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Predictors of health-related quality of life in Parkinson's disease

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ABSTRACT

Background: Health-related quality of life in Parkinson's disease may be affected by a wide range of motor and non-motor symptoms. Identifying which symptoms are significant predictors of health-related quality of life in Parkinson's disease prioritizes symptoms for treatment, therapeutic development, and clinical outcomes.
Objectives: To determine predictors of health-related quality of life in patients with Parkinson's disease.
Methods: We recruited 102 subjects into a prospective study to investigate neuropsychiatric symptoms in Parkinson's disease. Health-related quality of life was measured with the 39-item Parkinson's Disease Questionnaire. Subjects completed the Movement Disorder Society Unified Parkinson's Disease Rating Scale Parts I-IV as well as validated scales to assess anxiety, depression, apathy, cognition, psychosis, impulsive-compulsive disorder, autonomic dysfunction, sleep quality, excessive daytime sleepiness, and rapid eye movement sleep behavior disorder. We used univariate analyses to select clinical predictors to construct a multivariate regression model to determine which predictors were independently associated with worse health-related quality of life.
Results: In a multivariate linear regression model adjusted for age and gender, higher scores for the International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale part II as well more severe symptoms of depression, anxiety, apathy, and excessive daytime sleepiness were associated with worse health-related quality of life. The model explained 78% of the variance of health-related quality of life, and the non-motor symptoms explained 49% of the variance.
Conclusions: Anxiety, depression, excessive daytime sleepiness, apathy, and impairment in activities of daily living related to motor symptoms were independently associated with worse health-related quality of life.

1. Introduction

Health-related quality of life (HRQoL) has been defined as "the patient's own perception and self-evaluation regarding the effects of an illness and its consequences on her or his life." [1] HRQoL is an important factor to consider when managing chronic, progressive, and complex diseases such as Parkinson's disease (PD), because it incorporates the patient's experience with the disease. HRQoL in PD is affected by a wide range of clinical features, including both motor and non-motor symptoms [2]. Several studies have shown that non-motor symptoms [3,4] including depression [2,5] have a greater impact on HRQoL than motor symptoms. However, depression is also the most commonly investigated neuropsychiatric non-motor symptom which could overemphasize its importance relative to other non-motor symptoms [6]. Determining which PD symptoms best predict HRQoL can help guide discussions in clinic and prioritize future symptomatic therapy trials. Identifying clinical features most salient to the patient can also inform outcome measures in future disease-modifying clinical trials. The objective of this study was to determine which motor and non-motor symptoms are significant predictors of HRQoL for patients with PD. We considered a wide range of commonly and less frequently investigated PD-related symptoms using scales validated in PD.

2. Methods

2.1. Study population

PD patients without a clinical diagnosis of dementia were referred

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by movement disorders neurologists at the University of Virginia to participate in a prospective study investigating neuropsychiatric symptoms in PD.

PD diagnosis was confirmed with the United Kingdom Brain Bank Criteria with the exception that subjects were not excluded if they had more than one family member with PD [7]. For the current study, data from the baseline research visit for 112 subjects were considered for analysis. Ten potential subjects were excluded because they did not complete the 39-item Parkinson's disease Questionnaire (PDQ-39) or individual questions were not answered or answered ambiguously. The study was conducted with the remaining 102 subjects. The local Institutional Review Board for Health Sciences Research approved this study and participants provided informed consent.

2.2. Outcome measure

The PDQ-39 is a validated disease specific HRQoL measure in PD [8]. Each question of the PDQ-39 is scored on a 5-point Likert scale and is assigned to 1 of 8 dimensions: mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items). A ratio of points scored to points possible for each dimension is calculated and multiplied by 100 with higher scores indicating worse quality of life. Of note, one of the three questions in the social support dimension allows for subjects to omit the question if they do not have a spouse or partner. In cases where this question was omitted or not answered (n = 10, 9.8%), we calculated the social support dimension score using the remaining 2 items. The PDQ-39 summary index (SI), which ranges from 0 to 100, is calculated by taking the mean of the 8 dimension scores [9].

