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First comprehensive tool for screening pain in Parkinson's disease: The King's Parkinson's Disease Pain Questionnaire (KPPQ)

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Abstract

Background: Pain is highly prevalent in Parkinson's disease (PD), impacting patients' ability, mood, and quality of life. Detecting the presence of pain in its multiple modalities is necessary for adequate personalized management of PD. A 14-item, PD-specific, patient-based questionnaire (the King's Parkinson's disease Pain Questionnaire, KPPQ) was designed corresponding to the rater-based KPP Scale (KPPS). The present multi-center study was aimed at testing the validity of this screening tool. **Methods**: First, a comparison between the KPPQ scores of patients and matched controls was performed. Next, convergent validity, reproducibility (test-retest), and diagnostic performance of the questionnaire were analyzed.

Results: We report data from 300 patients and 150 controls. PD patients declared significantly more pain symptoms than controls (3.96±2.56 vs. 2.17±1.39; $p<0.0001$). KPPQ convergent validity with KPPS total score was high ($r_S = 0.80$), but weak or moderate with other pain assessments. Test-retest reliability was satisfactory with kappa values ≥0.65, except for item 5, Dyskinetic pains (kappa=0.44) and ICC for the KPPQ total score 0.98.

After the scores of the KPPS were adapted for screening (0= no symptom; ≥1= symptom present), a high agreement was found between the KPPQ and the KPPS (ICC =0.88). A strong correlation ($r_S = 0.80$) between both instruments was found. The diagnostic parameters of the KPPQ were very satisfactory as a whole, with a global accuracy of 78.3%-98.3%.

Conclusions: These results suggest that the KPPQ is a useful, reliable, and valid screening instrument of pain in PD to advance patient-related outcomes.

Key words: Parkinson's disease; Pain; Assessment; Screening; King's Parkinson's disease Pain Questionnaire; KPPQ; Validation

Introduction

The prevalence of pain in PD has been estimated to be around 68% (range: 40%-85%) [1]. However, pain in PD is still underdiagnosed and often undeclared [2], and only about half (52.4%) of PD patients with pain use analgesics [1].

Furthermore, PD patients with pain are more likely to suffer from anxiety, depression, and worsened sleep quality [3]. Pain has also been shown to interfere with work and other activities of daily living to some extent in these PD patients [4,5]. Because of the multi-dimensional effect of pain in PD, it is one of the most relevant determinant factors of health-related quality of life in general [6] and in PD [7,8].

Several types of pain may be present in PD (e.g. dystonic, musculoskeletal, central, and radicular) [9] and accumulate in a single patient, complicating the management of this non-motor symptom [10]. Moreover, the pathophysiology of pain in PD is complex, with peripheral- (rigidity, dystonia), spinal cord- (intermediolateral cell column), and brain-related (deficiency of monoamines in the brain stem) origins [11,12].

Due to their inherent difficulty for assessment, the rater-based King's Parkinson's disease Pain Scale (KPPS) was developed to evaluate the multiple pain modalities present in PD patients [13]. However, the KPPS is administered by healthcare professionals; therefore, a need for a valid patient-completed questionnaire exists. For this reason, the King's College Parkinson's Disease Pain Questionnaire (KPPQ) was created with the support of CRISP (Community for Involvement and Support for people with Parkinson's), an expert patient group based at King's College Hospital, to ensure comprehensibility for laypersons by using appropriate wording and logically ordering the questions.

The KPPQ (Appendix 1), a time-efficient and easy-to-understand 14-item screening questionnaire is composed solely of "Yes" or "No" questions that assess whether or not a

specific type of pain is present, similarly to the widely-used Non-Motor Symptoms Questionnaire [14]. Since the patient-completed KPPQ is a derivative of the rater-completed KPPS, each question of the KPPQ corresponds to one of the items of the KPPS. Even though the KPPQ does not use domains to group these 14 items, both the KPPS and the KPPQ address the same specific types of pain.

The objective of this multicenter study is to determine the validity and reliability of the KPPQ using a sample of PD patients and healthy controls.

