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# **Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease**

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## **Abstract**

Fatigue is an important contributor to poor quality of life. The aim of our research was to identify factors associated with fatigue among patients with Parkinson's disease (PD). The sample consisted of 150 patients. The Multidimensional Fatigue Inventory (MFI), Unified Parkinson's Disease Rating Scale (UPDRS), Hospital Anxiety and Depression Scale (HADS) and Charlson co-morbidity index were used for analysis. Demographic data were obtained in a structured interview. T-test,  $\chi^2$ -test and general linear regression were used. Fatigue was reported in 81% of the patients, with the worst scores in physical fatigue. Mood disorders and worse UPDRS scores were associated with fatigue.

## **Introduction**

Fatigue is a frequent complaint of patients with Parkinson's disease (PD) with up to 40-56% of patients reporting it during the course of their disease [01 - 04], of whom 15-33% describe it as the most disabling symptom [05]. Like other non-motor problems, fatigue is often an under-appreciated and neglected symptom, despite the fact that it may even precede the appearance of cardinal motor signs [06]. Fatigue may be present as a transient or persistent feature of PD [07]. Fatigue is also an important contributor to poor quality of life in PD and it is connected to worse physical and mental health [08, 09].

Fatigue is a subjective experience. Although lacking a standard definition, fatigue can be defined as a state of extreme tiredness, weakness, lack of energy or exhaustion, physical, mental, or both [10]. Physical fatigue in PD patients is reported after inadequate sleep or rest, or after physical exertion, and may be associated with physical condition, or decline in strength generation or in speed of repetitive movements due to parkinsonism. Mental fatigue is reported after mental effort or when patients lack the motivation to initiate activities, and may result from sleep disturbances, slowed mental processes, or depression [11].

Fatigue has been described in various chronic diseases, neurological and non-neurological. It is reported to be the major problem in multiple sclerosis patients, 55-79% of them suffering from fatigue [12, 13] up to 42-80% of patients with rheumatoid arthritis [14], and 57% of patients with primary Sjögren's syndrome [15]. Several studies have been performed to identify correlates of fatigue in chronic disorders. Associations between fatigue, disease severity or disease activity have been found, as well as associations between fatigue and depression or sleep disorders, but not with age or disease duration [12, 13, 15].

In recent years fatigue has become an important research variable

and several studies have highlighted its clinical significance in Parkinson's disease. While more is known about its prevalence and impact on the lives of patients, little progress has been made so far in understanding its etiology and pathogenesis. Biological [16], clinical and psychosocial variables may play a role [07, 11]. As yet there are few findings suggesting how to manage the problem clinically. One possible way is the recognition and proper management of factors leading to occurrence of fatigue.

Parkinson's disease is a disorder particularly affecting more elderly patients. This population suffers from a higher incidence of cardiovascular, neurovascular disorders, diseases of bones and joints [17, 18], and these conditions also require more frequent hospital admissions [18]. As these disorders are often associated with patients' complaints of fatigue [14, 15, 19], it is possible that the presence of these accompanying problems may lead to fatigue or may increase feelings of fatigue. As this disease mainly worsens patients' functional status (through worsening of movement abilities or pain), we expect co-morbidities to influence the physical dimensions of fatigue.

So far the variables predicting fatigue in Parkinson's disease have not been clarified. The aim of this study is to identify some clinical and psychosocial factors associated with the occurrence of fatigue in PD patients.

## **Methods**

### *Patients*

This cross-sectional study evaluated fatigue in a study population of 150 patients with Parkinson's disease. The patients were recruited from the hospitals and outpatients departments in the East Slovakian region between February 2004 and November 2005, based on medical records. All patients were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Clinical Criteria [20] and their mental abilities were assessed with the Mini-Mental State Exam (MMSE) [21]. The sample included patients with idiopathic Parkinson's disease. Exclusion criteria were defined as follows: 1. MMSE lower than 24; 2. disease duration longer than 15 years and 3. comorbidities associated with fatigue.

The study was approved by the local Ethical Committee. Informed consent was obtained from each patient.

### *Data collection*

All participating patients received a mailed questionnaire accompanied by a written informed consent form. After three weeks all patients were

interviewed on relevant issues that were no part of the questionnaire. After this structured interview, a neurologist assessed the patient's disease severity with the Unified Parkinson's Disease Rating Scale (UPDRS Version 3.0, [22]), including Hoehn and Yahr staging [23] and the Schwab and England disability scale [24]. Patients who were unable to fill in the questionnaire because of tremor, motor impairment of their hand or visual problems answered the questions during an oral interview.

