

University of Groningen

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

Havlikova, Eva

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2008

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Havlikova, E. (2008). *Fatigue, mood disorders and sleep problems in patients with Parkinson's disease*.  
s.n.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# **Fatigue in Parkinson's disease is influenced by depression and worse functional status**

Eva Havlikova, Jitse P van Dijk, Jaroslav Rosenberger, Iveta Nagyova, Zuzana Gdovinova, Willem Lok, Berrie Middel, Johan W Groothoff

## **Abstract**

### **Background**

Fatigue is a frequent nonmotor complaint of patients with Parkinson's disease (PD). Despite increasing knowledge on fatigue, the factors leading to its development are still not recognized. The aim of our study was to examine how disease severity explains the different fatigue domains, how disease severity explains depression, and how disease severity explains via depression the different fatigue domains.

### **Methods**

The sample consisted of 190 PD patients (93 men, 48.9%, mean age 68.2±9.3 years, mean disease duration 6.4±4.7 years), recruited from the hospitals and outpatients in East Slovakia region. The Multidimensional Fatigue Inventory, the Hospital Anxiety and Depression Scale and the Unified Parkinson's Disease Rating Scale (UPDRS) were used for the analysis. LISREL analysis was performed to evaluate the data.

### **Results**

UPDRS increased the level of fatigue in General fatigue ( $\beta=.35$ ), Physical fatigue ( $\beta=.82$ ), Reduced activity ( $\beta=.34$ ) and Mental fatigue ( $\beta=.29$ ), but not Reduced motivation. UPDRS increased directly the level of depression ( $\beta=.26$ ), and via this pathway the levels of General fatigue ( $\beta=.25$ ), Reduced activity ( $\beta=.31$ ), Reduced motivation ( $\beta=.82$ ) and Mental fatigue ( $\beta=.28$ ) were enhanced. UPDRS did not influence Physical fatigue through its influence on depression

### **Discussion**

Worse disease severity together with increased depression leads to worse General fatigue, Reduced activity and Mental fatigue. Worse disease severity separately causes worse Physical fatigue and depression alone causes more fatigue in the Reduced motivation domain. As currently there are no proved strategies to manage fatigue clinically, the recognition and the proper management of factors leading to fatigue is essential.

### **Introduction**

Fatigue is a frequent nonmotor symptom of Parkinson's disease (PD) affecting 33-58% of PD patients (1-5) and remains persistent in 44% of PD patients (6). Only recently it was recognized as one of the most disabling features of PD (1,7), negatively influencing quality of life of PD patients (8,9).

Fatigue is difficult to define, as it is a subjective experience occurring on a continuum that affects both a normal state and a pathological disturbances (1). Lou (2001) described fatigue as a state of extreme tiredness, weakness, lack of energy, exhaustion, which could be physical, mental, or both (10). Krupp et al. (1989) subdivided fatigue into two components, to a peripheral fatigue and a central fatigue (11). The first refers to a fatigue after repeated muscle use or exercise, the latter occurs despite the absence of physical activities (12), and it is frequently observed in patients with chronic diseases (11).

Several studies have been performed to identify correlates of fatigue in PD. Sleep disorders (6), and anxiety (13,14) have been found to be related to fatigue, but not higher age (14), or gender (14).

Conflicting results have been found when an association between fatigue and disease severity was studied. Some studies did not find correlations of fatigue with motor dysfunction (5,15), while others have found such a relationships (6), for both physical and mental fatigue domains (13).

Depression, another important nonmotor feature of PD, was found to be one of the factors related to fatigue (5), not only to mental but to physical fatigue domain as well (10; 13). Although the association between these two symptoms is problematic, as some overlap exists between these two conditions; fatigue is one of the diagnostic criteria for depression, it is clear that even nondepressed PD patients often suffer from fatigue, concluding that fatigue is an independent symptom from depression (6).

The aim of our study was to examine how disease severity explains the different fatigue domains, how disease severity explains depression, and how disease severity explains via depression the different fatigue domains.

## **Methods**

### *Patients*

This cross-sectional study evaluated fatigue in a study population of 190 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. All patients were diagnosed according to 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. disease duration longer than 15 years; 3. presence of co-morbidity associated with the fatigue variable.

