



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

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Abstract:	<p>Background: Little research has been conducted regarding the relationship between sleep disorders and different pain types in Parkinson’s disease (PD).</p> <p>Objective: To explore the influence of the various pain subtypes experienced by PD patients on sleep.</p> <p>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.</p> <p>Results: According to the PDSS-2, 99.3% of our sample suffered from at</p>

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.

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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.

1 Introduction

2

3 A range of sleep disorders and subtypes of pain, are very prevalent non-motor symptoms of
4 Parkinson's disease (PD) that occur from the prodromal to the palliative stages of PD (1-5).

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

12 On the other hand, using the King's Parkinson's Disease Pain Scale (KPPS) (11), the syndromic
13 nature of pain has been formally subdivided into several patterns. Prior research has shown that
14 the prevalence of pain is 68-81% in PD patients (12-14) and that it can be manifested in several
15 modalities, such as musculoskeletal (41-89%), dystonic (15-17%), radicular-neuropathic (27-
16 32%), and central pain (4-22%) (2,12,14-18). Furthermore, 35% of PD patients are affected by
17 two types of pain, 10% by three, and 2% by four (14). Pain can become crippling in a subset of
18 PD patients, affect their ability to conduct activities of daily living (ADL) (13,19), and negatively
19 impact their QoL (20-22). Yet, despite the impact of this non-motor symptom, pain often remains
20 underdiagnosed and undeclared (23).

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

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

27

28 **Methods**

29 Design

30 International, multicenter, observational, cross-sectional study.

31 Patients

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

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

42 Ethical issues

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

45 Assessments

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

49 The following instruments were used to assess each patient:

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

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

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

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

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

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

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

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

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

77 9 Hospital Anxiety and Depression Scale (HADS) (35), which is a 14-item, patient-
78 completed scale with subscales for anxiety and depression.

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

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

84

85 Data Analysis

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

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

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

99 The association of the PDSS-2 with the KPPS and other clinical variables evaluating pain
100 present in the study was assessed by Spearman correlations. Partial correlations were also
101 used to adjust these associations for age, PD duration, SCOPA motor examination, and LEDD.
102 Coefficient values higher than 0.50 were deemed strong correlations and those from 0.30 to
103 0.49 moderate ones.

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

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

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

119

120 **Results**

121 Three hundred PD patients, most of them males (59.7%) and predominantly Caucasians
122 (84.8%) were included in the study. Median HY was 2 with an interquartile range of 2–3 (limits:
123 1–5). One hundred and fifty one patients (50.3%) had Postural instability and gait difficulty PD
124 subtype; 93 (31.0%) showed tremor predominant subtype; and 56 (18.7%) were indeterminate
125 (38,39). Other descriptive data of the sample are displayed in the Table 1. On the PDSS-2, the
126 average total score was 18.57 ± 10.89 (range: 0–51), while scores were 22.85 ± 19.45 (0–102) on
127 the KPPS, 3.96 ± 2.56 (1–12) on the KPPQ, and 32.78 ± 24.40 (0–100) on the VAS-Pain.

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

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

139 correlation coefficients with total scores decreased 0.06-0.07 (KPPS, 0.50; KPPQ, 0.51, VAS-
140 Pain, 0.28), and 0.04 in average (0.01-0.08) with KPPS domains. Furthermore, the two QoL
141 assessments showed moderate-to-high associations with the three pain measures in the study:
142 -0.45 to -0.60 for the EQ-5D-3L and 0.42 to 0.59 for the PDQ-8.

143 Using "PDSS-2 Pain" (the sum of items 10-12), the following correlations were found between
144 this pain score and other measures in the study: the KPPS domains of musculoskeletal
145 ($r_s=0.30$), fluctuation-related (0.32), nocturnal (0.52), and radicular (0.37) pain as well as its total
146 score (0.56); the KPPQ (0.54); VAS-Pain (0.42); the EQ-5D-3L's pain/discomfort question
147 (0.37); and PDQ-8 item 8 (0.43).