### Sample description

150 patients (77 men – 51.3%, 73 women – 48.7%) completed the questionnaire and the interview, followed by examination by the neurologist. The mean age of the patients was  $68.4 \pm 8.8$  years (range 44 – 83 years);  $69.1 \pm 8.6$  of men and  $67.7 \pm 8.9$  of women. Mean age at disease onset was  $61.5 \pm 11.1$  years. Mean disease duration was  $7.9 \pm 7.9$  years;  $7.09 \pm 5.4$  for the male population and  $8.9 \pm 9.8$  for women. These gender differences were statistically not significant. Details of the clinical profile and variables of the patients are shown in Table 1.

**Table 1** Clinical variables of Parkinson's disease patients (N = 150).

Variable		%, Mean $\pm$ SD
1. UPRDS*		36.9 $\pm$ 20.9
	Male (n = 77)	38.8 $\pm$ 21.1
	Female (n = 73)	34.9 $\pm$ 19.4
2. Anxiety		8.2 $\pm$ 3.9
	$\geq 11$	46 (30.6%)
	$< 11$	104 (69.4%)
3. Depression		6.7 $\pm$ 3.7
	$\geq 11$	21 (14.0%)
	$< 11$	129 (86.0%)
4. Charlson index		3.9 $\pm$ 1.8
5. Scores for MFI* domains	General fatigue	13.8 $\pm$ 4.1
	Physical fatigue	14.1 $\pm$ 3.6
	Reduced activity	12.7 $\pm$ 3.8
	Reduced motivation	11.0 $\pm$ 3.8
	Mental fatigue	11.9 $\pm$ 3.8
6. Antiparkinsonian drugs used	L-dopa	18 (12%)
	Dopamine agonists	36 (24%)
	L-dopa + COMT inhibitors	38 (25.3%)
	L-dopa + Dopamine agonists	20 (13.3%)
	L-dopa + COMT inhibitor + Dopamine agonists	16 (10.7%)
	Other	22 (14.7%)

\*UPDRS - Unified Parkinson's Disease Rating Scale, MFI - Multidimensional Fatigue Inventory

## Measures

### *Multidimensional Fatigue Inventory (MFI)*

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI) as the primary outcome measure in PD patients. The MFI is a 20-item self-report instrument designed and validated by Smets et al. [25]. It measures five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. There are four items in each dimension. The score on each item ranges from 1 (no fatigue) to 5 (very fatigued). The score in each dimension ranges from 4 (no fatigue) to 20 (highest possible fatigue). This instrument is a frequently-used fatigue questionnaire in Europe, repeatedly used in patients with neurological diseases [11]. It has been successfully applied in several clinical groups. In the present research the instrument was found to have good internal consistency with Cronbach's alpha coefficient of 0.84.

### *Hospital Anxiety and Depression Scale (HADS)*

Anxiety and depression 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 assessment of anxiety and 7 for assessment of depression) scoring from 0 (no problem) to 3 (extreme problem). The cut-off values were applied in order to determine the proportion of patients considered unimpaired (not anxious or not depressed, scoring  $\leq 7$  on each subscale), possibly impaired (8–10 on each subscale), or probably impaired ( $\geq 11$  on each subscale) [26]. In the present study Cronbach's alpha was 0.82 for the anxiety domain and 0.79 for the depression domain.

### *The Unified Parkinson's Disease Rating Scale*

The Unified Parkinson's Disease Rating Scale is a four-subscale measure (mental state, activities of daily living, motor examination, and complications). Two further instruments are attached to the UPDRS, namely: (1) a modified Hoehn & Yahr Staging; and (2) the Schwab & England Scale. Ratings are observation-based, and scores are obtained by interview and physical examination. As a consequence of its design, the UPDRS allows for partial and total scores. [22 – 24].

### *Comorbidities*

The Charlson index was used to evaluate the presence of comorbidities. It consists of 19 conditions (some of them representing two degrees of severity of the same condition) with values of 1 - 6, based on the adjusted risk of one-year mortality. The overall comorbidity score reflects the cumulative increased likelihood of one-year mortality. It has been combined with age to form an age-comorbidity index [27, 28]. Two independent researchers

assessed comorbidities on the basis of patients' questionnaires. Differences were resolved through discussion with reference to a third reviewer if necessary.

### **Personal characteristics**

Age, gender, disease duration and educational level of the patient were based on the Neurology Department registry information and confirmed at the time of interview. Gender (0 = male and 1 = female) and educational level were used in the regression analysis as covariates with the level of education coded as: 1. basic (primary education or for secondary education without school leaving examination, 2. middle (secondary education with school leaving examination) and 3. higher (college or university degrees).

