, Silverdale M, Sharma J, et al. Non-Motor Symptoms Profile and Burden in Drug Naïve Versus Long-Term Parkinson's Disease Patients. J Parkinson Dis 2014; 4: 541–547.

4. Zis P, Erro R, Walton CC, Sauerbier A, Chaudhuri KR. The range and nature of non-motor symptoms in drug-naive Parkinson's disease patients: a state-of-the-art systematic review. NPJ Parkinson's Dis 2015; 1: 15013.

5. Antonini A, Tinazzi M, Abbruzzese G, et al. Pain in Parkinson's disease: facts and uncertainties. Eur J Neurol. 2018. doi: 10.1111/ene.13624.

6. Swick TJ. Parkinson's disease and sleep/wake disturbances. Parkinsons Dis 2012; 2012: 205471.

7. Kurtis MM, Rodriguez-Blazquez C, Martinez-Martin P; ELEP Group. Relationship between sleep disorders and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2013; 19: 1152-1155.

8. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev 2017; 35: 33-50.

9. Ylikoski A, Martikainen K, Sieminski M, Partinen M. Sleeping difficulties and health-related quality of life in Parkinson's disease. Acta Neurol Scand 2017; 135: 459-468.

10. Shafazand S, Wallace DM, Arheart KL, et al. Insomnia, Sleep Quality, and Quality of Life in Mild to Moderate Parkinson's Disease. Annals of the American Thoracic Society 2017; 14: 412-419.

11. Chaudhuri KR, Rizos A, Trenkwalder C, et al. King's Parkinson's disease pain scale, the first scale for pain in PD: An international validation. Mov Disord 2015; 30: 1623-1631.

12. Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: A systematic review using the modified QUADAS tool. Mov Disord 2012; 27: 480-484.

13. Allen NE, Wong CM, Canning CG, Moloney N. The Association Between Parkinson's Disease Motor Impairments and Pain. Pain Med 2016; 17: 456-462.

14. Valkovic P, Minar M, Singliarova H, et al. Pain in Parkinson's disease: A cross-sectional study of its prevalence, types, and relationship to depression and quality of life. PLoS One 2015; 10: e0136541.

15. Ford B. Pain in Parkinson's disease. Mov Disord 2010; 25 (Suppl 1):S98-103.

16. Ha AD, Jankovic J. Pain in Parkinson's disease. Mov Disord 2012; 27:485-491.

17. Wasner G, Deuschl G. Pains in Parkinson disease--many syndromes under one umbrella. Nat Rev Neurol 2012; 8: 284-294.

18. Ozturk EA, Gundogdu I, Kocer B, Comoglu S, Cakci A. Chronic pain in Parkinson's disease: Frequency, characteristics, independent factors, and relationship with health-related quality of life. J Back Musculoskelet Rehabil 2017; 30: 101-108.

19. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: Findings from the 2011 National Health and Aging Trends Study. Pain 2013; 154: 2649-2657.

20. Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: A controlled cross-sectional study. Parkinsonism Relat Disord 2004; 10: 129-136.

21. Choi SM, Kim BC, Jung HJ, et al. Impact of pain and pain subtypes on the quality of life of patients with Parkinson's disease. J Clin Neurosci 2017; 45: 105-109.

22. Martinez-Martin P, Manuel Rojo-Abuin J, Rizos A, et al. Distribution and impact on quality of life of the pain modalities assessed by the King's Parkinson's disease pain scale. NPJ Parkinsons Dis 2017; 3: 8.

23. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. Mov Disord 2010; 25: 704-709.

24. Rana AQ, Qureshi ARM, Shamli Oghli Y, et al. Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity, and correlates with pain intensity and quality. Neurol Res 2018. DOI: 10.1080/01616412.2018.1462880.

25. Trenkwalder C, Kohnen K, Högl B, et al. Parkinson Disease Sleep Scale – Validation of the Revised Version PDSS-2. Mov Disord 2011; 26: 644-652.

26. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745-752.

27. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: The NMSQuest study. Mov Disord 2006; 21: 916-923.

28. Martinez-Martin P, Rizos AM, Wetmore J, et al. First comprehensive tool for screening pain in Parkinson's disease: The King's Parkinson's Disease Pain Questionnaire (KPPQ). Eur J Neurol. Accepted: 11-5-2018. DOI: 10.1111/ene.13691.

29. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010; 25: 2649-2653.

30. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. Neurology 1967; 17: 427-442.

31. Marinus J, Visser M, Stiggelbout AM, et al. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: The SPES/SCOPA. J Neurol Neurosurg Psychiatry 2004; 75: 388–395.

32. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 2007; 22: 1901-1911.

33. Martinez-Martin P, Forjaz MJ, Cubo E, Frades B, de Pedro Cuesta J, ELEP Project Members. Global versus factor-related impression of severity in Parkinson's disease: A new clinimetric index (CISI-PD). Mov Disord 2006; 21: 208-214.

34. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R. Eds. Handbook of Pain Assessment. 2001; p15-34.

35. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–370.

36. EuroQol Group. EuroQol- a new facility for the measurement of health related quality of life. Health Policy 1990; 16: 199-208.

37. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire. Psychology & Health 1997; 12: 805-814.

38. Verbaan D, Marinus J, Visser M, et al. Cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007; 78: 1182-1187.

39. van der Heeden JF, Marinus J, Martinez-Martin P, et al. Postural instability and gait are associated with severity and prognosis of Parkinson disease. Neurology. 2016; 86: 2243-2250.

40. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. Mov Disord 2002; 17: 775-781.

41. Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease. A self-reported, community-based survey. Sleep Med 2002; 3: 147-149.

42. Falup-Pecurariu C, Diaconu Ş. Sleep Dysfunction in Parkinson's Disease. Int Rev Neurobiol 2017; 133: 719-742.

43. Rana AQ, Qureshi ARM, Kachhvi HB, Rana MA, Chou KL. Increased likelihood of anxiety and poor sleep quality in Parkinson's disease patients with pain. J Neurol Sci 2016; 369: 212-215.

44. Scherder E, Wolters E, Polman C, Sergeant J, Swaab D. Pain in Parkinson's disease and multiple sclerosis: its relation to the medial and lateral pain systems. Neurosci Biobehav Rev 2005; 29: 1047-1056.

45. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen SEN, Braak E. Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol Aging 2003; 24: 197-211.

46. Wolters ECh, Braak H. Parkinson's disease: premotor clinico-pathological correlations. J Neural Transm 2006; 70(Suppl.): 309-319.

47. Rana AQ, Qureshi AR, Rahman L, Jesudasan A, Hafez KK, Rana MA. Association of restless legs syndrome, pain, and mood disorders in Parkinson's disease. Int J Neurosci 2016; 126: 116-120.

48. Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord 2016; 22 (Suppl 1): S41-46.