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

155 An additional multiple linear regression model using the KPPS pain modalities as predictors of
156 the PDSS-2 was explored. In this model, only nocturnal ($p<0.001$; $\beta=0.38$) and
157 musculoskeletal ($p=0.003$; $\beta=0.15$) pain were significant determinants of overall nocturnal
158 sleep disorder, a finding that was not modified by excluding the pain-related items of the PDSS-
159 2 (Table 5).

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

163 Anxiety (0.50); HADS-Depression (0.54); EQ-5D summary index (-0.49); PDQ-8 summary index
164 (0.60); SCOPA-Motor ADL (0.43), complications (0.38), and total score (0.40); the NMSS
165 domains of sleep/fatigue (0.58), mood/apathy (0.34), gastrointestinal (0.37), urinary (0.35), and
166 its total score (0.54).

167

168 **Discussion**

169 In line with previous findings, almost all patients in our sample (99.3%) declared having at least
170 one nocturnal sleep dysfunction according to the PDSS-2, confirming the high prevalence of this
171 non-motor symptom in PD (6). The most prevalent of these issues in our study were nocturia
172 (85.0%), tiredness and sleepiness upon waking (72.0%), and poor sleep quality (71.7%). While
173 some studies have found figures that are similar to ours, other studies did not (40-42); however,
174 the PDSS-2 has never been used to analyze the prevalence of nocturnal sleep disorders in PD,
175 and, therefore, our results cannot be compared at present with other studies. For example,
176 problems related to "PDSS-2 Pain" showed prevalence rates of 44.1-54.2%, but data
177 encompassing a similar combination of items has not been explored previously to our
178 knowledge. Yet, a limitation of our study is that it included only patients who experience at least
179 some form of pain, and, thus, our findings cannot be generalized.

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

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

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

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

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

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

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

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

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

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

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

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

243 Sleep disturbances and pain are significant factors in patients' lives as demonstrated by the
244 moderate-to-high correlations of the PDSS-2, KPPS, KPPQ, and VAS-Pain with both the EQ-
245 5D-3L and the PDQ-8, the two measures of QoL utilized in this study. When considering only
246 "PDSS-2 Pain," there were moderate correlations with the EQ-5D-3L's pain/discomfort question
247 and PDQ-8 item 8, findings in line with previous studies that identified pain is a determinant
248 factor of QoL (54).

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

253

254

255

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- 2) Statistical Analysis
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Expert Testimony: Lobsor Pharma, Zambon

Advisory Boards: AbbVie, Bial, Grunenthal, Lobsor Pharma, Nordic Infucare
Honoraria: AbbVie, Bial, Decitin, Grunenthal, Lobsor Pharma, Nordic Infucare, Zambon

CC

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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

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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	
<i>F=41.52, p<0.0001; Adj. R-squared=0.49</i>						<i>F=33.90, p<0.0001; Adj. R-squared=0.44</i>				
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	
<i>F=42.29, p<0.0001; Adj. R-squared=0.49</i>						<i>F=35.43, p<0.0001; Adj. R-squared=0.45</i>				
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	
<i>F=35.40, p<0.0001; Adj. R-squared=0.45</i>						<i>F=31.67, p<0.0001; Adj. R-squared=0.42</i>				

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	<i>t</i>	<i>p</i>	Beta	Coef	SE	<i>t</i>	<i>p</i>	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	
<i>F</i> =22.13, <i>p</i> <0.0001; Adj. <i>R</i> -squared=0.33					<i>F</i> =14.13, <i>p</i> <0.0001; Adj. <i>R</i> 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.

1 Introduction

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3 A range of sleep disorders and subtypes of pain, are very prevalent non-motor symptoms of
4 Parkinson's disease (PD) that occur from the prodromal to the palliative stages of PD (1-5).

