Fatigue, mood disorders and sleep problems in patients with Parkinson's disease

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Chapter 2

The impact of sleep and mood disorders on quality of life in Parkinson's disease patients

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Abstract

Background

Sleep disturbances are common and often severe in patients with Parkinson's disease (PD) and can occur at any time of day. The purpose of our study was to examine how excessive daytime sleepiness or poor nocturnal sleep quality and mood disorders influence the quality of life (QoL) in PD patients.

Methods

Ninety-three PD patients from Eastern Slovakia were recruited (49.5% males, mean age 68.0±9.5 years, mean disease duration 6.1±5.9 years). Sleep disturbances were measured using the Epworth Sleepiness Scale (ESS) and the Pittsburgh Sleep Quality Index (PSQI); QoL with the Parkinson's Disease Quality of Life Questionnaire (PDQ-39); depression and anxiety with the Hospital Anxiety and Depression Scale (HADS) and disease severity with the Unified Parkinson's Disease Rating Scale (UPDRS). χ^2-test, bivariate correlations and multiple linear regressions were performed.

Results

PSQI and ESS had significant associations with worse QoL ($p<.01$, $p<.05$, resp.). HADS-D ($p<.01$), HADS-A ($p<.01$), UPDRS ($p<.01$) and disease duration ($p<.05$) were also significantly related to worse QoL. In the linear regression analysis, however, only PSQI ($p<.01$), anxiety ($p<.001$) and UPDRS ($p<.001$) remained significant. The model with PSQI explained 82% of the variance, and the model with ESS explained 76% of the variance in PDQ-39 when analyses were performed separately. In an overall model, however, only PSQI remained significant, accounting for 82% of the variance in PDQ-39.

Discussion

Nighttime poor sleep and anxiety are important contributors leading to a worse QoL. As these are treatable conditions, they should be recognized by clinicians, managed properly and thus used to improve the quality of life for PD patients.

Key words:

Parkinson's disease, quality of sleep, sleepiness, anxiety, depression, disease severity, quality of life

Introduction

Sleep disorders are common and often severe in patients with Parkinson's disease (PD). They can occur at any time day or night. As many as 98% of PD patients suffer from nocturnal symptoms that can disturb their sleep [1]. Nighttime problems such as reduced total sleep time and sleep efficiency and an increased number of sleep arousals and fragmentations of sleep have all been reported in PD patients [1]. Sleep disturbance correlates with disease severity, cognitive decline and pain. Depression is another factor strongly related to sleep problems [2]. Borek et al. found that poor quality of sleep also showed significant correlations with elevated anxiety scores and longer duration of PD, but in their regression model only depression and sleep medication use were significant predictors of poor sleep [3].

Excessive daytime sleepiness (EDS) was reported in approximately 15% of PD patients, with an 8-year prevalence of 54% [4]. Its manifestation may be either rapid – so-called 'sleep attacks' – or slow, meaning patients may feel sleepy and slowly drift off to sleep [1]. If unrecognized and untreated, sleepiness can result in poor attention and memory and even in accidents. A study by Borek et al. found that EDS correlated with depression, anxiety, disease duration, male gender and use of dopamine agonists. In the linear regression model they found only anxiety, male gender and disease duration to be significant predictors of EDS [3].

Patients with PD have lower Quality of Life (QoL) scores compared to the general population. Schrag et al. [5] and Karlsen et al. [6], using the Nottingham Health Profile, reported worse scores in the emotional reactions, energy, pain, sleep, social isolation and physical mobility domains, social functioning, physical role limitations and general health perceptions. Various clinical and psychosocial variables have been evaluated with regard to QoL. Disease severity [7], motor complications [8,9], sleep problems [10], pain [11], depression [7,12], anxiety [13] and cognitive impairment [12] have all been found to significantly worsen QoL. Karlsen et al. found a significant relationship between higher age and the physical mobility domain [14], while other studies did not report such a relationship [6,12]. Longer disease duration was a significant predictor of the worse QoL domains [8]. Female gender was also associated with worse QoL [15].

The aim of our study was to evaluate how sleep problems – poor quality of sleep or daytime somnolence, mood disorders and disease severity – affect quality of life, controlled for age, gender and disease duration.

Methods

Patients

This cross-sectional study evaluated quality of life and sleep disturbances in a study population of 93 patients with Parkinson's disease. The patients were recruited from the hospitals and outpatient departments in the East Slovakian region between February 2004 and November 2005. All patients were diagnosed in accordance with the United Kingdom Parkinson's Disease Society Brain Clinical Criteria [16] and their mental abilities were assessed with the Mini-Mental State Examination (MMSE) [17]. Exclusion criteria were defined as follows: 1. MMSE lower than 24; 2. presence of severe comorbidity associated with the study variables.