49. Titova N, Padmakumar C, Lewis SJG, Chaudhuri KR. Parkinson's: A syndrome rather than a disease? J Neural Transm (Vienna); 124: 907-914.

50. Albers JA, Chand P, Anch AM. Multifactorial sleep disturbance in Parkinson's disease. Sleep Med 2017; 35: 41-48.

51. Bhidayasiri R, Trenkwalder C. Getting a good night sleep? The importance of recognizing and treating nocturnal hypokinesia in Parkinson's disease. Parkinsonism Relat Disord 2018; 50: 10-18.

52. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: Frequency and progression over time. J Neurol Neurosurg Psychiatry 2007; 78: 476-479.

53. Kovács M, Makkos A, Aschermann Z, et al. Impact of Sex on the Nonmotor Symptoms and the Health-Related Quality of Life in Parkinson's Disease. Parkinsons Dis 2016; 2016: 7951840.

54. Martinez-Martin P. The importance of non-motor disturbances to quality of life in Parkinson's disease. J Neurol Sci 2011; 310: 12-16.

Table 1 – Descriptive characteristics of the sample

	Mean	SD	Maximum	Minimum
Age	64.86	10.54	29	88
Age at PD onset	59.49	11.15	29	83
PD duration	5.23	4.83	0	22
Years of education	14.11	3.99	0	24
LEDD	587.81	464.15	0	2620
Scales for Outcomes in PD-Motor				
Examination	9.57	5.43	0	30
Activities of daily living	5.71	3.46	0	18
Motor complications	2.13	2.64	0	11
Total score	17.41	9.27	1	48
Non-Motor Symptoms Scale				
Cardiovascular	2.31	3.45	0	24
Sleep/Fatigue	12.45	10.22	0	48
Mood/Apathy	9.66	13.85	0	72
Perceptual problems/Hallucinations	1.42	3.61	0	24
Attention/Memory	5.80	7.77	0	36
Gastrointestinal tract	5.32	6.47	0	36
Urinary	8.02	8.86	0	36
Sexual function	2.48	5.07	0	24
Miscellaneous	10.91	7.88	0	40
Total score	58.37	42.61	0	235
Clinical Impression of Severity Index-PD				
Motor impairment	2.51	1.16	0	5
Disability	2.17	1.27	0	5
Motor complications	1.42	1.45	0	5
Cognitive status	0.69	0.96	0	4
Total score	6.79	3.71	0	16
Hospital Anxiety and Depression Scale				
Anxiety	6.62	4.39	0	19
Depression	5.45	3.82	0	18
EQ-5D Index	0.57	0.27	-0.15	1
PDQ-8 Index	28.67	20.25	0	93.75

PD: Parkinson's disease. LEDD: Levodopa-equivalent daily dose.

EQ-5D: EuroQoL questionnaire- 5 dimensions.

PDQ-8: Parkinson's disease questionnaire- 8 items.

SD: Standard deviation.

Table 2: Prevalence of Sleep Problems as Assessed by the PDSS-2

Item		**Prevalence**
1	Bad sleep quality	71.7%
2	Difficulties falling asleep	45.0%
3	Difficulties staying asleep	66.0%
4	Restlessness of legs or arms at nights	53.3%
5	Urge to move your legs or arms	46.2%
6	Distressing dreams at night	41.3%
7	Distressing hallucinations at night	15.3%
8	Get up at night to pass urine	85.0%
9	Uncomfortable and immobility at night	54.7%
10	Pain in arms or legs	50.2%
11	Muscle cramps in your arms or legs	54.2%
12	Painful posturing in the morning	44.1%
13	Tremor on waking	48.2%
14	Tired and sleepy after waking in the morning	72.0%
15	Snoring or difficulties in breathing	25.0%
	Total	**99.3%**

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

Table 3 – Differences in PDSS-2 non-pain-related score based on KPPS pain modality prevalence

KPPS Pain Domain	Prevalence	PDSS-2 Non-Pain-Related Score	Significance (*p*)*
Musculoskeletal Pain	Absent	11.80±7.33	0.0024
	Present	15.95±8.80	
Chronic Pain	Absent	13.31±7.71	<0.0001
	Present	18.97±9.32	
Fluctuation-Related Pain	Absent	13.05±7.99	<0.0001
	Present	17.91±8.80	
Nocturnal Pain	Absent	11.51±7.70	<0.0001
	Present	18.00±8.35	
Oro-Facial Pain	Absent	14.49±8.43	0.0010
	Present	19.64±9.13	
Discoloration & Oedema/Swelling	Absent	13.59±8.00	<0.0001
	Present	18.76±9.14	
Radicular Pain	Absent	13.24±7.98	<0.0001
	Present	17.88±8.93	

KPPS: King's Parkinson's Disease Pain Scale

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

*Mann-Whitney U Test

Table 4 – Multiple linear regression models of the PDSS-2 using pain measures

Multiple Linear Regression Model with the KPPS

	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
	Coeff	**SE**	**t**	**p**	**Beta**	**Coeff**	**SE**	**t**	**p**	**Beta**
HADS-Anxiety	0.48	0.14	3.44	0.001	0.19	0.41	0.12	3.51	0.001	0.21
HADS-Depression	0.74	0.17	4.47	<0.001	0.26	0.53	0.14	3.84	<0.001	0.23
NMSS Urinary Domain	0.21	0.06	3.81	<0.001	0.17	0.22	0.05	4.63	<0.001	0.22
KPPS	0.16	0.03	5.25	<0.001	0.29	0.08	0.03	2.98	0.003	0.17
Constant	2.87	3.23	0.89	0.375		5.24	0.83	6.30	<0.001	
	F=41.52, p<0.0001; Adj. R-squared=0.49					*F=33.90, p<0.0001; Adj. R-squared=0.44*				

Multiple Linear Regression Model with the KPPQ

	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
	Coeff	**SE**	**t**	**p**	**Beta**	**Coeff**	**SE**	**t**	**p**	**Beta**
HADS-Anxiety	0.47	0.14	3.40	0.001	0.19	0.39	0.12	3.39	0.001	0.20
HADS-Depression	0.72	0.16	4.39	<0.001	0.25	0.52	0.14	3.79	<0.001	0.23
NMSS Urinary Domain	0.21	0.06	3.79	<0.001	0.17	0.21	0.05	4.59	<0.001	0.22
KPPQ	1.24	0.22	5.53	<0.001	0.29	0.72	0.19	3.87	<0.001	0.21
Constant	4.27	1.04	4.10	<0.001		4.40	0.87	5.08	<0.001	
	F=42.29, p<0.0001; Adj. R-squared=0.49					*F=35.43, p<0.0001; Adj. R-squared=0.45*				