Methods

Design

International, multi-center, observational, cross-sectional study.

Patients

Consecutive PD patients with a diagnosis of PD (according to the UK PD Brain Bank criteria) [15] who answered "Yes" to question 10 of the Non-Motor Symptoms Questionnaire, "Unexplained pains (not due to known conditions)," [14] were included in this study. Exclusion criteria were: (1) Patients with alternative or uncertain diagnosis of Parkinson's and drug-induced Parkinson's; (2) inability to give consent; (3) presence of dementia formally diagnosed following internationally-accepted criteria; and (4) diagnosis of identifiable conditions causing pain unrelated to PD (e.g. severe osteoarthritis, known malignancy, rheumatoid arthritis, polymyalgia rheumatica, fibromyalgia, etc.).

For this study, a sample size of 300 patients was proposed considering both the potential variability and confounding effect of a patient-completed assessment and the number of participating sites.

Patients were recruited from August 2013 to February 2016 from movement disorder units of nine different centers across the UK as well as Romania. In the UK, the study was adopted to the National Institute of Health Research portfolio of studies (UKCRN No. 13344).

Controls

A sample of 150 controls (ratio of patients:controls = 2:1) matched by age and sex was assessed by means of the KPPQ. Exclusion criteria overlapped exclusion criteria 2 through 4 for patients.

Assessments

For both patients and controls, information regarding socio-demographic and PD historical data were recorded.

In addition to the KPPQ, the following instruments for PD were applied (see Supplementary material for details): KPPS [13], Hoehn and Yahr classification (HY) [16], Scales for Outcomes in Parkinson's Disease-Motor (SCOPA-Motor) [17], Non-Motor Symptoms Scale (NMSS) [18], Clinical Impression of Severity Index for PD (CISI-PD) [19], Visual Analog Scales (VAS) for pain severity and frequency [20], Hospital Anxiety and Depression Scale (HADS) [21], EQ-5D [22], PD Quality of Life Questionnaire (PDQ-8) [23], and Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) [24].

Levodopa Equivalent Dose (LEDD) was calculated according to Tomlinson et al. 2010 [25].

In the control group, the following assessments were collected: KPPQ, HADS, and EQ-5D.

Procedures

Patients were assessed in the optimally "on" state. Test-retest reliability of the KPPQ was evaluated by means of a second application of the questionnaire in patients who remained stable with respect to pain as per the pain VAS.

Ethical Issues

This study was approved by the hospital ethical committees/institutional review boards of the participant centers. All participants provided informed consent prior to joining the study.

Data Analysis

For each participant, a KPPQ "total score" (KPPQ-TS) was calculated by summing the number of "Yes" responses. Also, to compare the performance of the KPPQ with the KPPS that was taken as "gold standard," the KPPQ items were grouped in domains according to those of the scale. For both the NMSQ and NMSS, the prevalence of the diverse types of pain was determined by the proportion of individuals responding positively each item (score ≥1), considering a score of 0 as the absence of the symptom.

Distribution of data was not normal (Shapiro-Francia test); therefore, non-parametric statistics were used. The differences between patients and controls were analyzed using the chi-square, Mann-Whitney U, and McNemar chi-square tests. Association between measures was determined by the Spearman rank correlation coefficient. A high correlation (r_S >0.70) of the KPPQ-TS with KPPS total score was hypothesized, whereas moderate or weak correlations (r_S= ≤0.70) [26] were expected with other variables.

For concordance between the prevalence detected by corresponding items of KPPQ and KPPS, and for test-retest reliability, Cohen's kappa index for items, and ICC for total scores were determined.

Finally, sensitivity, specificity, positive and negative predictive values, and accuracy of the KPPQ were calculated against the corresponding components of the KPPS.

For more detail, see the Supplementary material.