2.3. Clinical assessments

Demographic information and details about PD diagnosis, medical history, and current medications were collected through patient interview. Duration of disease was calculated using the reported onset date of PD motor symptoms. Levodopa equivalent dose (LED) was calculated from antiparkinsonian medication doses [10]. Subjects completed the International Parkinsonism and Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPRDS), Hoehn and Yahr staging (H&Y), and Schwab and England activities of daily living scale (S&E). The MDS-UPRDS is a standardized, validated PD scale that captures non-motor experiences of daily living (part I), motor experiences of daily living (part II), a disease relevant motor examination (part III), and motor complications including motor fluctuations and dyskinesias (part IV) [11]. Motor subscores of MDS-UPRDS part III were calculated for tremor (items 3.15–18), rigidity (3.3), bradykinesia (3.4–8, 3.14), and axial signs (3.1-2, 3.9–13). Dyskinesia and motor fluctuations subscores were calculated from MDS-UPRDS part IV items 4.1–4.2 and 4.3–4.6, respectively.

Using the Scale for the Assessment of Positive Symptoms (SAPS) and a separate standardized assessment of visual illusions and sense of presence over the previous month, the NINDS-NIMH diagnostic criteria were applied to determine the presence of psychosis [12]. Apathy was assessed with the 14-item Apathy Scale (AS) [13]. The Montreal Cognitive Assessment (MoCA) was performed to determine the presence of cognitive impairment [14]. Three scales for sleep were included to assess different aspects of sleep: the ESS measures excessive daytime sleepiness [15], the SCOPA-Sleep NS measures quality of nighttime sleep [16], and the RBDSQ assesses for RBD [17]. Subjects also completed the following validated questionnaires: Scales for Outcomes in Parkinson's disease (SCOPA) Autonomic Scale (SCOPA-AUT); Beck Anxiety Inventory (BAI) [18]; Beck Depression Inventory-II (BDI-II) [19]; and Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP) [20].

2.4. Statistical analysis

For univariate analyses, we divided the cohort into tertiles according to PDQ-39 SI score. All questionnaires and scales were considered as continuous variables except for current psychosis which was considered as a dichotomous variable. We applied Chi-squared tests for categorical variables and one-way ANOVA tests or Kruskal-Wallis tests for continuous variables as appropriate. Covariates with p-value < 0.2 in univariate analyses were considered for inclusion in a multivariate linear regression model with PDQ-39 SI as the dependent variable. We applied a forward selection method with significance of $p < 0.05$ for entry into the model and $p > 0.1$ for removal after subsequent variables were included. All models were adjusted for age and gender. The H&Y and S&E scales were not considered for inclusion in the model because they are considered global measures of disease severity. Motor subscores derived from MDS-UPDRS part III were not considered for inclusion in the primary linear regression model. To assess the effect of motor subscores on prediction of HRQoL, we constructed a second linear regression model with the motor subscores meeting the predefined p-value for inclusion. An R-squared was calculated to determine how much of the variance in HRQoL was explained by the group of predictor variables in the final model. An eta squared was calculated to determine the effect size of subgroups of motor and non-motor predictor variables. Two secondary analyses were also performed to assess the correlation between specific predictor variables. Spearman rank coefficients were calculated for BDI-II and PDQ-39 emotional well-being domain as well as ESS and SCOPA sleep NS. The overlap in content between BDI-II and PDQ-39 emotional well-being domain has been previously reported [21]. A strong correlation between these variables would suggest collinearity. The association between sleep quality and excessive daytime sleepiness was performed to determine if these two variables are strongly associated because poor nighttime sleep may reasonably lead to excessive daytime sleepiness. Analyses were performed using Stata 11.2 (College Station, TX: StataCorp LP).

3. Results

Clinical characteristics and symptom assessments for 102 PD participants are reported in Table 1. The median PDQ-39 SI was 13.6 (interquartile range (IQR): 7.9, 20.7), and two participants had a PDQ-39 SI score of 0. Sixteen subjects (15.8%) were H&Y stage 1, 81 (80.2%) were stage 2, and 4 (4.0%) were stage 3. Most subjects were independent with activities of daily living as quantified by the S&E scale. The S&E scale was 100% for 10 subjects (9.9%), 90% for 59 subjects (58.4%), 80% for 24 subjects (24.0%), 70% for 6 subjects (5.9%), and 60% for 2 subjects (2.0%). There were 35 (34.7%) subjects with dyskinesia and 49 (48%) subjects with motor fluctuations.

Univariate comparisons between predictor variables and PDQ-39 SI are included in Table 1. Gender, BDI-II, BAI, AS, SCOPA-AUT, SCOPA-Sleep NS, LED, MDS-UPDRS Part I-III, MDS-UPRS part IV motor fluctuation score, bradykinesia subscore, axial subscore, and rigidity subscore met predefined criteria for inclusion in the multivariate analysis. Age, years of education, duration of disease, QUIP, MoCA, tremor subscore, and MDS-UPRDS part IV dyskinesias score were not significantly associated with PDQ-39 SI score.