Multiple Linear Regression Model with the VAS-Pain

	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
	Coeff	**SE**	***t***	***p***	**Beta**	**Coeff**	**SE**	***t***	***p***	**Beta**
SCOPA-Motor Complic.	0.60	0.21	2.88	0.004	0.14	0.50	0.17	2.98	0.003	0.15
HADS-Anxiety	0.56	0.14	3.90	<0.001	0.23	0.47	0.12	3.96	<0.001	0.24
HADS-Depression	0.74	0.17	4.29	<0.001	0.26	0.54	0.14	3.86	<0.001	0.24
NMSS Gastrointestinal	0.21	0.08	2.44	0.015	0.12	0.15	0.07	2.18	0.030	0.11
NMSS Urinary Domain	0.24	0.06	4.07	<0.001	0.19	0.23	0.05	4.84	<0.001	0.23
VAS-Pain	0.04	0.02	2.03	0.043	0.10					
Constant	5.50	1.07	5.13	<0.001		5.41	0.88	6.18	<0.001	
	F=35.40, p<0.0001; Adj. R-squared=0.45					*F=31.67, p<0.0001; Adj. R-squared=0.42*				

HADS-Anxiety: Hospital Anxiety and Depression Scale – Anxiety

HADS-Depression: Hospital Anxiety and Depression Scale – Depression

KPPS: King's Parkinson's Disease Pain Scale

NMSS: Non-Motor Symptoms Scale

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

SCOPA-Motor: Scales for Outcomes in Parkinson's Disease – Motor

VAS-Pain: Visual Analog Scale – Pain

Table 5 – KPPS pain modalities as predictors of the PDSS-2 using a multiple linear regression model

Multiple Linear Regression Model Using the KPPS Pain Modalities										
	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
PDSS-2 Total Score	**Coef**	**SE**	***t***	***p***	**Beta**	**Coef**	**SE**	***t***	***p***	**Beta**
Musculoskeletal Pain	0.41	0.14	2.99	0.003	0.15	0.28	0.12	2.44	0.015	0.13
Chronic Pain	0.18	0.12	1.55	0.122	0.09	0.13	0.10	1.33	0.184	0.08
Fluctuation-related Pain	0.14	0.08	1.86	0.064	0.10	0.12	0.67	1.80	0.073	0.11
Nocturnal Pain	0.71	0.11	6.40	<0.001	0.35	0.47	0.09	4.96	<0.001	0.29
Oro-facial Pain	0.21	0.26	0.79	0.427	0.04	0.18	0.22	0.80	0.422	0.04
Discoloration, Oedema/SP	0.23	0.15	1.52	0.128	0.08	0.15	0.13	1.20	0.232	0.07
Radicular Pain	0.32	0.17	1.93	0.054	0.10	0.19	0.14	1.26	0.210	0.07
Constant	10.50	0.97	10.82	<0.001		9.65	0.83	11.67	<0.001	
	F=22.13, p<0.0001; Adj. R-squared=0.33					*F=14.13, p<0.0001; Adj. R squared=0.24*				

KPPS: King's Parkinson's Disease Pain Scale

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

Relationship of nocturnal sleep dysfunction and pain subtypes in Parkinson's disease

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Abstract

Background: Little research has been conducted regarding the relationship between sleep disorders and different pain types in Parkinson's disease (PD).

Objective: To explore the influence of the various pain subtypes experienced by PD patients on sleep.

Methods: Three-hundred consecutive PD patients were assessed with the PD Sleep Scale-Version 2 (PDSS-2), King's PD Pain Scale (KPPS), King's PD Pain Questionnaire (KPPQ), Visual Analog Scales for Pain (VAS-Pain), and Hospital Anxiety and Depression Scale.

Results: According to the PDSS-2, 99.3% of our sample suffered from at least one sleep issue. Those who reported experiencing any modality of pain suffered significantly more from sleep disorders than those who did not (all, $p<0.003$). The PDSS-2 showed moderate-to-high correlations with the KPPS ($r_S=0.57$), KPPQ (0.57), and VAS-Pain (0.35). When PDSS-2 items 10-12 (pain-related) were excluded, the correlation values decreased to 0.50., 0.51, and 0.28, respectively, while these items showed moderate-to-high correlations with KPPS (0.56), KPPQ (0.54), and VAS-Pain (0.42). Among the variables analyzed, multiple linear regression models suggested that KPPS and KPPQ were the most relevant predictors of sleep disorders (as per the PDSS-2), although following exclusion of PDSS-2 pain items depression was the relevant predictor. Depression and anxiety were the most relevant predictors in the analysis involving the VAS-Pain. Regression analysis considering only the KPPS domains showed that nocturnal and musculoskeletal pain were the best predictors of overall nocturnal sleep disorder.

Conclusions: Pain showed a moderate association with nocturnal sleep dysfunction in PD. Some pain subtypes had a greater effect on sleep than others.

Introduction

A range of sleep disorders and subtypes of pain, are very prevalent non-motor symptoms of Parkinson's disease (PD) that occur from the prodromal to the palliative stages of PD (1-5). Sleep dysfunction, which affects 60-98% of PD patients, may be manifested as insomnia, sleep disruption, sudden onset of sleep, rapid-eye-movement (REM) sleep behavior disorder, non-REM parasomnias, and restless legs syndrome (6-8). Surveys suggest that insomnia affects 46% of PD patients, vivid dreams 34%, acting out while dreaming 36%, and restless legs syndrome 42% (1). Depression, anxiety, cognitive problems, stress, and daytime sleepiness have been found to result from these conditions, and sleep disorders in PD have a negative impact on patients' quality of life (QoL) (9,10).

On the other hand, using the King's Parkinson's Disease Pain Scale (KPPS) (11), the syndromic nature of pain has been formally subdivided into several patterns. Prior research has shown that the prevalence of pain is 68-81% in PD patients (12-14) and that it can be manifested in several modalities, such as musculoskeletal (41-89%), dystonic (15-17%), radicular-neuropathic (27-32%), and central pain (4-22%) (2,12,14-18). Furthermore, 35% of PD patients are affected by two types of pain, 10% by three, and 2% by four (14). Pain can become crippling in a subset of PD patients, affect their ability to conduct activities of daily living (ADL) (13,19), and negatively impact their QoL (20-22). Yet, despite the impact of this non-motor symptom, pain often remains underdiagnosed and undeclared (23).

PD patients with pain have been found to experience poorer sleep quality and more sleep disorders than patients without pain (24). Using the Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) (25) and the KPPS (11), the present study seeks both to explore the influence of the various modalities of pain experienced by PD patients on sleep disorders and to examine the

relationship between sleep disorders and other factors, such as anxiety and depression, motor complications, and QoL.

Methods

Design

International, multicenter, observational, cross-sectional study.