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

12 On the other hand, using the King's Parkinson's Disease Pain Scale (KPPS) (11), the syndromic
13 nature of pain has been formally subdivided into several patterns. Prior research has shown that
14 the prevalence of pain is 68-81% in PD patients (12-14) and that it can be manifested in several
15 modalities, such as musculoskeletal (41-89%), dystonic (15-17%), radicular-neuropathic (27-
16 32%), and central pain (4-22%) (2,12,14-18). Furthermore, 35% of PD patients are affected by
17 two types of pain, 10% by three, and 2% by four (14). Pain can become crippling in a subset of
18 PD patients, affect their ability to conduct activities of daily living (ADL) (13,19), and negatively
19 impact their QoL (20-22). Yet, despite the impact of this non-motor symptom, pain often remains
20 underdiagnosed and undeclared (23).

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

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

27

28 **Methods**

29 Design

30 International, multicenter, observational, cross-sectional study.

31 Patients

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

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

42 Ethical issues

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

45 Assessments

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

49 The following instruments were used to assess each patient:

- 50 1. Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) (25), a 15-item, patient-completed
51 clinical tool used to assess the frequency of sleep disturbances during the past week in PD
52 patients. Items 10, 11, and 12 of the PDSS-2 directly assess pain while sleeping or when
53 waking up.
- 54 2. Hoehn-Yahr classification (HY) (30), a five-stage system that classifies PD on a
55 continuum from unilateral expression of the disease to the most severe.
- 56 3. Scales for Outcomes in Parkinson's Disease-Motor (SCOPA-Motor) (31), a 21-item
57 scale that measures motor impairment, difficulty with ADL, and motor complications.
- 58 4. Non-Motor Symptoms Scale (NMSS) (32), a 30-item scale that considers the frequency
59 and severity of the non-motor symptoms of PD grouped into nine domains: cardiovascular,
60 sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory,
61 gastrointestinal tract, urinary function, sexual function, and miscellaneous. Item 27 of the NMSS
62 directly inquires about unexplained pains.
- 63 5. Clinical Impression of Severity Index for PD (CISI-PD) (33), an overall estimate of PD
64 based on motor signs, disability, motor complications, and cognitive status.
- 65 6. King's Parkinson's Pain Scale (KPPS) (11), a 14-item scale that evaluates the types of
66 pain suffered by PD patients: musculoskeletal, chronic, fluctuation-related, nocturnal, oro-facial,
67 discoloration and oedema/swelling, and radicular pain. Each item is rated by the clinician
68 according to its severity (from 0 to 3) and frequency (from 0 to 4). An item's score is then

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

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

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

77 9 Hospital Anxiety and Depression Scale (HADS) (35), which is a 14-item, patient-
78 completed scale with subscales for anxiety and depression.

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

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

84

85 Data Analysis

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

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

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

99 The association of the PDSS-2 with the KPPS and other clinical variables evaluating pain
100 present in the study was assessed by Spearman correlations. Partial correlations were also
101 used to adjust these associations for age, PD duration, SCOPA motor examination, and LEDD.
102 Coefficient values higher than 0.50 were deemed strong correlations and those from 0.30 to
103 0.49 moderate ones.

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

112 **To exclude the influence of the PDSS-2 pain-related items on the findings, the correlation**
113 **coefficients and multiple regression models were recalculated after excluding the “PDSS-2 Pain”**
114 **dimension.**

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

119

120 Results

121 Three hundred PD patients, most of them males (59.7%) and predominantly Caucasians
122 (84.8%) were included in the study. Median HY was 2 with an interquartile range of 2–3 (limits:
123 1–5). One hundred and fifty one patients (50.3%) had Postural instability and gait difficulty PD
124 subtype; 93 (31.0%) showed tremor predominant subtype; and 56 (18.7%) were indeterminate
125 (38,39). Other descriptive data of the sample are displayed in the Table 1. On the PDSS-2, the
126 average total score was 18.57 ± 10.89 (range: 0–51), while scores were 22.85 ± 19.45 (0–102) on
127 the KPPS, 3.96 ± 2.56 (1–12) on the KPPQ, and 32.78 ± 24.40 (0–100) on the VAS-Pain.