Results

We report data from 300 patients and 150 controls matched by age and gender. There were no significant differences between patients and controls in reference to age (mean±SD: 64.86±10.54 vs. 64.86±10.23; p=0.90), sex (males, 59.7% vs. 60%; p=0.95), ethnics (p=0.63), and education years (14.11±3.99 vs. 14.39±3.93; p=0.33). Median (and interquartile range) HY of patients was 2 (2 – 3; limits: 1–5).

HADS and EQ-5D assessments showed significantly higher levels of depression (6.62±4.39), anxiety (5.45±3.82), and worse quality of life (0.57±0.27) in PD patients when compared to the levels of depression (5.09±3.57), anxiety (3.90±3.01), and overall quality of life (0.78±0.22) in

controls (p<0.0001 to p=0.0006). Significant differences were also found in the proportion of subjects with positive responses on the KPPQ for 50% of the items and three out of the seven domains after Bonferroni correction (Table 1). When comparing KPPQ-TS, patients declared more pain symptoms than controls (3.96±2.56 vs. 2.17±1.39; p<0.0001).

In patients, the proportion of positive responses to the KPPQ was compared with those of the KPPS, and a significant difference was found in only one item (6. Painful cramps during off periods) of the KPPQ and one domain (3. Fluctuation-related pain) (Table 1).

The agreement between KPPQ and KPPS prevalence showed kappa values from 0.56 (KPPQ items 6 and 7) to 0.86 (item 14), with 11 items (78.6%) reaching kappa values greater than 0.60 (substantial agreement). Overall, the KPPQ-TS and KPPS “total score of prevalence” displayed a high level of concordance (ICC =0.88).

Table 2 shows the correlations of the KPPQ-TS with other pain measures. While a tight correlation with the KPPS total score (r_S=0.80) was found, coefficients were weak/moderate with the other pain measures (r_S=0.31-0.46). The KPPS total score, however, showed mildly higher correlation coefficient values with these pain assessments (r_S=0.47-0.50).

To test the reproducibility of the KPPQ, a second application was carried out in 52 patients at a mean interval of 11.8±4.4 days (range: 7-28). No significant differences between applications were found for the VAS-TS (Wilcoxon signed-rank test; p=0.52) and the KPPQ-TS (p=0.76). Kappa values were ≥0.65 for all KPPQ items, with exception of one item (5. Dyskinetic pains; kappa=0.44) (Table 3). ICC for the KPPQ-TS was 0.98.

The results of KPPQ diagnostic parameters were satisfactory, with values running from 61.4% to 99.3% (Table 4). The global accuracy of the KPPQ components ranged from 78.3% to 98.3%

Discussion

This is the first report of a validation of a patient-completed pain questionnaire specifically developed for PD. This patient-completed screening tool was derived from the KPPS and allows for the direct declaration of the pain each patient experiences.

Prevalent in the prodromal, early, advanced, and palliative stages of PD, pain is one of its most important non-motor symptoms [27-29] and was described by James Parkinson himself in his case number 4 [30,31]. Neuropathological correlates of pain in early and untreated PD have

been described, [32] and pain is also featured as one of the most prevalent and troublesome symptoms in the late palliative stage of PD [28,33].

Despite the importance and high frequency of pain in PD [34], studies suggest that pain is under-reported and often not considered in clinical consultations [2]. In part, this is related to the lack of a validated self-declared tool specifically developed considering the diversity of pain in PD. KPPQ was developed considering this conceptual framework and to empower patients to declare pain.

Our analysis showed that, when the KPPQ was applied in patients and matched controls, the prevalence of the different varieties of pain was significantly greater in PD patients in half of the pain modalities and in three out of the seven domains. These results are expected because pain is experienced by both the elderly and PD patients. However, when considering the differences between KPPQ-TS, patients declared significantly more symptoms than controls.

Consistent with previous findings, patients with pain displayed higher rates of depression and anxiety [3]. Some estimates show that chronic pain can increase the risk for depression, yet a link in the opposite direction is unclear [35,36,37]. It is hypothesized that the link between pain and depression could be due to neuroinflammation [36]. In PD, pain-related disability also correlates with depression and anxiety [38].