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

#### *Data collection*

Data were collected by means of a mailed questionnaire comprising questions on socio-demographic background, medical history and current medication, as well as self-report questionnaires including the Multidimensional Fatigue Inventory (MFI) and Hospital Anxiety and Depression Scale (HADS). After three weeks all patients were interviewed in the structured interview and a neurologist assessed each patient's disease severity with 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). Caregivers were not allowed to make inputs into the questionnaires, patients who were not able to fill in the questionnaires by themselves because of motor impairment of their hands answered the questions during an oral interview (15 patients in our sample).

#### *Measures*

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI). It is a 20-item self-report instrument designed and validated by Smets et al. (21). It measures five fatigue domains: General fatigue, Physical fatigue, Mental fatigue, Reduced motivation, and Reduced activity. There are four items in each domain. The score on each item ranges from 1 (no fatigue) to 5 (very fatigued), so the score in each dimension ranges from 4 (no fatigue) to 20 (highest possible fatigue). This instrument is used among patients with neurological diseases (10). The instrument was found to have good internal consistency with Cronbach's alpha coefficient of 0.89 in our sample. Cronbach's alpha for the subscales were as follows: General fatigue 0.84, Physical fatigue 0.79, Reduced activity 0.80, Reduced motivation 0.71, Mental fatigue 0.82.

Depression was assessed using the Hospital Anxiety and Depression Scale (HADS). This self-administered scale simultaneously evaluates anxiety (HADS-A) and depression (HADS-D). It was designed to identify mood disorders in non-psychiatric outpatients. 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 cut-off values as proposed by the HADS developers (22) were applied in order to determine the proportion of patients considered unimpaired (not depressed, scoring  $\leq 7$  on each subscale), possibly impaired (8–10 on each subscale), or probably impaired ( $\geq 11$  on each subscale). Schrag et al. demonstrated good properties of HADS for screening purposes for depression in PD (23,24), with proposed cutoff scores of 23/24 for diagnostic purposes (24). In the

present study Cronbach's alpha was 0.77 for the depression domain.

The Unified Parkinson's Disease Rating Scale is a four-subscale combined scale (mental state, activities of daily living, motor examination, and complications). Two further instruments are attached to the UPDRS, namely: (a) a modified Hoehn & Yahr Staging, an ordinal scale that is applied to gauge the course of disease over time; and (b) the Schwab & England Scale, a measure of functional independence providing scores that, though expressed as percentages, form an ordinal scale. Scores are obtained by interview and examination. It is currently used as a standard reference scale in clinical practice and research (18-20).

Basic socio-demographic data (age, gender) and disease duration were obtained from the structured interview.

#### *Statistical analysis*

First, the demographic and clinical characteristics of the sample were described. Second, a path model was analyzed to test the estimates of the magnitude of the effects of disease severity and depression on the five dimensions of fatigue, and to estimate whether our data fit the proposed model.

For model fit we used multiple criteria as suggested by Bentler and Bonett (25). Using LISREL 8.7, we tested a recursive model (see Figure 1) in which direct pathways go from the background (exogenous) variable disease severity (UDPRS) to the five dimensions of fatigue (MFI) and a pathway through which disease severity (UDPRS) influenced depression (HADS-D), from which pathways go to the five dimensions of fatigue (MFI). To allow for mutual comparisons between the path coefficients, the completely standardized solution was used. The analysis was performed with structural equation modelling using the maximum likelihood method. The fit of the model was evaluated by means of (1) the comparative fit index (CFI), (2) the normed fit index (NFI), (3) the non-normed fit index (NNFI), (4) the standardized root mean square residual (SRMR) and (5) the root mean square error of approximation (RMSEA), in addition to (6) the chi-square ( $\chi^2$ ) test; non-significant  $\chi^2$  indicating that a non-significant amount of variance in the data remains unexplained. An adequate fit of the model is indicated by NFI, NNFI and CFI  $\geq$  .90, and SRMR  $<$  .08, RMSEA  $<$  0.05 and NFI  $>$  0.90 are considered to indicate good fit. (26-33) (Table1).