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

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

139 correlation coefficients with total scores decreased 0.06-0.07 (KPPS, 0.50; KPPQ, 0.51, VAS-
140 Pain, 0.28), and 0.04 in average (0.01-0.08) with KPPS domains. Furthermore, the two QoL
141 assessments showed moderate-to-high associations with the three pain measures in the study:
142 -0.45 to -0.60 for the EQ-5D-3L and 0.42 to 0.59 for the PDQ-8.

143 Using "PDSS-2 Pain" (the sum of items 10-12), the following correlations were found between
144 this pain score and other measures in the study: the KPPS domains of musculoskeletal
145 ($r_s=0.30$), fluctuation-related (0.32), nocturnal (0.52), and radicular (0.37) pain as well as its total
146 score (0.56); the KPPQ (0.54); VAS-Pain (0.42); the EQ-5D-3L's pain/discomfort question
147 (0.37); and PDQ-8 item 8 (0.43).

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

155 An additional multiple linear regression model using the KPPS pain modalities as predictors of
156 the PDSS-2 was explored. In this model, only nocturnal ($p<0.001$; $\beta=0.38$) and
157 musculoskeletal ($p=0.003$; $\beta=0.15$) pain were significant determinants of overall nocturnal
158 sleep disorder, a finding that was not modified by excluding the pain-related items of the PDSS-
159 2 (Table 5).

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

163 Anxiety (0.50); HADS-Depression (0.54); EQ-5D summary index (-0.49); PDQ-8 summary index
164 (0.60); SCOPA-Motor ADL (0.43), complications (0.38), and total score (0.40); the NMSS
165 domains of sleep/fatigue (0.58), mood/apathy (0.34), gastrointestinal (0.37), urinary (0.35), and
166 its total score (0.54).

167

168 **Discussion**

169 In line with previous findings, almost all patients in our sample (99.3%) declared having at least
170 one nocturnal sleep dysfunction according to the PDSS-2, confirming the high prevalence of this
171 non-motor symptom in PD (6). The most prevalent of these issues in our study were nocturia
172 (85.0%), tiredness and sleepiness upon waking (72.0%), and poor sleep quality (71.7%). While
173 some studies have found figures that are similar to ours, other studies did not (40-42); however,
174 the PDSS-2 has never been used to analyze the prevalence of nocturnal sleep disorders in PD,
175 and, therefore, our results cannot be compared at present with other studies. For example,
176 problems related to "PDSS-2 Pain" showed prevalence rates of 44.1-54.2%, but data
177 encompassing a similar combination of items has not been explored previously to our
178 knowledge. Yet, a limitation of our study is that it included only patients who experience at least
179 some form of pain, and, thus, our findings cannot be generalized.

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

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

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

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

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

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

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

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

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

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

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

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

243 Sleep disturbances and pain are significant factors in patients' lives as demonstrated by the
244 moderate-to-high correlations of the PDSS-2, KPPS, KPPQ, and VAS-Pain with both the EQ-
245 5D-3L and the PDQ-8, the two measures of QoL utilized in this study. When considering only
246 "PDSS-2 Pain," there were moderate correlations with the EQ-5D-3L's pain/discomfort question
247 and PDQ-8 item 8, findings in line with previous studies that identified pain is a determinant
248 factor of QoL (54).

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

253

254

255

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- 2) Statistical Analysis
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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

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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	
<i>F=41.52, p<0.0001; Adj. R-squared=0.49</i>						<i>F=33.90, p<0.0001; Adj. R-squared=0.44</i>				
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	
<i>F=42.29, p<0.0001; Adj. R-squared=0.49</i>						<i>F=35.43, p<0.0001; Adj. R-squared=0.45</i>				
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	
<i>F=35.40, p<0.0001; Adj. R-squared=0.45</i>						<i>F=31.67, p<0.0001; Adj. R-squared=0.42</i>				

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	<i>t</i>	<i>p</i>	Beta	Coef	SE	<i>t</i>	<i>p</i>	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	
<i>F</i> =22.13, <i>p</i> <0.0001; Adj. <i>R</i> -squared=0.33					<i>F</i> =14.13, <i>p</i> <0.0001; Adj. <i>R</i> squared=0.24					

KPPS: King's Parkinson's Disease Pain Scale

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