Prior research has shown that pain is a determinant of quality of life in all populations [39] and that PD considerably deteriorates patients' HRQoL [40,41]. The non-motor symptom burden of PD, which includes pain, can affect HRQoL with a greater impact than the motor symptoms [42-45].

The convergent validity of the KPPQ was assessed using other pain measures. While weak and moderate correlations were found between these measures and the KPPQ, the KPPS showed higher levels of correlations with these scales. However, it is important to note that the KPPQ is only a screening tool, whereas the KPPS is a quantitative measure of pain severity and frequency in PD and is more closely related to the scales with which both were compared. Nevertheless, the KPPQ showed moderate correlations with PD-related variables (i.e. SCOPA – Motor, NMSS, CISI-PD, PDSS-2, and PDQ-8) as well as other measures (i.e. HADS – Anxiety, HADS – Depression, and EQ-5D). The weak correlation between the KPPQ and LEDD and between the KPPQ and HY staging suggest that there is no relation between PD progression and the number of pain symptoms experienced by the patient despite previous findings suggesting a relationship between pain and motor impairment severity [4].

Concerning the reproducibility of the KPPQ, there was significant agreement in each item between both applications of the KPPQ, except for one (5. Dyskinetic pains), and for the KPPQ-TS. These findings lead to the conclusion that the KPPQ is an instrument with satisfactory reproducibility.

When comparing the KPPQ to the KPPS, there were significant differences in the proportion of positive responses for only one item and one domain. This can be explained by the differences in the wording of the corresponding item in the KPPQ (6. Painful cramps in a region during “off” periods) and in the KPPS (5. Pain in a region during “Off” dystonia). Otherwise, there was significant agreement between KPPQ and KPPS prevalence for each item, suggesting that they are equivalent when the KPPS is used as a screening tool. There were also a high level of concordance and a strong correlation between the total scores for both instruments.

Finally, the satisfactory capabilities of the KPPQ for screening are clear based on its high sensitivity, specificity, and predictive values. Overall, the KPPQ was shown to detect with a high accuracy the presence of the diverse pain modalities in PD. Yet, a limitation of our study is the assumption that a variety of comorbidities may not cause significantly increased pain and may be evenly-distributed among patients and controls. Therefore, we did not control for comorbidities that may not necessarily cause pain, such as diabetes.

However, from these results, it is inferred that the KPPQ is a useful, valid, and reliable, patient-completed instrument to assess pain in PD. We propose that KPPQ be provided to every patient who answers “yes” to the relevant pain related question in the Non-Motor Symptoms Questionnaire, which is now globally applied and regarded as a quality standard for the clinical assessment of PD. As both are patient-completed tools, they can be completed while waiting to be seen, optimizing consultation time. Utilization of this strategy in clinics would ensure that pain is not under-reported or under-recognized in clinical practice.

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Table 1 – Prevalence† of pain modalitites according to the King's Parkinson's Disease Pain Questionnaire

Items	KPP Questionnaire			KPP Scale	
	Controls	Patients	p*	Patients	p**
1. Pain around joints	77.33	78.67	0.75	81.33	0.046
2. Pain related to internal organ	13.33	19.67	0.096	21.00	0.41
3. Generalised non-specific pain in your stomach area	11.33	19.00	0.039	17.67	0.43
4. Pain deep within the body	19.33	32.33	0.0004	31.67	0.77
5. Dyskinetic pain	0	16.67	<0.0001	17.00	0.86
6. Painful cramps in a region during "off" periods	11.33	48.33	<0.0001	32.67	<0.0001
7. Generalized "off" period pain	0.67	24.67	<0.0001	22.33	0.31
8. PLM or RLS-associated pain	14.67	32.67	<0.0001	28.00	0.023
9. Pain while turning in bed	18.67	48.33	<0.0001	47.67	0.69
10. Pain when chewing	4.67	6.67	0.40	6.67	1.0
11. Pain due to grinding teeth	6.00	6.00	1.00	5.67	0.74
12. Burning sensation in the mouth	5.33	3.00	0.22	2.67	0.65
13. Burning pain in the limbs	12.00	18.00	0.10	18.33	0.87
14. Shooting pain/pins & needles	22.00	42.33	<0.0001	41.67	0.65
Domains	**Controls**	**Patients**	**p***	**Patients**	**p****
1. Musculoskeletal pain	77.33	78.67	0.75	81.33	0.05
2. Chronic pain	30.00	40.00	0.003	40.00	1.0
3. Fluctuation-related pain	12.00	56.33	<0.0001	44.00	<0.0001
4. Nocturnal pain	28.67	57.33	<0.0001	66.00	0.41
5. Oro-facial pain	14.00	13.00	0.71	13.33	0.76
6. Discoloration, oedema/swelling	23.33	31.67	0.009	30.33	0.54
7. Shooting pain/pins & needles	22.00	42.33	<0.0001	41.67	0.65

