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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.

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Impact of Fatigue on Quality of Life in Patients with Parkinson's Disease

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Eur J Neurol. 2008; 15(5): 475-80.

Abstract

Fatigue is frequent and important in the lives of Parkinson's disease (PD) patients. It is multidimensional, with physical and mental aspects. The aim of our study was to explore the impact of fatigue on quality of life for PD patients. The sample consisted of 175 PD patients from Eastern Slovakia (52% males, mean age 68.2 ± 9.2 , mean disease duration 7.4 ± 6.7). The Multidimensional Fatigue Inventory (5 dimensions), the Parkinson's Disease Quality of Life Questionnaire (8 dimensions) and the Unified Parkinson's Disease Rating Scale were used. Demographic data were obtained in a structured interview. T-test, Fisher's exact test and multiple linear regression analysis were used. Different aspects of fatigue selectively explained different domains of QoL – physical dimensions of fatigue were connected with Mobility and Activities of daily living; mental fatigue dimensions affected Cognition, Emotional well-being, Communication and Activities of daily living; general fatigue was related to Bodily discomfort. The explained variances varied from 5% (Social Support) to 65% (Activities of daily living). Fatigue combined with worse functional status appears to be a significant contributor to poor quality of life. Its multidimensional construct can be used to develop strategies for improving specific aspects of fatigue to improve QoL for PD patients.

Introduction

The cardinal motor features in Parkinson's Disease (PD) have an important impact on the patients' quality of life (QoL). However, PD is often complicated by additional problems such as depression, anxiety or fatigue, which may have even greater impact on their QoL [1].

Patients with PD have worse QoL scores compared to the general population, whether measured by a generic or by a disease-specific instrument. Karlsen et al. reported, using the Nottingham Health Profile, worse scores in emotional reactions, energy, pain, sleep, social isolation and physical mobility domains [2]. Schrag et al. found worse scores in the domains of physical and social functioning, physical role limitations and general health perceptions, particularly in the younger age group [3]. When using the Parkinson's Disease Questionnaire (PDQ-39), a disease-specific instrument, Schrag et al. reported deterioration of aspects of QoL related to physical and social functioning [3]. Various clinical and psycho-social variables have been evaluated with regard to QoL. Disease severity [4], motor complications [5,6], sleep problems [7], pain [8], depression [4,9], cognitive impairment [9] have been found to significantly worsen QoL. Karlsen et al. found a significant relationship between higher age and the physical mobility domain [1], while other studies did not report such a relationship [2, 9]. Longer disease duration was a significant predictor of the QoL domains [5]. Female gender was associated with worse QoL [10].

Only recently fatigue has been recognized as an important clinical feature of PD, reported by 45% of patients [11,12]. To our knowledge only the study by Herlofson and Larsen was performed to evaluate the influence of fatigue on quality of life in PD patients [13]. They found a strong correlation between higher fatigue and worse QoL. Fatigue is a subjective experience, defined as a state of extreme tiredness, weakness, lack of energy or exhaustion, physical, mental, or both [14]. Recent studies report that the physical and mental components of fatigue seem to be independent from each other [15,16]. Physical fatigue in PD patients is reported after inadequate sleep or rest, or after physical exertion, and may be associated with decline in strength or in speed of movements due to parkinsonism. Mental fatigue is reported after mental effort or when patients lack the motivation to initiate activities [16].

The aim of our study was to explore the impact of the various dimensions of fatigue controlled for age, gender, disease duration, level of education and functional status on the quality of life of PD patients.

Methods

Patients

This cross-sectional study evaluated fatigue in patients with Parkinson's disease 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 [17], and their mental abilities were assessed with the Mini- Mental State Examination (MMSE) [18]. Exclusion criteria were defined as follows: 1. MMSE lower than 24; 2. disease duration longer than 15 years, to avoid a sample of very old people, who might be expected to have serious co-morbidities that could affect QoL; 3. presence of co-morbidity associated with the fatigue variable.

The study was approved by the local Ethical 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 Parkinson's Disease Quality of Life Questionnaire (PDQ-39). After three weeks all patients were interviewed on relevant issues that were no part of the questionnaire. After this structured interview, a neurologist assessed each patient's disease severity with the Unified Parkinson's Disease Rating Scale

(UPDRS) Version 3.0 [19], including Hoehn and Yahr staging [20] and the Schwab and England disability scale [21]. 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.