The study was approved by the local Ethics Committee. Informed consent was obtained from each patient prior to the study.

Data collection

Data were collected by means of a mailed questionnaire comprising questions on sociodemographic background, medical history and current medication, and self-report questionnaires: the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS) and Parkinson`s Disease Quality of Life Questionnaire (PDQ-39). After three weeks, all patients were interviewed on relevant issues that were not part of the questionnaires. After this structured interview, a neurologist assessed the disease severity of each patient using the Unified Parkinson's Disease Rating Scale (UPDRS) Version 3.0 [18], including Hoehn and Yahr staging [19] and the Schwab and England disability scale [20]. Patients who were not able to fill in the questionnaires answered the questions during an oral interview. Caregivers were not allowed to provide questionnaires inputs.

Measures

Sleep disorders

The Pittsburgh Sleep Quality Index (PSQI) [21] was used to assess nighttime sleep problems. PSQI assesses global sleep quality and disturbances in sleep patterns during the previous month in seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Scoring of the answers ranges from 0 (no difficulty) to 3 (severe difficulty). After recoding, each component has possible scores of 0 – 3, where 3 indicates the negative extreme. The global PSQI score is the sum of all the component scores (range 0 – 21), with a score of 5 or more indicating a poor sleeper. This instrument was found to have good internal consistency, with a Cronbach's alpha coefficient of 0.81 in our sample.

For evaluation of daytime somnolence the Epworth Sleepiness Scale (ESS) [22] was used. ESS relies on measuring dozing behavior in eight different situations. The questionnaire asks the respondent to rate the likelihood of falling asleep on a scale from 0 to 3, were 0 indicates no chance and 3 represents the greatest chance of dozing. The total ESS score is the sum of all the responses and ranges from 0 to 24, higher scores reflect a greater propensity for sleep. A score of 10 was used as the cutoff point for normal, while scores above this imply pathological sleepiness [23]. This instrument has been found to have good psychometric properties in PD patients [24]. In our sample we also found good internal consistency, with a Cronbach's alpha coefficient of 0.84

Mood disorders

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS). This self-administered scale simultaneously evaluates anxiety (HADS-A) and depression (HADS-D). It consists of 14 items (7 for the assessment of anxiety and 7 for the assessment of depression) scoring from 0 (no problem) to 3 (extreme problem). The cutoff values proposed by the HADS developers [25] were applied in order to determine the proportion of patients considered as unimpaired (not depressed, scoring ≤ 7 on each subscale), possibly impaired (8–10 on each subscale), or probably impaired (≥ 11 on each subscale). In the present study Cronbach's alpha was 0.69 for anxiety and 0.79 for the depression subscale.

Disease severity

The Unified Parkinson's Disease Rating Scale is a four-subscale combined instrument for assessing mental state, activities of daily living, motor examination and complications. Two further instruments are used together with the UPDRS, namely: (1) a modified Hoehn & Yahr Staging, and (2) the Schwab & England Scale. Scores are obtained by interview and examination. It is currently used as a standard reference scale in clinical practice and research [18-20]. For our research we used the UPDR-III section.

Quality of life

Quality of life was assessed using the Parkinson's Disease Quality of Life Questionnaire (PDQ-39) as the primary outcome measure [26]. It comprises 39 questions, each of them using a five-point ordinal scoring system ranging from 0 (never had this problem) to 4 (always have this problem), from which a single summary index can be calculated. For the summary index the scores were standardized from 0 to 100, so that higher scores indicate more problems. PDQ-39 has been shown to be feasible, reliable, valid, and responsive to change in patients with PD and to have

good internal consistency [27]; in our sample Cronbach's alpha was 0.94.

Basic sociodemographic data (age, gender) and disease duration were obtained from a structured interview.

Statistical analysis

Discrete variables were compared using the χ^2 – test. Continuous variables were compared with the Student t-test. Multiple linear regression analysis was performed to provide the coefficients for examining the relative strength of the effects of PSQI, age, gender and disease duration, UPDRS, HADS-D and HADS-A on Quality of Life – the variables were entered in this order into the analysis using the enter method. The same method was then used with the ESS in place of the PSQI. As a final step, multiple linear regression analysis was performed with the PSQI and the ESS together, using the enter method. These analyses were performed using the statistical software program SPSS 14.0 for Windows.