For the primary multivariate linear regression model adjusted for age and gender, BAI, BDI-II, ESS, AS, and MDS-UPDRS part II were significant independent predictors of PDQ-39 SI ($p < 0.05$, n = 98; see Table 2). The adjusted R-squared value indicated that 78% of the variance in the PDQ-39 SI was explained by these factors. Of note, age and gender were forced into the multivariate model and were not significantly associated with PDQ-39 SI. The non-motor symptoms alone accounted for 48% of the variance in the PDQ-39 SI. MDS-UPDRS part II accounted for 25.6% of the variance in the PDQ-39 SI. MDS-UPDRS part I, RBDSQ, SCOPA-AUT, SCOPA-Sleep NS, current psychosis, MDS-UPDRS part III, MDS-UPDRS part IV motor fluctuations score, and LED

Table 1
Clinical characteristics and symptom scale assessments.

	Total Study Population	PDQ39 Summary Index			p-value
		Tertile 1 (0–9.5)	Tertile 2 (9.8–17.8)	Tertile 3 (18.3–66.2)	
Subjects, n	102	34	34	34	
Men, n (%)	62 (60.8)	16 (47.1)	21 (61.8)	25 (73.5)	0.08
Age, mean (SD)	68.2 (10.1)	67.8 (7.4)	66.7 (13.5)	70.0 (8.5)	0.39
Years of education, median (IQ range)	16 (14–18)	16 (14–18)	16.5 (15–18)	16 (13–18)	0.87
Duration of disease, median (IQ range)	5.2 (3.5–7.8)	5.6 (3.5–7.4)	4.6 (3.4–8.1)	5.9 (3.5–8.6)	0.58
MDS-UPDRS part I, median (IQ range)	9 (7–14) n = 101	7 (3–9) n = 33	8.5 (7–12)	15 (12–19)	0.0001
SCOPA-AUT, median (IQ range)	13 (8–18) n = 97	8 (4–12)	11 (9.5–17) n = 32	18 (15–19) n = 31	0.0001
SCOPA-Sleep NS, median (IQ range)	4 (2–7)	3 (1–6)	4 (3–7)	5 (3–7)	0.03
ESS, median (IQ range)	8 (5–13) n = 101	4.5 (4–8)	7.5 (5–12)	13 (8–15) n = 33	0.0001
BDI-II, median (IQ range)	8 (5–12)	5 (3–9)	9 (7–10)	13.5 (8–20)	0.0001
BAI, median (IQ range)	9 (4–15)	4 (3–8)	9 (5–12)	18 (10–21)	0.0001
QUIP, median (IQ range)	0 (0–1) n = 100	0 (0–1)	0 (0–1) n = 33	0 (0–1) n = 33	0.86
RBDSQ, median (IQ range)	5 (2–8) n = 94	3 (1–6) n = 30	4 (2–6.5) n = 32	8 (4.5–9) n = 32	0.0014
Current Psychosis, n (%)	38 (37.3)	6 (17.7)	12 (35.3)	20 (59)	0.002
AS, median (IQ range)	9 (6–16)	6.5 (4–10)	8 (5–13)	15.5 (9–21)	0.0001
MoCA, median (IQ range)	24 (22–26)	24 (23–27)	25 (22–27)	24 (22–26)	0.26
MDS-UPDRS part II, median (IQ range)	9 (6–15) n = 99	6 (3–9) n = 33	10 (7–13) n = 33	16 (10–20) n = 33	0.0001
MDS-UPDRS part III, median (IQ range)	25 (17–37)	22 (14–30)	22.5 (15–36)	35.5 (25–46)	0.0007
Tremor subscore, median (IQ range)	4 (2–7)	4.5 (2–8)	3 (1–6)	4 (2–9)	0.3
Rigidity subscore, median (IQ range)	5 (2–8)	3 (2–7)	4 (2–7)	7 (4–10)	0.0099
Bradykinesia subscore, median (IQ range)	12 (7–17)	9 (5–13)	11 (6–17)	16 (13–19)	0.001
Axial subscore, median (IQ range)	5 (3–7)	3 (2–5)	5 (3–6)	6 (4–10)	0.0001
MDS-UPRDS part IV dyskinesia score, median (IQ range)	0 (0–1) n = 101	0 (0–1)	0 (0–1)	0 (0–1) n = 33	0.881
MDS-UPRDS part IV motor fluctuations score, median (IQ range)	0 (0–5) n = 101	0 (0–3)	0 (0–4)	3.5 (0–6) n = 33	0.038
LED, median (IQ range)	600 (400–750)	400 (300–625)	512.5 (400–750)	706 (600–950)	0.0004