† Proportion of subjects with positive response.
KPP Questionnaire/Scale: King's Parkinson's Disease Pain Questionnaire/Scale.
* Chi-square for prevalence, patients vs. controls.
** McNemar test for prevalence with KPPQ vs. KPPS in patients.
Bonferroni correction: p=0.0024.

Table 2 – Correlations of the the King's Parkinson's Disease Pain Questionnaire total score

	Measure	Spearman r
With other pain measures	KPPS total score	0.80
	VAS Pain (frequency * severity)	0.31
	PDQ-8 Item 8	0.46
	EQ-5D Item Pain/Discomfort	0.32
With PD-related variables	SCOPA - Motor	0.42
	Non-Motor Symptoms Scale	0.47
	Clinical Impression of Severity Index-PD	0.37
	Parkinson's Disease Sleep Scale	0.57
	Parkinson's Disease Questionnaire-8 items	0.56
	Hoehn and Yahr staging	0.15*
	Levodopa-equivalent daily dose	0.24
With other measures	HADS – Anxiety	0.45
	HADS – Depression	0.43
	EQ-5D	-0.45

All coefficient values, $p \leq 0.001$, except *, $p=0.008$.

Table 3 – Test-retest reliability of the King's Parkinson's Disease Pain Questionnaire

Items	Agreement (%)	Kappa	
		kappa	CI 95%
1. Pain around joints	96.2	0.85	0.65 – 1.00
2. Pain related to internal organ	92.3	0.73	0.49 – 0.98
3. Generalised non-specific pain in your stomach area	96.2	0.85	0.65 – 1.00
4. Pain deep within the body	88.5	0.68	0.44 – 0.91
5. Dyskinetic pain	82.7	0.44	0.15 – 0.73
6. Painful cramps in a region during "off" periods	84.6	0.69	0.49 – 0.89
7. Generalized "off" period pain	92.3	0.82	0.65 – 0.99
8. PLM or RLS-associated pain	96.2	0.91	0.78 – 1.00
9. Pain while turning in bed	94.2	0.88	0.75 – 1.00
10. Pain when chewing	96.2	0.65	0.20 – 1.00
11. Pain due to grinding teeth	100	1.00	1.00 – 1.00
12. Burning sensation in the mouth	100	1.00	1.00 – 1.00
13. Burning pain in the limbs	94.2	0.82	0.63 – 1.00
14. Shooting pain/pins & needles	92.3	0.84	0.69 – 0.99

Table 4 – Screening potential of pain modalities using the King's Parkinson's Disease Pain Questionnaire when considering the King's Parkinson's Disease Pain Scale as the gold standard