Results

Descriptive Data

Of the 218 PD patients who met the inclusion criteria, 14 did not wish to participate in the study and 91 did not respond to the invitation. Patients were selected based on the database records of outpatient neurologists. The total response rate was 43.0%. Out of those who agreed to participate, 7 patients were eliminated because of the exclusion criteria, 13 patients were not included because of missing data (these patients agreed to participate in the study, filled in the questionnaire, but refused to come for the oral interview), and 93 remained for analysis. Non-responders did not differ significantly from the analyzed group in age (mean difference 1.6 yrs., SE=1.22; t=1.315; 95%CI -0.798 – 4.003) or gender (difference between proportions 0.095, SE = 0.066, 95% CI -0.0343–0.224) (difference of proportions test) [28].

Ninety-three patients (46 men, 49.5%) completed the questionnaire. The mean age of the patients was 68.0±9.5 years. Mean disease duration was 6.1±5.9 years. Details of the clinical profile and the study variables of the patients are shown in Table 1 and Table 2.

Table 1. Demographic and clinical description of the sample (n=93)

	Variable	N (%), Mean±SD
1.	Gender Male	46 (49.5%)
	Female	47 (50.5%)
2.	Age	68.0±9.5
3.	Disease duration	6.1±5.9
4.	UPDRS total	35.3±20.4
	UPDRS III	15.6±10.7
	UPDRS IV	3.1±3.0
5.	H&Y	2.0±1.2
	≤ 2.0	65 (69.9%)
6.	S&E	69.6±22.1
	≤ 70%	41 (44.0%)
7.	Antiparkinsonian drugs used	
	L-dopa	10 (10.7%)
	Dopamine agonists	21 (22.6%)
	L-dopa + COMT inhibitors	12 (12.9%)
	L-dopa + Dopamine agonists	8 (8.6%)
	L-dopa + COMT inhibitor + Dopamine agonists	6 (6.5%)
	Other	36 (38.7%)

UPDRS - Unified Parkinson's Disease Rating Scale. S&E - Schwab & England Scale. H&Y - Hoehn & Yahr Staging.

Table 2. Clinical description of the sample (n=93)

	Variable	Mean±SD, n, %
1.	HADS-D	6.12±3.1
	≥ 11	9 (9.7%)
2.	HADS-A	7.6±3.6
	≥ 11	28 (30.1%)
3.	PSQI	9.1±4.9
	≥ 5	68 (73.1%)
4.	ESS	7.76±4.9
	> 10	22 (23.7%)
5.	PDQ-39 – Summary Index	38.3±19.9

HADS – Hospital Anxiety and Depression Scale. PSQI – Pittsburgh Sleep Quality Index. ESS – Epworth Sleepiness Scale. PDQ-39 – Parkinson's Disease Quality of Life Questionnaire.

Bivariate correlations between QoL and study variables

Table 3 presents the correlations between sociodemographic variables, disease severity, mood disorders, daytime and nighttime sleep disturbances and the quality of life summary index. The PDQ-39 Summary Index correlated significantly with higher UPDRS-III (p<.01), increased levels of HADS-A and HADS-D (both p<.01), a higher PSQI score (p<.01) and higher ESS scores (p<.01). Sleep problems correlated positively with both HADS-D (p<.05) and HADS-A (p<.01), but only PSQI showed a significant correlation with higher UPDRS scores (p<.05). No significant correlations were found between ESS and UPDRS-III.

Table 3. Bivariate correlations between QoL and sociodemographic and clinical variables

	Age	Gender	Disease duration	UPDRS	HADS-D	HADS-A	PSQI	ESS
Gender	-.04							
Disease duration	.10	-.03						
UPDRS-III	.13	-.10	**.24***					
HADS-D	.09	.14	.19	.38**				
HADS-A	-.19	.14	.07	**.35****	**.48****			
PSQI	-.03	.09	.15	**.30***	**.28***	**.38****		
ESS	.12	-.01	.16	.23	**.28***	**.36***	.08	
PDQ-39 SI	.10	.01	**.29***	**.76****	**.57****	**.60****	**.46****	**.27***

Displayed are Pearson's coefficients.

UPDRS – Unified Parkinson` s Disease Rating Scale, total score. HADS – Hospital Anxiety and Depression Scale (HADS-D for depression, HADS-A subscale for anxiety). PSQI – Pittsburgh Sleep Quality Index. ESS – Epworth Sleepiness Scale. PDQ-39 SI – Parkinson's Disease Quality of life Questionnaire Summary Index

Multiple regression analysis. Associations of QoL and study variables

A series of linear regression analyses was performed in order to evaluate the influence of sleep problems and mood disorders on quality of life; they are summarized in Tables 4 and 5. The variables were entered in hierarchical order into a linear regression model using the enter method in order to evaluate the changes in explained variance in PDQ-39. Table 4 shows the analysis for PSQI and ESS separately, and Table 5 shows the analysis for PSQI and ESS together.