Patients

Consecutive PD patients were included in this study if they were diagnosed with PD according to the UK PD Brain Bank criteria (26) and if they declared unexplained pains on item 10 of the Non-Motor Symptoms Questionnaire (27). However, if patients had an alternative or uncertain diagnosis of PD or drug-induced PD, were unable to consent, had dementia as diagnosed by international criteria, or were diagnosed with known conditions that cause pain unrelated to PD (e.g. arthritis, malignancy, etc.), they were excluded from this study (28).

Patients were recruited from nine different movement disorder centers across the United Kingdom (eight) and Romania (one) from August 2013 to February 2016. This study was conducted under the UK's National Institute of Health Research's portfolio of studies (UKCRN No. 13344) (28).

Ethical issues

The study was approved by the respective hospital ethical committees/institutional review boards. All participants provided informed consent before inclusion in the study.

Assessments

Socio-demographic data and disease history (i.e. sex, age, ethnicity, PD duration, current treatment, and surgery) were collected from all patients. According to Tomlinson et al., levodopa equivalent daily dose (LEDD) was also calculated (29).

The following instruments were used to assess each patient:

1. Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) (25), a 15-item, patient-completed clinical tool used to assess the frequency of sleep disturbances during the past week in PD patients. Items 10, 11, and 12 of the PDSS-2 directly assess pain while sleeping or when waking up.

2. Hoehn-Yahr classification (HY) (30), a five-stage system that classifies PD on a continuum from unilateral expression of the disease to the most severe.

3. Scales for Outcomes in Parkinson's Disease-Motor (SCOPA-Motor) (31), a 21-item scale that measures motor impairment, difficulty with ADL, and motor complications.

4. Non-Motor Symptoms Scale (NMSS) (32), a 30-item scale that considers the frequency and severity of the non-motor symptoms of PD grouped into nine domains: cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary function, sexual function, and miscellaneous. Item 27 of the NMSS directly inquires about unexplained pains.

5. Clinical Impression of Severity Index for PD (CISI-PD) (33), an overall estimate of PD based on motor signs, disability, motor complications, and cognitive status.

6. King's Parkinson's Pain Scale (KPPS) (11), a 14-item scale that evaluates the types of pain suffered by PD patients: musculoskeletal, chronic, fluctuation-related, nocturnal, oro-facial, discoloration and oedema/swelling, and radicular pain. Each item is rated by the clinician according to its severity (from 0 to 3) and frequency (from 0 to 4). An item's score is then

calculated as the product of each pain type's frequency and severity, and a total score is calculated by summing the scores of each item. KPPS time frame is "the past month".

7. King's Parkinson's Pain Questionnaire (KPPQ) (28), a patient-completed derivative of the KPPS, asks about the same pain modalities as the KPPS, and only provides information regarding the presence or absence of 14 specific types of pain in a given patient. The time framework is "past month".

8. Visual Analog Scales for Pain Severity and Frequency (VAS-Pain) (34). A VAS-Pain total score was calculated by multiplying both scales, whose time framework was "past month".

9 Hospital Anxiety and Depression Scale (HADS) (35), which is a 14-item, patient-completed scale with subscales for anxiety and depression.

10. EQ-5D-3L (36), which contains five items that inquire about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that assesses current health status.

11. Parkinson's Disease Questionnaire-8 items (PDQ-8) (37), a PD-specific health-related QoL measure. Item 8 of the PDQ-8 specifically asks about painful muscle cramps or spasms.

Data Analysis

Data were anonymized and sent to the National Center of Epidemiology, Carlos III Institute of Health, in Madrid, Spain for analysis.

Socio-demographic, historical data, and rating scales scores were examined using descriptive statistics (i.e. mean, median, and, standard deviation). Main data showed non-normal distribution (Shapiro-Francia test); therefore non-parametric statistical tests were used.

The prevalence of each sleep symptom assessed by the PDSS-2 was calculated by considering an item score ≥1 to be the presence of that symptom and an item score of 0 to be its absence. Furthermore, patients were divided into groups using the prevalence of each of the seven pain modalities (domains) assessed by the KPPS, which were calculated using the same method described above (15). Then, after excluding the PDSS-2 pain-related items (items 10-12: "PDSS-2 Pain"), the effect of each type of pain on non-pain-related PDSS-2 score was determined by comparing the means of the two groups (with and without that specific pain) and by applying the Mann-Whitney test.

The association of the PDSS-2 with the KPPS and other clinical variables evaluating pain present in the study was assessed by Spearman correlations. Partial correlations were also used to adjust these associations for age, PD duration, SCOPA motor examination, and LEDD. Coefficient values higher than 0.50 were deemed strong correlations and those from 0.30 to 0.49 moderate ones.

The influence of pain on PDSS-2 score was determined using multiple linear regression models in which the dependent variable was the PDSS-2 and the independent ones were (after checking for association, collinearity, and interaction): SCOPA-Motor ADL and complications sections, HADS-Anxiety, HADS-Depression, and the NMSS gastrointestinal and urinary domains. Each model also included one of the following pain measures as an independent variable: KPPS, KPPQ, and VAS-Pain. In order to explore the influence of each type of pain on nocturnal sleep issues, another multiple linear regression analysis was conducted using the KPPS domains as predictors of PDSS-2 total score.

To exclude the influence of the PDSS-2 pain-related items on the findings, the correlation coefficients and multiple regression models were recalculated after excluding the "PDSS-2 Pain" dimension.

For further analysis regarding the PDSS-2 total score, Kruskal-Wallis and Mann-Whitney tests were conducted to determine if there were significant differences between sexes, groups of age, PD duration, and LEDD (based on quartiles) in reference to the scale. Finally, Spearman rank correlations were calculated between PDSS-2 and the remaining assessments in the study.

Results

Three hundred PD patients, most of them males (59.7%) and predominantly Caucasians (84.8%) were included in the study. Median HY was 2 with an interquartile range of 2–3 (limits: 1–5). One hundred and fifty one patients (50.3%) had Postural instability and gait difficulty PD subtype; 93 (31.0%) showed tremor predominant subtype; and 56 (18.7%) were indeterminate (38,39). Other descriptive data of the sample are displayed in the Table 1. On the PDSS-2, the average total score was 18.57±10.89 (range: 0–51), while scores were 22.85±19.45 (0–102) on the KPPS, 3.96±2.56 (1–12) on the KPPQ, and 32.78±24.40 (0–100) on the VAS-Pain.

Table 2 shows the prevalence rates for each sleep issue assessed by the PDSS-2; 99.3% of our sample was afflicted by at least one sleep problem. Moreover, as shown in Table 3, those who reported experiencing any modality of pain suffered from significantly more severe non-pain-related sleep disorders than those who did not (all, $p<0.003$).