**Table 1.** Parameter estimates of the path model relations between disease severity, depression and fatigue

	$\chi^2$	df	P	RMSEA	SRMR	NFI	NNFI	CFI
Parameter estimates of the model	6.58	5	0.25	0.045	0.020	0.99	0.99	0.99
Critical values of parameter estimates			>0.05	<0.06	<0.05	>.90	>.90	> .90

RMSEA - root mean square error of approximation; SRMR - standardized root mean square residual; NFI - normed fit index; NNFI - non-normed fit index; CFI - comparative fit index

The model was evaluated by examining the parameter estimates and measures of overall fit provided by LISREL. A residual correlation between depression and reduced motivation was allowed and also between dimensions of fatigue since standardized residuals indicated this correlation to exist (not depicted). Only the path coefficients significant at  $P < 0.05$  level are depicted in the final model.

## Results

Out of 512 patients with PD meeting the inclusion criteria 29 did not wish to participate in the study; and 271 did not respond to the invitation. Total response rate was 37.1%. Out of those who agreed to participate, 2 patients were eliminated because of the exclusion criteria, 10 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 190 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) (34).

190 patients (93 men, 48.9%) completed the questionnaire and were interviewed, followed by examination by the neurologist. The mean age of the patients was  $68.2 \pm 9.3$  years. Mean age at disease onset was  $59.5 \pm 11.1$  years. Mean disease duration was  $6.4 \pm 4.7$  years. Details of the clinical profile and the study variables of the patients are shown in Table 2 and Table 3.

**Table 2.** Demographic and clinical description of the sample (n=190)

Variable	n, %, Mean±SD
1. Gender	
Male (n=93)	48.9%
Female (n=97)	51.1%
2. Age	68.2 ± 9.3
3. Disease duration	6.4 ± 4.7
4. UPDRS* total	36.3 ± 20.5
UPDRS III	16.1 ± 10.7
UPDRS IV	3.3 ± 3.3
5. H&Y*	2.2 ± 1.1
≤ 2.0	115 (60.5%)
> 2.0	75 (39.5%)
6. S&E*	69.3 ± 22.3
≤ 70%	88 (46.3%)
> 70%	102 (53.7%)

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

**Table 3.** Clinical description of the sample (n=190)

Variable	Mean±SD	n, %
1. HADS-D*	6.76 ± 3.7	
≥ 11		27, 14.2%
2. MFI		
General fatigue	13.7 ± 4.0	97, 51.1%
Physical fatigue	14.0 ± 3.6	103, 54.2%
Reduced activity	12.5 ± 3.8	71, 37.3%
Reduced motivation	10.7 ± 3.8	55, 29.0%
Mental fatigue	11.8 ± 3.8	70, 36.8%
3. Antiparkinsonian drugs used		
L-dopa		24 (12.6%)
Dopamine agonists		43 (22.6%)
L-dopa + COMT inhibitors		40 (21.1%)
L-dopa + Dopamine agonists		27 (14.2%)
L-dopa + COMT inhibitor + Dopamine agonists		23 (12.1%)
Other		33 (17.4%)

HADS-D - Anxiety and Depression Scale, depression subscale. MFI - Multidimensional Fatigue Inventory



Figure 1 depicts the results of a path analysis with LISREL 8.7 (35) (Joreskog & Sorbom, 1993) showing the direct path between disease severity and depression and the five domains of fatigue. Moreover, the mediated paths showing the influence of disease severity through enhanced levels of depression on domains of fatigue.

Disease severity (UPDRS) increases the level of fatigue in General fatigue, Physical fatigue, Reduced activity and Mental fatigue, but not in Reduced motivation. Disease severity increased directly the level of depression through which levels of General fatigue ( $\beta = .25$ ), Reduced activity ( $\beta = .31$ ), Reduced motivation ( $\beta = .82$ ) and Mental fatigue ( $\beta = .28$ ) were enhanced. UPDRS did not influence Physical fatigue through its influence on depression.