Items	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
1. Pain around joints	95.1%	92.9%	98.3%	81.3%	94.7%
2. Pain related to internal organ	77.8%	95.8%	83.1%	94.2%	92.0%
3. Generalised non-specific pain in your stomach area	79.2%	93.9%	73.7%	95.5%	91.3%
4. Pain deep within the body	75.8%	87.8%	74.2%	88.7%	84.0%
5. Dyskinetic pain	66.7%	93.6%	68.0%	93.2%	89.0%
6. Painful cramps in a region during "off" periods	90.8%	72.3%	61.4%	94.2%	78.3%
7. Generalized "off" period pain	70.1%	88.4%	63.5%	91.2%	84.3%
8. PLM or RLS-associated pain	85.7%	88.0%	73.5%	94.1%	87.3%
9. Pain while turning in bed	91.6%	91.1%	90.3%	92.3%	91.3%
10. Pain when chewing	80.0%	98.6%	80.0%	98.6%	97.3%
11. Pain due to grinding teeth	76.5%	98.2%	72.2%	98.6%	97.0%
12. Burning sensation in the mouth	75.0%	99.0%	66.7%	99.3%	98.3%
13. Burning pain in the limbs	65.5%	92.7%	66.7%	92.3%	87.7%
14. Shooting pain/pins & needles	92.8%	93.7%	91.3%	94.8%	93.3%
Domains	**Sensitivity**	**Specificity**	**Positive Predictive Value**	**Negative Predictive Value**	**Accuracy**
1. Musculoskeletal pain	95.1%	92.9%	98.3%	81.3%	94.7%
2. Chronic pain	80.0%	86.7%	80.0%	86.7%	84.0%
3. Fluctuation-related pain	92.4%	72.0%	72.2%	92.4%	81.0%
4. Nocturnal pain	94.0%	89.4%	91.9%	92.2%	92.0%
5. Oro-facial pain	85.0%	98.1%	87.2%	97.7%	96.3%
6. Discoloration, oedema/swelling	79.1%	89.0%	75.8%	90.7%	86.0%
7. Shooting pain/pins & needles	92.8%	93.7%	91.3%	94.8%	93.3%

PD PAIN QUESTIONNAIRE

Name: _____ Date: _____ Date of birth: _____

Centre: _____ Male ☐ Female ☐

PAIN IN PARKINSON'S

The movement symptoms of Parkinson's are well known. However, other problems like pain can occur as part of the condition or its treatment. It is important that the doctor knows about the specific type of your pain, particularly if it is troublesome for you.

Several types of pain are listed below. Please:

- Tick the box "Yes" if you have experienced this particular type of pain during the past month.
- If you have not experienced the type of pain in the past month tick the "No" box.
- The doctor or nurse may ask you some additional questions to help you decide.

Please note that this questionnaire only relates to the pain you experienced in the last 30 days.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING IN THE LAST MONTH?

	Yes	No
1. Pain around the joints (including pain related to arthritis)	☐	☐
2. Pain related to a specific internal organ (for example, pain around the liver, stomach or bowels)	☐	☐
3. Generalised non-specific pain in your stomach area.....	☐	☐
4. Non-specific pain deep within the body: a generalised constant, dull, aching pain.....	☐	☐
5. Pain related to abnormal involuntary movements (dyskinetic pain)	☐	☐
6. Painful muscle cramps in a specific region during "off" periods (when your medication is not working).....	☐	☐
7. Generalised pain during "off" periods (pain in the whole body or areas that are not affected by muscle cramps).....	☐	☐
8. Pain related to jerking leg movements during the night or an unpleasant burning sensation in the legs which improves with movement (restless legs syndrome)	☐	☐
9. Pain related to difficulties when turning in bed at night	☐	☐
10. Pain when chewing	☐	☐
11. Pain related to grinding teeth during the night	☐	☐
12. Burning sensation in your mouth.....	☐	☐
13. Burning pain in the limbs (often associated with swelling or medication).....	☐	☐
14. Shooting pain/pins and needles down the limbs	☐	☐

Supplementary material

Assesments

For both patients and controls, information regarding age, sex, and ethnicity was collected. For patients, information regarding the duration of PD (in years), years of treatment for PD, current treatment, and surgery was also addressed.