The PDSS-2 was moderately or highly correlated with the KPPS domains of fluctuation-related pain (r_S=0.34), nocturnal pain (0.52), discoloration and oedema/swelling related pain (0.31), and radicular pain (0.32) as well as with the KPPS total score (0.57), whereas it showed weak relationships with the remaining KPPS domains (r_S=0.20–0.28). Similarly, the correlations with KPPQ (0.57) and VAS-Pain (0.35) were moderate-to-high. These coefficients were only slightly modified in the partial correlation analysis of total scores (KPPS, 0.51; KPPQ, 0.52; and VAS-Pain, 0.31). When the “PDSS-2 Pain” component was excluded from the PDSS-2 total score, all

correlation coefficients with total scores decreased 0.06-0.07 (KPPS, 0.50; KPPQ, 0.51, VAS-Pain, 0.28), and 0.04 in average (0.01-0.08) with KPPS domains. Furthermore, the two QoL assessments showed moderate-to-high associations with the three pain measures in the study: -0.45 to -0.60 for the EQ-5D-3L and 0.42 to 0.59 for the PDQ-8.

Using "PDSS-2 Pain" (the sum of items 10-12), the following correlations were found between this pain score and other measures in the study: the KPPS domains of musculoskeletal (r_S=0.30), fluctuation-related (0.32), nocturnal (0.52), and radicular (0.37) pain as well as its total score (0.56); the KPPQ (0.54); VAS-Pain (0.42); the EQ-5D-3L's pain/discomfort question (0.37); and PDQ-8 item 8 (0.43).

Table 4 shows the results of six multiple linear regression models. In the analyses using the KPPS and KPPQ, pain was shown to be the most powerful predictor of the sleep disorders assessed by the PDSS-2 (p<0.001); however, in the analysis using the VAS-Pain, depression and then anxiety were the best predictors of these sleep problems (p<0.001). However, when the "PDSS-2 Pain" domain was excluded, depression and urinary disorders were first and second determinants in importance in the models with KPPS and KPPQ, whereas there were no changes in those of the VAS-Pain model (Table 4).

An additional multiple linear regression model using the KPPS pain modalities as predictors of the PDSS-2 was explored. In this model, only nocturnal (p<0.001; beta=0.38) and musculoskeletal (p=0.003; beta=0.15) pain were significant determinants of overall nocturnal sleep disorder, a finding that was not modified by excluding the pain-related items of the PDSS-2 (Table 5).

Patients who had longer PD duration (p=0.001) and higher LEDD (p<0.001) also reported significantly more severe sleep disturbances. Moreover, the PDSS-2 showed moderate-to-high correlations with the other clinical measures in the study: CISI total score (r_S=0.39); HADS-

Anxiety (0.50); HADS-Depression (0.54); EQ-5D summary index (-0.49); PDQ-8 summary index (0.60); SCOPA-Motor ADL (0.43), complications (0.38), and total score (0.40); the NMSS domains of sleep/fatigue (0.58), mood/apathy (0.34), gastrointestinal (0.37), urinary (0.35), and its total score (0.54).

Discussion

In line with previous findings, almost all patients in our sample (99.3%) declared having at least one nocturnal sleep dysfunction according to the PDSS-2, confirming the high prevalence of this non-motor symptom in PD (6). The most prevalent of these issues in our study were nocturia (85.0%), tiredness and sleepiness upon waking (72.0%), and poor sleep quality (71.7%). While some studies have found figures that are similar to ours, other studies did not (40-42); however, the PDSS-2 has never been used to analyze the prevalence of nocturnal sleep disorders in PD, and, therefore, our results cannot be compared at present with other studies. For example, problems related to “PDSS-2 Pain” showed prevalence rates of 44.1-54.2%, but data encompassing a similar combination of items has not been explored previously to our knowledge. Yet, a limitation of our study is that it included only patients who experience at least some form of pain, and, thus, our findings cannot be generalized.

On the other hand, it is very well known that pain can interfere with sleep. Specifically, it has been demonstrated that pain in PD is linked to poorer sleep quality (24,43). In fact, after removing the PDSS-2 pain-related items, those who reported the presence of any type of pain on the KPPS had significantly higher scores on the PDSS-2. Moreover, the PDSS-2 score was moderately or highly correlated with KPPS total score and several domains (i.e. fluctuation-related, nocturnal, discoloration and oedema/swelling, and radicular pain), the VAS-Pain, and the KPPQ. As these coefficient values were only slightly modified when adjusting for age, PD

duration, motor examination, and LEDD, our results suggest that these PD-related variables do not associate significantly with the impact of pain on nocturnal sleep. Similarly, Beiske et al. found that pain was not associated with age, disease duration, or disease severity (2).

Multiple linear regression analyses showed that, among the variables that have been analyzed, the KPPS and KPPQ were the most relevant predictors of the PDSS-2 total score in their respective models, while the predictive effect of the VAS-Pain was barely significant in its model; thus, it can be concluded that pain may have a greater impact on PD patients' sleep than other factors and that the PD-specific instruments for pain (i.e. KPPS and KPPQ) may perform better than generic pain tools (i.e. VAS-Pain). However, a limitation of this analysis is the presence of a pain-related domain ("PDSS-2 Pain") in the PDSS-2, which intensified the relationship between these instruments in such a way that urinary disorders replaced the PD-specific pain evaluations when the PDSS-2 Pain domain was kept out.

Pain and sleep in PD can be pathophysiologically linked. Noradrenergic cells of the locus coeruleus are known to modulate the cortical signal-to-noise ratio. They are also part of the medial pain system, which regulates the pain-control system that inhibits the relay nuclei for somatosensory and viscerosensory inputs (44). In Braak stage 2, stage 1-related PD pathology becomes more advanced and lesions (mainly Lewy neurites) occur in the medulla oblongata and pontine tegmentum, including the lower raphe nuclei, the magnocellular portions of the reticular formation, and the gigantocellular reticular nucleus (45). The coeruleus and raphe neurons exert an inhibitory effect on the tegmental pedunculopontine nucleus, which stimulates REM sleep. The reticular cholinergic neurons also regulate arousal mechanisms. As such, the origins of both pain and sleep dysfunction in PD, even at the premotor Braak stage 2, appear to be closely related pathophysiologically (46).

Furthermore, when considering only “PDSS-2 Pain,” it showed moderate or high correlations with several KPPS domains (i.e. musculoskeletal, fluctuation-related, nocturnal, and radicular pain) and with the KPPS, KPPQ, and VAS-Pain total scores.

Also, another multiple linear regression analysis showed that musculoskeletal and nocturnal pain were significant predictors of PDSS-2 total score using a model that included only the domains of the KPPS. These results suggest that specific types of pain are more relevant to nocturnal sleep problems (44,46).

However, this is not to say that pain is the only predictor of sleep problems in PD. Several studies have shown that anxiety and depression are also related to poor sleep quality (7,24,47). In the multiple linear regression model involving the VAS-Pain, the HADS-Depression, followed by the HADS-Anxiety, was the most pertinent predictor of PDSS-2 total score. These two psychiatric measures were also moderately or highly correlated with the PDSS-2.