## Discussion

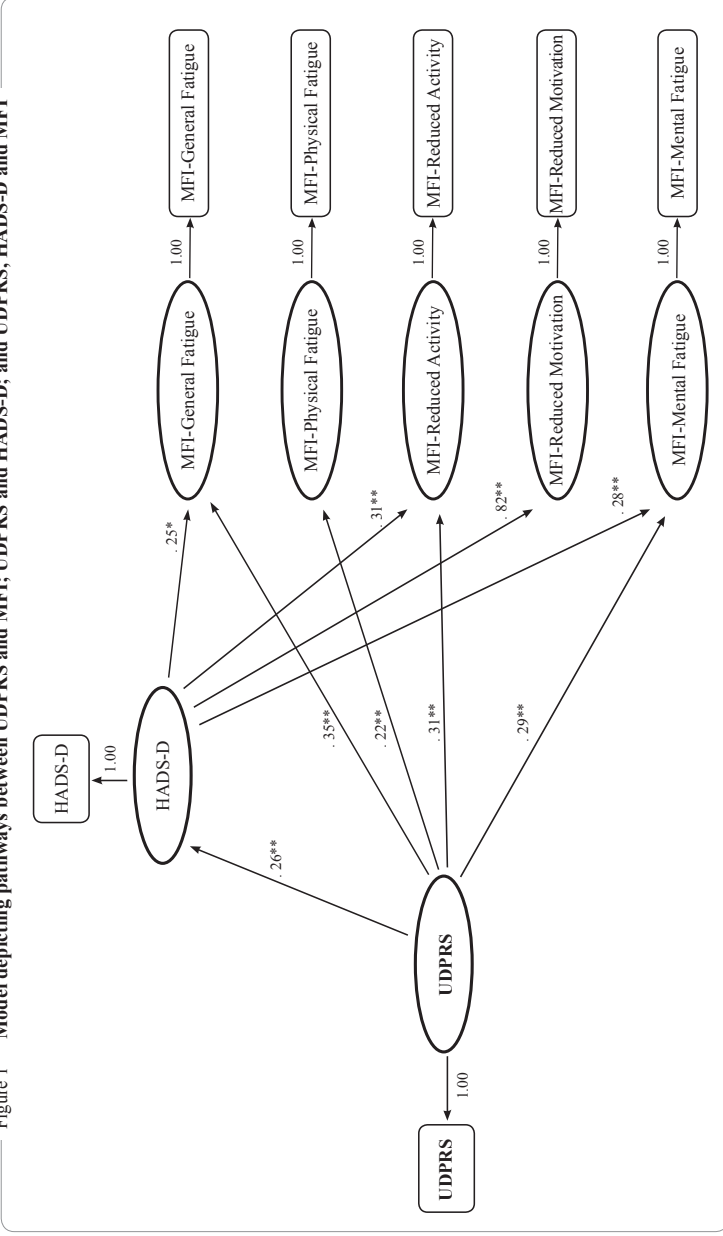
To our knowledge, this is the first study performed in order to examine how depression and disease severity lead to the different domains of fatigue. Our results show that worse disease severity and worse depression both lead to worse General fatigue, Reduced activity and Mental fatigue. Worse disease severity separately causes worse Physical fatigue. Only depression (but not worse disease severity) causes more fatigue in the Reduced motivation domain.

Fatigue till now used to be overlooked, or considered as a consequence of muscle rigidity or higher age of PD patients. Only recently it was recognized as a frequent complaint of PD patients, and recognized as a nonmotor feature of PD. Although new questionnaires were developed to actively search for this problem, clinicians lack strategies how to manage it. Despite increased knowledge on fatigue its etiology is not fully understood, biological, as well as psycho-social factors may play a role. Our own research showed associations of fatigue with depression, anxiety and worse disease severity (36). The frequency of fatigue in our sample is consistent with the studies reporting the frequency of fatigue in 33-58% of PD patients measured with the Nottingham Health Profile, or with the Fatigue Severity Scale (2,5,6,15).

Our results report worse disease severity to be an important factor leading to worse fatigue – not only in the physical domains (Physical fatigue, Reduced activity) but also in one mental domain (Mental fatigue), as until now it was generally considered to be to relatively independent of disease motor severity (5). Karlsen et al. did not show a relationship between disease severity and fatigue measured by Nottingham Health Profile in a sample of 233 PD patients (5). Abe et al. in their relatively small study of 26 PD patients did not find correlations between worse

**Fig. 1**

**Figure 1 Model depicting pathways between UDPRS and MFI; UDPRS and HADS-D; and UDPRS, HADS-D and MFI**



UDPRS – Unified Parkinson’s Disease Rating Scale, HADS-D – Hospital Anxiety and Depression Scale, depression dimension.