Abbreviations: AS = 14-Item Apathy Scale, BAI = Beck Anxiety Inventory, BDI-II = Beck Depression Inventory II, ESS = Epworth Sleepiness Scale, IQ = interquartile, LED = Levodopa equivalent dose, MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale, MoCA = Montreal Cognitive Assessment, QUIP = questionnaire for impulsive-compulsive disorders in Parkinson's disease, RBDSQ = REM sleep behavior disorder sleep questionnaire, SCOPA-AUT = Scales for Outcomes in Parkinson's Disease Autonomic questionnaire, SCOPA-sleep NS = Scales for Outcomes in Parkinson's Disease Sleep questionnaire nighttime symptoms, SD = standard deviation.

were excluded from the final model. A second multivariate analysis was performed which replaced MDS-UPDRS part III with those motor subscores meeting the predefined p-value for inclusion (i.e., rigidity, bradykinesia, and axial subscores). This did not change the findings of the primary linear regression model. BDI-II score and PDQ-39 emotional wellbeing domain were moderately correlated ($r_s = 0.57$, $p < 0.001$). ESS with SCOPA sleep NS were not significantly correlated ($r_s = 0.13$, $p = 0.2$).

4. Discussion

Our findings suggest that in mild to moderate PD, the most significant predictors of HRQoL are disability related to motor dysfunction, depression, anxiety, apathy, and excessive daytime sleepiness. Together these factors account for 78% of the variance in HRQoL as measured by the PDQ-39 SI. Consistent with previous reports, our results suggest that non-motor symptoms are significant contributors to HRQOL [2–4,22]. We found that the non-motor symptoms of depression, anxiety, apathy, and excessive daytime sleepiness as a group accounted for 48% of the variance in HRQoL.

A systematic review of studies using regression analysis to determine the impact of specific neuropsychiatric symptoms on HRQoL found depression to be most commonly associated with worse HRQoL and the most significant predictor of HRQoL [6]. Like our study, previous studies using multivariate regression analysis found an independent association between depression and HRQoL when considering motor symptoms, anxiety, and cognition as covariates [2,21,23–25]. Some of these studies also included measures of apathy as covariates [23–25]. Depression has also been shown to predict future decline in HRQoL [5]. Another factor which may explain the association between depression and worse HRQoL is the similarity in questionnaire content between BDI and PDQ39 emotional wellbeing domain [21], which accounts for 1/8 of the index score. This could falsely increase the association between measures of depression and HRQoL.

Table 2
Final multivariate linear regression model assessing predictors of HRQoL in PD.

Observations	98
R-squared	0.784

	Regression Coefficient	95% Confidence Interval	p-value
Gender	−2.16	−4.71–0.39	0.10
Age	−0.06	−0.18–0.06	0.30
MDS-UPDRS part II	0.58	0.37–0.80	< 0.001
BAI	0.33	0.12–0.54	0.003
BDI-II	0.35	0.11–0.59	0.005
AS	0.28	0.05–0.51	0.020
ESS	0.70	0.44–0.96	< 0.001

Abbreviations: AS = 14-Item Apathy Scale, BAI = Beck Anxiety Inventory, BDI-II = Beck Depression Inventory II, ESS = Epworth Sleepiness Scale, MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale.

However, we found that the BDI-II and PDQ-39 emotional wellbeing domain were moderately rather than highly correlated, which suggests they overlap but are distinct.

Anxiety is less commonly evaluated as a predictor of HRQoL in PD [6] but is a common non-motor symptom early in the disease process [3]. Previous studies have found anxiety to be an independent predictor of HRQoL [2,21,25] though there are a few exceptions where anxiety was not found to be an independent predictor [22–24]. Our study provides further evidence supporting anxiety as an independent predictor of HRQoL.