In addition to the KPPQ, information for each patient was collected using the following validated instruments for PD:

1. The KPPS [13], a specific measure of different pain modalities for PD patients. It includes 14 items grouped in seven domains (musculoskeletal, chronic, fluctuation-related, nocturnal, oro-facial, discolouration and oedema/swelling, and radicular pain). The score for each item is the product of severity (0 to 3) and frequency (0 to 4). Total scores for each domain are obtained by summing the corresponding items and for the overall scale by summing the domain scores.

2. The original Hoehn and Yahr classification (HY), which measures the staging of PD on a scale from one to five with one being unilateral expression of disease and five being the most severe stage [16].

3. The Scales for Outcomes in Parkinson's Disease-Motor (SCOPA-Motor), which measures motor impairment (10 items), activities of daily living (7 items), and motor complications (4 items) [17].

4. The Non-Motor Symptoms Scale for PD (NMSS) [18], a 30-item questionnaire grouped in 9 domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/cognition (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary function (3 items), sexual function (2 items), and miscellaneous (4 items).

5. The Clinical Impression of Severity Index for PD (CISI-PD) [19], a clinical estimate of the PD global severity in four areas: motor signs, disability, motor complications, and cognitive status.

6. Visual Analog Scales (VAS) for pain severity and frequency [20]. A total score (VAS-TS) was obtained by multiplying the two individual scores.

7. Hospital Anxiety and Depression Scale (HADS) [21], a self-administered, 14-item instrument to measure depression and anxiety disorders in non-psychiatric outpatients.

8. European Quality of Life – 5 Dimensions Scale (EQ-5D) [22], a generic, preference-based health-related quality of life (HRQoL) measure. It includes three components: (1) a descriptive part, consisting of 5 items, that can then be converted into a value (EQ-Index) representing the overall HRQoL; (2) a question about change in health status in the preceding 12 months; and (3) a visual analogue scale (EQ-VAS) for assessment of current health state.

9. PD Quality of Life Questionnaire (PDQ-8) [23], an 8-item instrument that specifically measures HRQoL in PD;

10. Parkinson's Disease Sleep Scale-Version 2 (PDSS-2) [24], an updated version of the 15-item PDSS.

Data Analysis

Data from each center were anonymized and sent to the National Center of Epidemiology, Carlos III Institute of Health, Madrid (Spain) for analysis under the supervision of PMM.

Distribution of data was not normal (Shapiro-Francia test); therefore, non-parametric statistics were used. For each participant, a KPPQ "total score" (KPPQ-TS) was calculated by summing the number of "Yes" responses. Also, to compare the performance of the KPPQ with the KPPS that was taken as "gold standard," the KPPQ items were grouped in domains according to those of the scale.

Differences between patients and controls with respect to demographic data were analyzed using the chi-square and Mann-Whitney U tests. The prevalence of the diverse types of pain assessed in the questionnaire was determined for each item by the proportion of individuals responding positively. In patients, a comparison of the prevalence for each item obtained from the KPPS application was carried out considering a score of 0 as the absence of the symptom and a score ≥1 ("positive response") as indicative of the presence of the symptom. The McNemar chi-square test was used to determine the statistical significance of the differences.

Furthermore, Spearman rank correlation coefficients between the KPPQ-TS and scores of the other aforementioned pain measures were assessed to determine convergent validity. In addition, the correlation between the KPPQ-TS and other variables in the study was calculated. A high correlation (rS >0.70) was hypothesized with the KPPS total score (sum of the 14 items´ scores), whereas moderate or weak correlations (rS= ≤0.70) [26] were expected with other PD and generic measures.

For test-retest reliability, the percentage of agreement, Cohen's kappa index for items, and ICC (1-way, random effect) for the KPPQ-TS were determined.

Cohen's kappa was used to determine the concordance between the prevalence detected by corresponding items of KPPQ and KPPS. In addition, a KPPS "total score of prevalence" was calculated as with the KPPQ-TS, and intraclass correlation coefficient (ICC, 2-way, random effect) was used to further analyze the concordance between both "total scores."

Finally, sensitivity, specificity, positive and negative predictive values, and accuracy of the KPPQ items and domains were calculated against the corresponding components of the KPPS, which were considered the gold standard.