UPDRS and fatigue measured by Fatigue Severity Scale (FSS) (11,15). On the contrast, other studies found the association between worse UPDRS and worse fatigue. Alves et al. in their longitudinal study found fatigue measured by the generic Nottingham Health profile to be related to disease severity (6), also in our previous research we found worse disease severity to be associated with worse fatigue, in all fatigue domains measured by MFI (13).

The prevalence of depression was relatively low in our sample, that seem to be consistent with the recent papers on depression in PD. Reijnders (37) in his review paper reports its prevalence as 17% average, which is substantial, but less than the prevalence rates are usually quoted, e.g. Martinez-Martin et al. reported 48% prevalence of depression (38). Depression is not related to age, not to disease duration, and also not to disease severity. The prevalence depends on what is considered as “depression” because depression in the meaning of psychiatry can be from ‘depressive mood’, through ‘minor depression’ till ‘major depression’. Different ranking scales do not differentiate all the depressive symptoms and some of them only score major or minor depression. Moreover, the difference between measures is also reported whether a study uses self reported questionnaires, or objective scales (37). In our research we decided to use the HADS, which was recently reported as being useful in Parkinson’s disease for screening of depression in PD patients, although not in adequately defining the severity of depression in this population (23).

Several studies have shown the relationship between fatigue and depression. First results were from the study of Friedman et al. who found fatigue to be correlated with depression (3), also later studies of Karlsen et al. in a study of 233 PD patients, or our previous study in 150 PD patients having similar results (5,13). On the contrast, the study of Abe et al. in their relatively small sample of 26 PD patients did not find correlations between depression and fatigue measured by FSS (15). In a study of Shulman et al. in a sample of 99 PD patients fatigue measured by Fatigue Severity Scale did not correlate with depression (14).

### *Limitations*

We had a relatively low response rate which is a limitation of our study. We suppose that this response rate is because patients with worse disease severity were not able to come for an interview. We suppose that our sample consisted of patients with a relatively better functional status. Our results thus cannot be generalized, but we suggest that even in this selected population of PD patients, fatigue is already a serious problem. We decided to use a generic measure with a multidimensional design instead of a disease specific fatigue measure, as its advantage is the

possibility of using a generic instrument for different patient groups and consequently, to compare them.

### *Implications*

Our study showed that the presence of depression and worse disease severity caused certain domains of fatigue. Thus proper management of the disease itself to improve disease severity is thus important. We stress the importance of the recognition of depression as its further treatment could improve fatigue.

Further research should be performed, cross-sectional as well as longitudinal, to better understand these causal relationships. The answer to this question is important as it may influence the future clinical management of PD patients.

### *Conclusions*

Despite increasing knowledge demonstrating fatigue to be frequent and disabling feature of PD, it is still likely to be underrecognized by neurologists and thus lacking appropriate management. As currently there are no proved strategies to manage this problem clinically, the proper management of factors leading to fatigue is essential.

## **Reference List**

- (1) Friedman JH, Brown RG, Comella C, et al. Fatigue in Parkinson's disease: a review. *Mov Disord* 2007 Feb 15; 22(3):297-308.
- (2) van Hilten JJ, Weggeman M, van d, V, Kerkhof GA, van Dijk JG, Roos RA. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. *J Neural Transm Park Dis Dement Sect* 1993; 5(3):235-244.
- (3) Friedman J, Friedman H. Fatigue in Parkinson's disease. *Neurology* 1993 Oct; 43(10):2016-2018.
- (4) Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord* 2002 Jan; 8(3):193-197.
- (5) Karlsen K. Fatigue in patients with Parkinson's disease. *Movement disorders* 1999; 14(2):237-241.
- (6) Alves G. Is fatigue an independent and persistent symptom in patients with Parkinson disease? *Neurology* 2004; 63(10):1908-1911.
- (7) Garber CE, Friedman JH. Effects of fatigue on physical activity and function in patients with Parkinson's disease. *Neurology* 2003 Apr 8; 60(7):1119-1124.
- (8) Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. *Acta Neurol Scand* 2003 Jan; 107(1):1-6.