Neurotransmitter-dysfunction-based non-motor endophenotypes of PD have been recently proposed, and pain and sleep dysfunction characterize some of these phenotype clusters, which form part of the limbic- and brainstem-generated cholinergic and serotonergic subtypes of PD (48,49).

Additionally, the NMSS urinary and gastrointestinal domains as well as the SCOPA-Motor complications section were also significant predictors of PDSS-2 total score in the models explored in this study. Similarly, the NMSS domains of sleep/fatigue, mood/apathy, gastrointestinal, and urinary as well as NMSS total score were also moderately or highly associated with the PDSS-2. Fatigue, cognitive impairment, and urinary issues were also found to be significantly associated with sleep quality in another study (7).

Moderate associations were found between the PDSS-2 and the SCOPA-Motor ADL, complications section, and its total score, as well as between the PDSS-2 and the CISI-PD,

suggesting that motor problems and disability may have some effect on sleep-related issues in PD (8,50). In fact, nocturnal hypokinesia has recently been highlighted as an important factor impairing sleep quality (51).

Although PD duration and LEDD were not significant predictors of PDSS-2 total scores, patient groups with longer PD duration and higher LEDD scored significantly higher on the PDSS-2 than those with shorter PD duration and lower LEDD, suggesting that problems with sleep could worsen with disease progression (52). Additionally, there were no significant differences between groups of age and sex in reference to PDSS-2 total score, although differences related to sex were found in another study (53).

Sleep disturbances and pain are significant factors in patients' lives as demonstrated by the moderate-to-high correlations of the PDSS-2, KPPS, KPPQ, and VAS-Pain with both the EQ-5D-3L and the PDQ-8, the two measures of QoL utilized in this study. When considering only "PDSS-2 Pain," there were moderate correlations with the EQ-5D-3L's pain/discomfort question and PDQ-8 item 8, findings in line with previous studies that identified pain is a determinant factor of QoL (54).

In conclusion, our results show that (1) nocturnal sleep disorders could affect the majority of PD patients; (2) pain, as a whole, showed a moderate association with the severity of nocturnal sleep disorders; and (3) nocturnal sleep disorders could be influenced more by certain subtypes of pain than others.

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    B. Organization: PMM, AR, KRC
    C. Execution: SP, RS, CC, DM, CFP, BK, TA, DP
2) Statistical Analysis
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Compliance with Journal Ethical Publication Guidelines Statement

- Ethics committees that approved the study:

In United Kingdom: Institute of Psychiatry, Psychology, & Neuroscience at King's College, London; King's College Hospital NHS Foundation Trust, London; Forth Valley Royal Hospital, Larbert, Scotland; Yeovil Hospital, Somerset; Derriford Hospital, Plymouth; Princess Royal University Hospital, King's College Hospital, Kent; Guy's Hospital, London; and Neurology, St. Georges's Hospital, London. In Romania: Ethics Committee of the Transilvania University from Brasov, Romania.

- All participants provided informed consent before inclusion in the study.
- We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

References

1. Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting; Study using nonmotor symptoms questionnaire in 545 patients. Mov Disord 2007; 22: 1623-1629.

2. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: Prevalence and characteristics. Pain 2009; 141: 173-177.

3. Zis P, Rizos A, Martinez-Martin P, Pal S, Silverdale M, Sharma J, et al. Non-Motor Symptoms Profile and Burden in Drug Naïve Versus Long-Term Parkinson's Disease Patients. J Parkinson Dis 2014; 4: 541–547.

4. Zis P, Erro R, Walton CC, Sauerbier A, Chaudhuri KR. The range and nature of non-motor symptoms in drug-naive Parkinson's disease patients: a state-of-the-art systematic review. NPJ Parkinson's Dis 2015; 1: 15013.

5. Antonini A, Tinazzi M, Abbruzzese G, et al. Pain in Parkinson's disease: facts and uncertainties. Eur J Neurol. 2018. doi: 10.1111/ene.13624.

6. Swick TJ. Parkinson's disease and sleep/wake disturbances. Parkinsons Dis 2012; 2012: 205471.

7. Kurtis MM, Rodriguez-Blazquez C, Martinez-Martin P; ELEP Group. Relationship between sleep disorders and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2013; 19: 1152-1155.

8. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. Sleep Med Rev 2017; 35: 33-50.

9. Ylikoski A, Martikainen K, Sieminski M, Partinen M. Sleeping difficulties and health-related quality of life in Parkinson's disease. Acta Neurol Scand 2017; 135: 459-468.

10. Shafazand S, Wallace DM, Arheart KL, et al. Insomnia, Sleep Quality, and Quality of Life in Mild to Moderate Parkinson's Disease. Annals of the American Thoracic Society 2017; 14: 412-419.

11. Chaudhuri KR, Rizos A, Trenkwalder C, et al. King's Parkinson's disease pain scale, the first scale for pain in PD: An international validation. Mov Disord 2015; 30: 1623-1631.

12. Broen MP, Braaksma MM, Patijn J, Weber WE. Prevalence of pain in Parkinson's disease: A systematic review using the modified QUADAS tool. Mov Disord 2012; 27: 480-484.

13. Allen NE, Wong CM, Canning CG, Moloney N. The Association Between Parkinson's Disease Motor Impairments and Pain. Pain Med 2016; 17: 456-462.

14. Valkovic P, Minar M, Singliarova H, et al. Pain in Parkinson's disease: A cross-sectional study of its prevalence, types, and relationship to depression and quality of life. PLoS One 2015; 10: e0136541.

15. Ford B. Pain in Parkinson's disease. Mov Disord 2010; 25 (Suppl 1):S98-103.

16. Ha AD, Jankovic J. Pain in Parkinson's disease. Mov Disord 2012; 27:485-491.

17. Wasner G, Deuschl G. Pains in Parkinson disease--many syndromes under one umbrella. Nat Rev Neurol 2012; 8: 284-294.

18. Ozturk EA, Gundogdu I, Kocer B, Comoglu S, Cakci A. Chronic pain in Parkinson's disease: Frequency, characteristics, independent factors, and relationship with health-related quality of life. J Back Musculoskelet Rehabil 2017; 30: 101-108.

19. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: Findings from the 2011 National Health and Aging Trends Study. Pain 2013; 154: 2649-2657.

20. Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: A controlled cross-sectional study. Parkinsonism Relat Disord 2004; 10: 129-136.

21. Choi SM, Kim BC, Jung HJ, et al. Impact of pain and pain subtypes on the quality of life of patients with Parkinson's disease. J Clin Neurosci 2017; 45: 105-109.

22. Martinez-Martin P, Manuel Rojo-Abuin J, Rizos A, et al. Distribution and impact on quality of life of the pain modalities assessed by the King's Parkinson's disease pain scale. NPJ Parkinsons Dis 2017; 3: 8.

23. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. Mov Disord 2010; 25: 704-709.

24. Rana AQ, Qureshi ARM, Shamli Oghli Y, et al. Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity, and correlates with pain intensity and quality. Neurol Res 2018. DOI: 10.1080/01616412.2018.1462880.

25. Trenkwalder C, Kohnen K, Högl B, et al. Parkinson Disease Sleep Scale – Validation of the Revised Version PDSS-2. Mov Disord 2011; 26: 644-652.

26. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745-752.

27. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: The NMSQuest study. Mov Disord 2006; 21: 916-923.

28. Martinez-Martin P, Rizos AM, Wetmore J, et al. First comprehensive tool for screening pain in Parkinson's disease: The King's Parkinson's Disease Pain Questionnaire (KPPQ). Eur J Neurol. Accepted: 11-5-2018. DOI: 10.1111/ene.13691.

29. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010; 25: 2649-2653.

30. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. Neurology 1967; 17: 427-442.

31. Marinus J, Visser M, Stiggelbout AM, et al. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: The SPES/SCOPA. J Neurol Neurosurg Psychiatry 2004; 75: 388–395.

32. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 2007; 22: 1901-1911.

33. Martinez-Martin P, Forjaz MJ, Cubo E, Frades B, de Pedro Cuesta J, ELEP Project Members. Global versus factor-related impression of severity in Parkinson's disease: A new clinimetric index (CISI-PD). Mov Disord 2006; 21: 208-214.

34. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R. Eds. Handbook of Pain Assessment. 2001; p15-34.

35. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–370.

36. EuroQol Group. EuroQol- a new facility for the measurement of health related quality of life. Health Policy 1990; 16: 199-208.

37. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: Development and validation of a short-form Parkinson's disease questionnaire. Psychology & Health 1997; 12: 805-814.

38. Verbaan D, Marinus J, Visser M, et al. Cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2007; 78: 1182-1187.

39. van der Heeden JF, Marinus J, Martinez-Martin P, et al. Postural instability and gait are associated with severity and prognosis of Parkinson disease. Neurology. 2016; 86: 2243-2250.

40. Kumar S, Bhatia M, Behari M. Sleep disorders in Parkinson's disease. Mov Disord 2002; 17: 775-781.

41. Oerlemans WG, de Weerd AW. The prevalence of sleep disorders in patients with Parkinson's disease. A self-reported, community-based survey. Sleep Med 2002; 3: 147-149.

42. Falup-Pecurariu C, Diaconu Ş. Sleep Dysfunction in Parkinson's Disease. Int Rev Neurobiol 2017; 133: 719-742.

43. Rana AQ, Qureshi ARM, Kachhvi HB, Rana MA, Chou KL. Increased likelihood of anxiety and poor sleep quality in Parkinson's disease patients with pain. J Neurol Sci 2016; 369: 212-215.

44. Scherder E, Wolters E, Polman C, Sergeant J, Swaab D. Pain in Parkinson's disease and multiple sclerosis: its relation to the medial and lateral pain systems. Neurosci Biobehav Rev 2005; 29: 1047-1056.

45. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen SEN, Braak E. Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol Aging 2003; 24: 197-211.

46. Wolters ECh, Braak H. Parkinson's disease: premotor clinico-pathological correlations. J Neural Transm 2006; 70(Suppl.): 309-319.

47. Rana AQ, Qureshi AR, Rahman L, Jesudasan A, Hafez KK, Rana MA. Association of restless legs syndrome, pain, and mood disorders in Parkinson's disease. Int J Neurosci 2016; 126: 116-120.

48. Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord 2016; 22 (Suppl 1): S41-46.

49. Titova N, Padmakumar C, Lewis SJG, Chaudhuri KR. Parkinson's: A syndrome rather than a disease? J Neural Transm (Vienna); 124: 907-914.

50. Albers JA, Chand P, Anch AM. Multifactorial sleep disturbance in Parkinson's disease. Sleep Med 2017; 35: 41-48.

51. Bhidayasiri R, Trenkwalder C. Getting a good night sleep? The importance of recognizing and treating nocturnal hypokinesia in Parkinson’s disease. Parkinsonism Relat Disord 2018; 50: 10-18.

52. Gjerstad MD, Wentzel-Larsen T, Aarsland D, Larsen JP. Insomnia in Parkinson's disease: Frequency and progression over time. J Neurol Neurosurg Psychiatry 2007; 78: 476-479.

53. Kovács M, Makkos A, Aschermann Z, et al. Impact of Sex on the Nonmotor Symptoms and the Health-Related Quality of Life in Parkinson's Disease. Parkinsons Dis 2016; 2016: 7951840.

54. Martinez-Martin P. The importance of non-motor disturbances to quality of life in Parkinson's disease. J Neurol Sci 2011; 310: 12-16.

Table 1 – Descriptive characteristics of the sample

	Mean	SD	Maximum	Minimum
Age	64.86	10.54	29	88
Age at PD onset	59.49	11.15	29	83
PD duration	5.23	4.83	0	22
Years of education	14.11	3.99	0	24
LEDD	587.81	464.15	0	2620
Scales for Outcomes in PD-Motor				
Examination	9.57	5.43	0	30
Activities of daily living	5.71	3.46	0	18
Motor complications	2.13	2.64	0	11
Total score	17.41	9.27	1	48
Non-Motor Symptoms Scale				
Cardiovascular	2.31	3.45	0	24
Sleep/Fatigue	12.45	10.22	0	48
Mood/Apathy	9.66	13.85	0	72
Perceptual problems/Hallucinations	1.42	3.61	0	24
Attention/Memory	5.80	7.77	0	36
Gastrointestinal tract	5.32	6.47	0	36
Urinary	8.02	8.86	0	36
Sexual function	2.48	5.07	0	24
Miscellaneous	10.91	7.88	0	40
Total score	58.37	42.61	0	235
Clinical Impression of Severity Index-PD				
Motor impairment	2.51	1.16	0	5
Disability	2.17	1.27	0	5
Motor complications	1.42	1.45	0	5
Cognitive status	0.69	0.96	0	4
Total score	6.79	3.71	0	16
Hospital Anxiety and Depression Scale				
Anxiety	6.62	4.39	0	19
Depression	5.45	3.82	0	18
EQ-5D Index	0.57	0.27	-0.15	1
PDQ-8 Index	28.67	20.25	0	93.75

PD: Parkinson's disease. LEDD: Levodopa-equivalent daily dose.

EQ-5D: EuroQoL questionnaire- 5 dimensions.

PDQ-8: Parkinson's disease questionnaire- 8 items.

SD: Standard deviation.