### **Statistical analysis**

Discrete variables were compared with the  $\chi^2$  test and are presented as percentages. Continuous variables were compared with the Student *t* test and are presented as mean  $\pm$  SD. P-values  $< 0.05$  were considered statistically significant. Based on the conceptual model, a series of regression were established to provide the coefficients to examine the relative strength of disease duration, Charlson index, anxiety, depression and UPDRS, Hoehn and Yahr staging, and Schwab and England scores on five domains of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue.

The coefficients provided are standardized regression coefficients (beta) that identify the net effects (i.e. controlling for other covariates) of each variable on the respective outcome. The regression analysis also provides basic goodness-of-fit information ( $R^2$  and p-values) for the respective equations.

Statistical analyses were performed using the statistical software program SPSS 12.0 for Windows.

## **Results**

Out of 497 patients with PD meeting the inclusion criteria, 41 did not wish to participate in the study; and 284 did not respond to the invitation. Total response rate was 30.2%. Out of those who agreed to participate, 11 patients were excluded because of the exclusion criteria, 11 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 150 remained for analysis. Non-responders did not differ significantly from the analyzed group in age (mean difference, 1.9 yrs., SE=0.78;  $t=1.965$ ; 95%CI 0.46 – 3.54). However, males were overrepresented in the study sample, difference 8.1%, SE = 0.049; 95% CI -0.015 – 17.6% (difference of proportions test) [29].

**Table 2** General linear model: Associations of Clinical and Psychological factors with each of the five domains of MFI (controlled for age, gender and education level)

Variables	General fatigue		Physical fatigue		Reduced activity		Reduced motivation		Mental fatigue	
	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p
<b>Disease-related</b>										
Disease duration	-.03	.419	-.03	.339	-.02	.543	-.02	.522	.03	.474
Charlson index	-.20	.473	.17	.497	-.21	.405	-.06	.825	.04	.872
UPDRS	<b>.07</b>	<b>.000</b>	<b>.08</b>	<b>.000</b>	<b>.09</b>	<b>.000</b>	<b>.04</b>	<b>.002</b>	<b>.08</b>	<b>.000</b>
<b>Psychological distress</b>										
Anxiety	<b>.16</b>	<b>.049</b>	-.02	.822	-.14	.067	-.17	<b>.029</b>	.02	.777
Depression	<b>.34</b>	<b>.000</b>	<b>.31</b>	<b>.000</b>	<b>.34</b>	<b>.000</b>	<b>.55</b>	<b>.000</b>	<b>.29</b>	<b>.000</b>
	R = .58		R = .60		R = .61		R = .59		R = .59	
	R <sup>2</sup> = .34		R <sup>2</sup> = .36		R <sup>2</sup> = .038		R <sup>2</sup> = .35		R <sup>2</sup> = .34	
	Adjusted R <sup>2</sup> = .29		Adjusted R <sup>2</sup> = .32		Adjusted R <sup>2</sup> = .34		Adjusted R <sup>2</sup> = .30		Adjusted R <sup>2</sup> = .30	
	P < .000		P < .000		P < .000		P < .000		P < .000	

R<sup>2</sup> – explained variance



Looking first at the disease-related factors, comorbidity and disease duration were not significant for any of the five fatigue outcomes. However, the Unified Parkinson's Disease Rating Scale had significant effects on all domains of fatigue, as well as depression. Depression ( $\beta = -0.55$ ) had the strongest association with reduced motivation. Both depression and UPDRS were significantly related to higher levels of reduced motivation ( $\beta = 0.55$ ), but anxiety was related to lower levels of motivation.

Depression also had an important relation to general fatigue, physical fatigue, activity and mental fatigue ( $\beta = 0.34, 0.31, 0.34$  and  $0.29$ , respectively). Importantly, these relationships persisted when the effects of gender and educational level were statistically controlled.

The proposed models explained 34% of the variance in general fatigue, 36% of the variance in physical fatigue, 38% in activity, 35% in motivation and 34% in mental fatigue respectively.

## Discussion

Fatigue is considered to be a part of normal aging [30], but the high prevalence of fatigue in PD patients cannot be explained only by the advanced age of these patients. Our study moreover shows fatigue as not being related to gender and age. This corresponds with the findings of studies in other chronic disorders, where age as well as gender was not related to fatigue; in fact, these disorders affect much younger populations [11, 13, 31]. Similarly, the level of education proved not to be associated with fatigue. Existing studies on PD patients and other progressive disorders also failed to show significant relationship between fatigue and disease duration [07, 12, 15].