- (9) Havlikova E, Rosenberger J, Nagyova I, et al. Impact of Fatigue on Quality of Life in Patients with Parkinson's Disease. 2008.
- (10) Lou JS. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Movement disorders* 2001; 16(2):190-196.
- (11) Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989 Oct; 46(10):1121-1123.
- (12) Chaudhuri A. Fatigue and basal ganglia. *Journal of the neurological sciences* 2000; 179(S 1-2):34-42.
- (13) Havlikova E, Rosenberger J, Nagyova I, et al. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. *Parkinsonism Relat Disord* 2007 Sep 21.
- (14) Shulman LM. Comorbidity of the nonmotor symptoms of Parkinson's disease. *Movement disorders* 2001; 16(3):507-510.
- (15) Abe K. Fatigue in patients with Parkinson's disease. *Behavioural neurology* 2000; 12(3):103-106.
- (16) Hughes AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinic-pathological study of 100 cases. *Journal of neurology, neurosurgery and psychiatry* 1992; 55(3):181-184.
- (17) Folstein MF. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research* 1975; 12(3):189-198.
- (18) Fahn S MCDLAE. Recent developments in Parkinson's disease. Fahn S ERmotUDC, editor. Unified Parkinson's disease rating scale. 2, 153-163. 1987. Florham Park, NJ, MacMillan Healthcare Information.
- (19) Hoehn MM. Parkinsonism: onset, progression and mortality. *Neurology* 1967; 17(5):427-442.
- (20) Schwab RS EA. Projection technique for evaluating surgery in Parkinson's disease. Gillingham FJ Dle, editor. Third symposium on surgery in Parkinson's disease. 152-157. 1969. Edinburg, Livingstone.
- (21) Smets EM. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of psychosomatic research* 1995; 39(3):315-325.
- (22) Zigmond AS. The hospital anxiety and depression scale. *Acta psychiatrica Scandinavica* 1983; 67(6):361-370.
- (23) Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2007 Jun 15; 22(8):1077-1092.
- (24) Leentjens AFG, Lousberg R, Verhey FRJ. The psychometric properties of the Hospital Anxiety and Depression Scale in patients with Parkinson's disease. *Acta Neuropsychiatrica* 13, 83-85. 2001.
- (25) Bentler PM, Bonett DG. Significance Tests and Goodness of Fit in the Analysis of Covariance-Structures. *Psychological Bulletin* 88(3), 588-606. 1980.

- (26) Bentler PM. Comparative fit indices in structural models. *Psychological Bulletin* 1990; 107:238-246.
- (27) Bentler PM. On the fit of models to covariances and methodology to the Bulletin. *Psychological Bulletin* 1992; 112:400-404.
- (28) Browne MW, Cudeck R. Alternative ways of assessing model fit. In: Bollen KA, Long JS, eds. Testing structural equation models. Newbury Park (CA): Sage, 1993:136-162.
- (29) Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Structural Equation Modeling* 1999; 6:1-55.
- (30) Hu LT, Bentler PM. Evaluating model fit. In: Hoyle RH, ed. Structural Equation Modelling: Concepts, Issues and Applications. Thousand Oaks, CA: Sage, 1995:77-99.
- (31) Maruyama GM. Basics of structural equation modeling. Thousand Oaks (CA): Sage, 1998.
- (32) Raykov T, Widaman KF. Issues in applied structural equation modeling research. *Structural Equation Modeling* 1995; 2(4):289-319.
- (33) Rigdon E. CFI versus RMSEA: A comparison of two fit indices for structural equation modelling. *Structural Equation Modeling* 1996; 3(4):369-379.
- (34) Newcombe RG AD. Proportions and their differences. Altman DG MDBGMe, editor. Statistics with confidence. 45-56. 2005. Bristol, British Medical Journal.
- (35) Jöreskog KG, Sörbom D. LISREL 8.7 for Windows: User's reference guide. Lincolnwood, IL: Scientific Software International, Inc, 2005.
- (36) Havlikova E, Rosenberger J, Nagyova I, Middel B, Dubayova T, Gdovinnova Z, W Groothoff J, P van Dijk J. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. *Parkinsonism & related disorders* 2008; 14(3):187-192.
- (37) Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 2007 Nov 6.
- (38) Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of non-motor symptoms in Parkinson's disease in an international setting; study using nonmotor symptoms questionnaire in 545 patients. *Mov Disord* 2007 Aug 15; 22(11):1623-1629.