Table 2: Prevalence of Sleep Problems as Assessed by the PDSS-2

Item		**Prevalence**
1	Bad sleep quality	71.7%
2	Difficulties falling asleep	45.0%
3	Difficulties staying asleep	66.0%
4	Restlessness of legs or arms at nights	53.3%
5	Urge to move your legs or arms	46.2%
6	Distressing dreams at night	41.3%
7	Distressing hallucinations at night	15.3%
8	Get up at night to pass urine	85.0%
9	Uncomfortable and immobility at night	54.7%
10	Pain in arms or legs	50.2%
11	Muscle cramps in your arms or legs	54.2%
12	Painful posturing in the morning	44.1%
13	Tremor on waking	48.2%
14	Tired and sleepy after waking in the morning	72.0%
15	Snoring or difficulties in breathing	25.0%
	Total	**99.3%**

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

Table 3 – Differences in PDSS-2 non-pain-related score based on KPPS pain modality prevalence

KPPS Pain Domain	Prevalence	PDSS-2 Non-Pain-Related Score	Significance (*p*)*
Musculoskeletal Pain	Absent	11.80±7.33	0.0024
	Present	15.95±8.80	
Chronic Pain	Absent	13.31±7.71	<0.0001
	Present	18.97±9.32	
Fluctuation-Related Pain	Absent	13.05±7.99	<0.0001
	Present	17.91±8.80	
Nocturnal Pain	Absent	11.51±7.70	<0.0001
	Present	18.00±8.35	
Oro-Facial Pain	Absent	14.49±8.43	0.0010
	Present	19.64±9.13	
Discoloration & Oedema/Swelling	Absent	13.59±8.00	<0.0001
	Present	18.76±9.14	
Radicular Pain	Absent	13.24±7.98	<0.0001
	Present	17.88±8.93	

KPPS: King's Parkinson's Disease Pain Scale

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

*Mann-Whitney U Test

Table 4 – Multiple linear regression models of the PDSS-2 using pain measures

Multiple Linear Regression Model with the KPPS

	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
	Coeff	**SE**	**t**	**p**	**Beta**	**Coeff**	**SE**	**t**	**p**	**Beta**
HADS-Anxiety	0.48	0.14	3.44	0.001	0.19	0.41	0.12	3.51	0.001	0.21
HADS-Depression	0.74	0.17	4.47	<0.001	0.26	0.53	0.14	3.84	<0.001	0.23
NMSS Urinary Domain	0.21	0.06	3.81	<0.001	0.17	0.22	0.05	4.63	<0.001	0.22
KPPS	0.16	0.03	5.25	<0.001	0.29	0.08	0.03	2.98	0.003	0.17
Constant	2.87	3.23	0.89	0.375		5.24	0.83	6.30	<0.001	
	F=41.52, p<0.0001; Adj. R-squared=0.49					*F=33.90, p<0.0001; Adj. R-squared=0.44*				

Multiple Linear Regression Model with the KPPQ

	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
	Coeff	**SE**	**t**	**p**	**Beta**	**Coeff**	**SE**	**t**	**p**	**Beta**
HADS-Anxiety	0.47	0.14	3.40	0.001	0.19	0.39	0.12	3.39	0.001	0.20
HADS-Depression	0.72	0.16	4.39	<0.001	0.25	0.52	0.14	3.79	<0.001	0.23
NMSS Urinary Domain	0.21	0.06	3.79	<0.001	0.17	0.21	0.05	4.59	<0.001	0.22
KPPQ	1.24	0.22	5.53	<0.001	0.29	0.72	0.19	3.87	<0.001	0.21
Constant	4.27	1.04	4.10	<0.001		4.40	0.87	5.08	<0.001	
	F=42.29, p<0.0001; Adj. R-squared=0.49					*F=35.43, p<0.0001; Adj. R-squared=0.45*				

Multiple Linear Regression Model with the VAS-Pain

	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
	Coeff	**SE**	***t***	***p***	**Beta**	**Coeff**	**SE**	***t***	***p***	**Beta**
SCOPA-Motor Complic.	0.60	0.21	2.88	0.004	0.14	0.50	0.17	2.98	0.003	0.15
HADS-Anxiety	0.56	0.14	3.90	<0.001	0.23	0.47	0.12	3.96	<0.001	0.24
HADS-Depression	0.74	0.17	4.29	<0.001	0.26	0.54	0.14	3.86	<0.001	0.24
NMSS Gastrointestinal	0.21	0.08	2.44	0.015	0.12	0.15	0.07	2.18	0.030	0.11
NMSS Urinary Domain	0.24	0.06	4.07	<0.001	0.19	0.23	0.05	4.84	<0.001	0.23
VAS-Pain	0.04	0.02	2.03	0.043	0.10					
Constant	5.50	1.07	5.13	<0.001		5.41	0.88	6.18	<0.001	
	F=35.40, p<0.0001; Adj. R-squared=0.45					*F=31.67, p<0.0001; Adj. R-squared=0.42*				

HADS-Anxiety: Hospital Anxiety and Depression Scale – Anxiety

HADS-Depression: Hospital Anxiety and Depression Scale – Depression

KPPS: King's Parkinson's Disease Pain Scale

NMSS: Non-Motor Symptoms Scale

PDSS-2: Parkinson's Disease Sleep Scale – Version 2

SCOPA-Motor: Scales for Outcomes in Parkinson's Disease – Motor

VAS-Pain: Visual Analog Scale – Pain

Table 5 – KPPS pain modalities as predictors of the PDSS-2 using a multiple linear regression model

Multiple Linear Regression Model Using the KPPS Pain Modalities										
	PDSS-2 Total Score					PDSS-2 Total Score without pain domain				
PDSS-2 Total Score	**Coef**	**SE**	***t***	***p***	**Beta**	**Coef**	**SE**	***t***	***p***	**Beta**
Musculoskeletal Pain	0.41	0.14	2.99	0.003	0.15	0.28	0.12	2.44	0.015	0.13
Chronic Pain	0.18	0.12	1.55	0.122	0.09	0.13	0.10	1.33	0.184	0.08
Fluctuation-related Pain	0.14	0.08	1.86	0.064	0.10	0.12	0.67	1.80	0.073	0.11
Nocturnal Pain	0.71	0.11	6.40	<0.001	0.35	0.47	0.09	4.96	<0.001	0.29
Oro-facial Pain	0.21	0.26	0.79	0.427	0.04	0.18	0.22	0.80	0.422	0.04
Discoloration, Oedema/SP	0.23	0.15	1.52	0.128	0.08	0.15	0.13	1.20	0.232	0.07
Radicular Pain	0.32	0.17	1.93	0.054	0.10	0.19	0.14	1.26	0.210	0.07
Constant	10.50	0.97	10.82	<0.001		9.65	0.83	11.67	<0.001	
	F=22.13, p<0.0001; Adj. R-squared=0.33					*F=14.13, p<0.0001; Adj. R squared=0.24*				

KPPS: King's Parkinson's Disease Pain Scale

PDSS-2: Parkinson's Disease Sleep Scale – Version 2