PSQI explained 28-29% of the variance, with a significant ΔR^2 change (beta .21, p=.004), while ESS did not contribute to PDQ-39 (beta .04, p =.582, ΔR^2 .09 was not significant). UPDRS was significant in all the models (beta .60-.64, p=.000). Anxiety was another variable that significantly explained 6-13% of the variance (betas .32-.44, p=.000). Depression was not a significant predictor of QoL in our sample (betas .11-.09). The model with PSQI explained 82%, the model with ESS 76%, and the overall model explained 82% of the variance.

Table 4. Multiple linear regression analysis: Associations of sleep disorders, disease severity and mood disorders with quality of life, separately for quality of sleep and for excessive daytime somnolence (controlled for age, gender and disease duration)

Variables	PDQ-39 Summary Index			
	beta	p	ΔR^2	Adjusted R^2
1. 1PSQI	**.20**	**.004**	**.28** ***	.27
2. Age	-.02	.757		
Gender	.13	.035		
Disease duration	.02	.797	.04	.27
3. UPDRS-III	**.60**	**.000**	**.42** ***	.72
4. HADS-D	.11	.133	.04 **	.76
5. HADS-A	**.32**	**.000**	**.06** ***	.82
Adjusted R^2				.82

Variables	PDQ-39 Summary Index			
	beta	p	ΔR^2	Adjusted R^2
1. ESS	-.02	.758	**.08** *	.07
2. Age	.04	.561		
Gender	.10	.154		
Disease duration	.02	.738	.04	.05
3. UPDRS-III	**.64**	**.000**	**.49** **	.57
4. HADS-D	.09	.243	**.06** **	.62
5. HADS-A	**.44**	**.000**	**.13** ***	.76
Adjusted R^2				.76

Linear regression model. Variables entered in a hierarchical way in 5 blocks – 1. PSQI or ESS, 2. age, gender and disease duration, 3. UPDRS total score, 4. depression and 5. anxiety. PSQI – Pittsburgh Sleep Quality Index, ESS – Epworth Sleepiness Score, UPDRS-III – Unified Parkinson's Disease Rating Scale, the part III, HADS-D – Hospital Anxiety and Depression Scale, depression subscale, HADS-A – Hospital Anxiety and Depression Scale, anxiety subscale. *p<.05, **p<.01, ***p<.001, represents the significance of R^2 change.

Table 5. Multiple linear regression analysis: Associations of sleep disorders, disease severity and mood disorders with quality of life (controlled for age, gender and disease duration)

Variables	PDQ-39 Summary Index				
	beta	p	ΔR^2	Sig. F Change	Adjusted R^2
1. ESS	.04	.582	.09	.026	.07
2. PSQI	.21	.004	.29	.000	.36
3. Age	-.03	.669			
Gender	.13	.038			
Disease duration	.01	.929	.02	.682	.34
4. UPDRS-III	.59	.000	.35	.000	.72
5. HADS-D	.11	.127	.04	.006	.76
6. HADS-A	.31	.000	.05	.000	
Adjusted R^2					**.82**

Linear regression model. Variables entered in a hierarchical way in 6 blocks – 1. ESS, 2. PSQI, 3. age, gender and disease duration, 4. UPDRS total score, 5. depression and 6. anxiety. ESS – Epworth Sleepiness Score, PSQI – Pittsburgh Sleep Quality Index, UPDRS-III – Unified Parkinson's Disease Rating Scale, part III, HADS-D – Hospital Anxiety and Depression Scale, depression subscale, HADS-A – Hospital Anxiety and Depression Scale, anxiety subscale.

Discussion

Sleep disorders

Our results show that sleep problems play an important role in the lives of the PD patients. Of our patients, 73.1% were poor sleepers during the nighttime. Adler et al. reported the occurrence of nocturnal sleep disturbances in 60-98% of PD patients [2], whereas in a more recent study, Martinez-Martin et al. in an their study reported insomnia in 45.7% of patients [29], using the Nonmotor Symptoms Questionnaire. Excessive daytime sleepiness was reported in 23.7% of our sample. Martinez-Martin reported sleepiness in 31.1% of PD patients [29]; Gjerstad et al. reported EDS in approximately 15% of PD patients, with an 8-year prevalence of 54% [30].