Nearly 50% of PD patients report the presence of at least one comorbidity [18]. Based on the findings of the high prevalence of fatigue in cerebrovascular diseases [19] and diseases of joints and bones [14, 15], we expected that these accompanying problems might affect patients' levels of fatigue. Co-morbidities were reported by 47% of our sample, especially vascular events (35%) and joints diseases (12%). For all the five domains, however, co-morbidities did not appear to be significant. The explanation of this observed non-significant relationship is not clear at this moment, and further studies should be performed in future.

Depression was significantly related to each of the five fatigue domains. It was identified in 14% of our sample, which is less prevalent than was documented in previous studies [01, 32]. A higher level of depression is associated with a higher level of fatigue. This relationship was the strongest for reduced motivation and reduced activity, weaker for general and physical fatigue and the weakest for mental fatigue. These findings are partly similar to the findings of Lou et al. [11]; in a sample of 39 PD patients depression was related to mental dimensions of fatigue

(mental fatigue), but not with physical fatigue. The association between depression and fatigue is still controversial because of the possible overlap in symptomatology between PD and major depression: fatigue and sleep problems are among the diagnostic criteria for both. Leentjens *et al.*, [33] in their study proposed the use of an adjusted cut-off score 18/19 for better discrimination between depressed and non-depressed PD patients; however, as the sample size was small relative to the number of items, this finding should be viewed with some caution.

The term anxiety is used to denote an intermittent or sustained emotional state characterized by subjective feelings of nervousness, irritability, uneasy anticipation and apprehension [34]. Anxiety signs usually accompany depression. Anxiety was reported in 30.6% of our sample. We found anxiety to be connected with reduced motivation and general fatigue. Although we found a correlation between anxiety and mental fatigue, in the multiple linear regression model anxiety did not prove to be associated with mental fatigue dimensions. Anxiety also has an overlap in symptomatology with fatigue, as has depression; increased muscular tension, giddiness, trembling and sweating are among the diagnostic criteria for anxiety disorder [34].

Patients scored higher in the physical fatigue domain. A possible explanation is that Parkinson's disease affects more physical abilities (stiffness, slow movements, tremor), although non-motor problems (depression, anxiety, sleep difficulties, sensory symptoms) are also frequent and disabling [01].

We found functional status to have a significant relationship with all five fatigue domains, strongest for the physical fatigue and weakest for the reduced motivation domain. The physical component of fatigue appears to be associated with worse functional status as patients may have less muscle strength and less energy supply. Garber *et al.* [05] evaluated fatigue, physical activity and physical function in a non-random sample of 37 PD patients, and they found that patients with more severe fatigue had poorer physical function compared with patients with less fatigue. Our findings on the relation between functional status and all the MFI components are in contrast with the study of Karlsen *et al.* [03], who found no relationship in a sample of 233 PD patients between disease severity measured by UPDRS and fatigue. However, in their study fatigue was measured not with a disease-specific instrument, but with the Nottingham Health Profile; fatigue was considered as a manifestation of the energy domain. The findings of the study of Lou *et al.* [11] in a sample of 39 PD patients also do not correspond with our results. In their study disease severity measured by Hoehn&Yahr did not correlate with any of the dimensions in the MFI.

There were limitations to the present research. Our sample consisted mostly of patients who were able to come for the examination and

interview – either alone or with a family member as a companion, so we suppose that non-responders were patients with worse functional status, mostly bedridden. Despite the rather low response rate, in this selected population fatigue is already a serious problem, so we expect this to be even worse in the total PD patients group.

This is the first time, to our knowledge, that factors related to the separate components of fatigue have been studied. Previous studies showed an association of depression with the mental dimensions of fatigue, but we have discovered in our study that depression has an important relationship not only with the mental dimensions of fatigue, but with the physical dimensions as well. Further studies focusing on behavioural and psychosocial factors should be performed in future, cross-sectional as well as longitudinal, to better understand this problem and to explore the role of these factors leading to fatigue over time.

Neurologists frequently fail to recognize fatigue. General problems in assessing fatigue are its subjective nature, and in PD particularly the high prevalence of other non-motor symptoms that may overlap. The new onset of fatigue in an older individual may be connected to the development of a somatic or psychiatric disease. We suggest that the elevated levels of fatigue in PD patients deserve special attention, with the development of strategies to relieve this complaint. As PD is a progressive disorder, in clinical practice neurologists often challenge the worsening of functional status, even in cases of optimal treatment with antiparkinsonian drugs. This is why we stress the importance of identifying other possible treatable disorders leading to fatigue. Treatment of depression may lead to improvement in both mental and physical dimensions of fatigue.

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