Apathy is another common non-motor symptom that can occur early in PD [26,27]. However, the impact of apathy on HRQoL is usually evaluated as part of a global non-motor symptom scale rather than a symptom specific scale [6]. Apathy is difficult to differentiate clinically from anhedonia, a symptom of depression [25,26]. It can also be difficult to disentangle apathy from executive dysfunction when they occur together [26,27]. Previous studies have mixed results when evaluating the impact of apathy on HRQoL. Some have found a significant association with HRQoL [23] while others have not [24,25]. For example, Jones et al. isolated pure dysphoria, decreased interest, and pure apathy derived from BDI-II and AS and found that pure apathy was not a significant predictor of HRQoL [25]. Nevertheless, we found that even when accounting for depression and cognition in addition to a number of other motor and non-motor symptoms of PD, apathy was an independent predictor of HRQoL.

Our finding of a relationship between excessive daytime sleepiness, as measured by ESS, and HRQoL, is also consistent with previous studies [22,24]. Interestingly, we did not demonstrate a relationship between measures of nighttime sleep quality or RBD with HRQoL. We also did not find an association between nighttime sleep quality and excessive daytime sleepiness. In this study, nighttime sleep quality is unlikely to have caused excessive daytime sleepiness. This suggests that excessive daytime sleepiness is an important symptom of PD and may not be related to other measures of sleep quality, which is supported by a previous study in which various objective measures of sleep by polysomnography were not associated with patient reported excessive daytime sleepiness [28].

Motor symptom burden and disability related to motor dysfunction have previously been identified as predictors of HRQoL [2,5]. Consistent with previous findings, we found greater motor disability to be associated with HRQoL while the motor examination was not [23,29]. This remained true even when considering specific motor exam subscores, as we did not find an association between bradykinesia, rigidity, tremor, nor axial symptoms and HRQoL. LED could be considered a proxy of motor symptoms, because more severe motor symptoms may warrant higher doses of symptomatic medications, but it was not an independent predictor of HRQoL. Others have also found motor fluctuations and/or dyskinesias to be associated with worse HRQoL [23,29]. We did not find this in our study population even after the MDS-UPDRS part IV score was divided into motor fluctuations and dyskinesia subscores. This could be explained by a difference in the presence and severity of these symptoms between studies.

We recognize that those predictors which were significantly associated with worse HRQoL in the univariate analysis but not multivariate analysis may still be important for HRQoL. The relationship may simply not be as strong or more complex than those included in our final multivariate model. This would include psychosis, autonomic dysfunction, nighttime sleep quality, RBD, rigidity, bradykinesia, axial motor symptoms, motor fluctuations, and LED.

Our study did have limitations. One limitation is that this study is cross-sectional and thus it cannot be concluded that these predictors cause worse HRQoL. Also, our study may not be generalizable to more advanced PD and other sub-populations. Lastly, there are factors (such as social support and exercise) which were not measured and may be relevant to HRQoL.

Our results have two important implications for PD research and management. First, our findings suggest that for clinical trials in PD using MDS-UPRDS as an outcome measure, the MDS-UPRDS part II may have more relevance for PD patients than MDS-UPDRS part III. Second, our finding that non-motor symptoms of depression, anxiety, apathy, and excessive daytime sleepiness account for the majority of variance in HRQoL emphasizes the importance of proactively and directly addressing these symptoms in PD. Treating these symptoms may improve HRQoL. For example, successful treatment of depression has been demonstrated to lead to an improvement in HRQoL [30]. The non-motor symptoms we found to be associated with HRQoL may serve as a guide for which non-motor symptoms to target to achieve the greatest improvement in HRQoL. Our study is unique in that we assessed a broad range of non-motor symptoms with validated symptom-specific measures. Our results add to the understanding of HRQoL in PD by finding an independent association of apathy and excessive daytime sleepiness with worse HRQoL. We have also confirmed previous findings that disability related to motor dysfunction, depression, and anxiety are important predictors of HRQoL.

Authors' roles

Greg D. Kuhlman, MD: research project conception and organization; statistical analysis design and execution; and manuscript writing of the first draft and review and critique.

Joseph L. Flanigan, BA: research project organization and execution; statistical analysis execution; and manuscript review and critique.

Scott A. Sperling, PsyD: statistical analysis review and critique and manuscript review and critique.

Matthew J. Barrett, MD, MSc: research project conception, organization, and execution; statistical analysis design, execution, and review and critique; and manuscript review and critique.

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Greg D. Kuhlman received funding from the Edmond J Safra Foundation for fellowship training in movement disorders and was employed by the University of Virginia Medical Center until July 2018.

Joseph L. Flanigan is employed by the University of Virginia School of Medicine, Department of Neurology.

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There are no conflicts of interest, financial or otherwise, to report for this study.

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