Sleep disorders correlated significantly with depression and anxiety, with the observed associations stronger for anxiety than for depression. Buysse et al. in their longitudinal study of insomnia and depression in young adults showed a strong relationship between these two problems [31]. Our research in PD patients shows significant correlations of sleep disturbances and mood disorders. These results are partly similar to the observations of Borek et al., who in a sample of 185 PD patients found

depression to have a significant association with worse PSQI scores. In their study, the use of sleep medication also appeared to be a significant predictor of worse PSQI scores, though anxiety and disease duration were not. Anxiety was also a significant predictor of worse ESS scores, together with male gender and longer disease duration, but depression and the use of dopamine agonists were not [3]. Additionally, poor nocturnal sleep showed a relationship with worse UPDRS scores.

Sleep disorders and QoL

Quality of life showed significant correlations with poor quality of nighttime sleep as well as with excessive daytime sleepiness. Different results were obtained when analyzing separately for the model with PSQI and for the model with ESS. PSQI appeared to be a significant predictor of QoL, but ESS was not. A study by McKinlay et al. with 49 patients did not report sleep disturbances influencing QoL, but only one item of UPDRS was used for measuring sleep [32]. A study by Weintraub et al. showed ESS as having no significant relationship with disability (measured by UPDRS-ADL score) in a sample of 114 PD patients [33]. Nocturnal sleep disturbances measured with the Parkinson's Disease Sleep Scale correlated with worse QoL in a study of 77 PD patients by Scaravilli [10].

Mood disorders and QoL

Mood disorders are currently recognized as important nonmotor features of PD, and depression especially is thought to worsen QoL in PD patients [33]. The prevalence of depression in our sample is less common compared to previous studies [32,33], while the prevalence of anxiety is consistent with other studies [29,31]. However, our results show only anxiety as being a significant factor associated with QoL, in both the model with PSQI and the model with ESS. Depression was not significant in either model. Earlier published studies did not include anxiety in their analyses [33]; only recent studies increasingly show the importance of anxiety for QoL. A study by McKinlay et al. [32] in a sample of 49 PD patients and a study by Carod-Artal [13] in 115 PD patients both report depression as well as anxiety as being important factors related to QoL. A recent review of the HADS-A and HADS-D concluded that although these instruments may be useful in Parkinson's disease for screening PD patients, they are not useful for adequately defining the severity of depression in this population [34].

Sociodemographic and clinical variables and QoL

Female gender was found to be a factor related to QoL in the model with PSQI. This result is similar to the finding of Behari et al, who also reported female gender as worsening QoL [15]. Karlsen et al. found a significant relationship of higher age with the worse physical mobility

domain of QoL [14], while a study by Weintraiub et al. did not report such a relationship [33]. Chapuis et al. found longer disease duration to be a significant predictor of worse QoL domains [8].

Disease severity was another factor significantly influencing QoL in both models. Previously published papers have shown conflicting results. The studies by Chapuis et al. and Gomez-Esteban et al. reported worse functional status as being related with worse QoL [8,35], while Karlsen did not find such a relationship [6].

Limitations

The relatively low response rate is the main limitation of our study. Patients were recruited mostly from outpatient neurologists, not from a specialized center for PD care, and only those who agreed to participate were included. For this reason, only patients who were able to come for the examination and interview – either alone or with a family member as a companion – formed our sample, so we assume that non-respondents were patients with worse disease severity, mostly bedridden. Despite the response rate, even this sample reported a high prevalence of sleep and mood problems, worsening quality of life, so we expect these factors to be even worse in the total PD patients group.

Clinical Implications

Sleep problems, anxiety and depression must all be assessed in every PD patient and managed properly. The treatment of disturbed nocturnal sleep should include recommendations for sleep hygiene – the maintenance of a regular sleep-wake cycle, bed-time sleep restriction, the avoidance of frequent naps during the day, moderate day-time physical exercise and exposure to bright light in the daytime, especially towards evening in order to counteract any tendency towards anticipation of the sleep phase.

Conclusions

Although sleep problems are not fully understood in their etiology (psychosocial determinants, treatment, neurodegeneration may play a role) [36], they are now regarded as important among the nonmotor symptoms of PD, closely associated, together with mood disorders, with worse QoL. Our study documents the importance of poor sleep at night and stresses not only the recognition of depression, but also the significant importance of anxiety within the factors having an impact on QoL. By influencing potentially treatable conditions, clinicians could improve the QoL of PD patients.

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