Measures

Quality of life was assessed with a disease-specific questionnaire, the Parkinson's Disease Quality of Life Questionnaire (PDQ-39), as the primary outcome measure. It was designed by Peto *et al.* [22], and 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 eight subdimension scores and one summary index can be calculated: Mobility – 10 items; Activities of daily living (ADL) – 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. For each QoL dimension the scores were standardized from 0 to 100, so that higher scores refer to more problems. PDQ-39 has been shown to be feasible, reliable, valid, and responsive to change in patients with PD with good internal consistency [23]; in our sample Cronbach's alpha was 0.94. Cronbach's alpha for each of the subscales was: Mobility 0.87, ADL 0.90, Emotion Well-Being 0.86, Stigma 0.88, Social Support 0.78, Cognition 0.67, Communication 0.76, Bodily Discomfort 0.81.

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI). The MFI is a 20-item self-report instrument designed and validated by Smets *et al.* [24]. 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 frequently used among patients with neurological diseases [16]. 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.

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: (1) a modified Hoehn & Yahr Staging, an ordinal scale that is applied to gauge the course of disease over time; and (2) 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 [19-21].

Basic socio-demographic data (age, gender, education) were obtained from a structured interview. The level of education was classified into three categories: 1. basic – for 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

The relationships between demographic variables, functional status, fatigue and quality of life were analyzed with multiple linear regression analysis, using all separate quality of life domains as dependent variables. Independent variables considered for the multivariate model were the five fatigue dimensions, controlled for age, gender, level of education, disease duration and UPDRS total scores. A stepwise method was used, with the variables entered in 2 blocks – the first block containing the variables that were controlled for, then a second block was added containing the fatigue domains. Only variables with significant correlations were entered. Statistical analyses were performed using the statistical software program SPSS 12.0 for Windows.

Results

Descriptive Data

Out of 497 patients with PD meeting the inclusion criteria, 41 did not wish to participate in the study; and 259 did not respond to the invitation. Total response rate was 35.2%. Out of those who agreed to participate, 11 patients were eliminated 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 175 remained for analysis. Non-responders did not differ significantly from the analyzed group in age (mean age of responders: 68.2 ± 9.2 years, non responders 71.8 ± 8.1 years, t test sig .280, CI -0.91 – .069). Responders differed significantly in gender ($P=0.023$, two-sided, Fisher`s exact test). Table 1.

175 patients completed the questionnaire and were interviewed, followed by examination by the neurologist (91 men, 52%). The mean age of the patients was 68.2 ± 9.2 years. Mean age at disease onset was 59.5 ± 11.1 years. Mean disease duration was 7.4 ± 6.7 years. Details of the clinical profile and variables of the patients are shown in Table 1 and Table 2.

Table 1 Socio-demographic variables of the sample (N=175) and non-responders (N=322)

Responders		Non responders	
Variable	n, %, Mean±SD	Variable	n, %, Mean±SD
1. Gender			
Male (n=91)	52.0%	Male (n=132)	41.0%
Female (n=84)	48.0%	Female (n=190)	59.0%
2. Age	68.2±9.2		71.8±8.1
3. Disease duration	7.4±6.7		
4. Level of education			
Basic		91 (52.0%)	
Middle		58 (33.1%)	
Higher		26 (14.9%)	

Table 2 Clinical variables of the sample (N=175)

		Mean±SD
UPRDS		36.2±21.2
H&Y		2.2±1.1
	≤ 2.0	110 (62.9%)
	> 2.0	65 (37.1%)
S&E		70.0±21.2
	≤ 70%	76 (43.4%)
	> 70%	99 (56.6%)
MFI		
	General fatigue	13.6±4.0
	Physical fatigue	13.9±3.6
	Reduced activity	12.5±3.9
	Reduced motivation	10.8±3.8
	Mental fatigue	11.8±3.7
PDQ-39		
	Mobility	63.4±24.8
	Activities of daily living	58.7±25.6
	Emotional well-being	62.5±20.6
	Stigma	53.0±25.7
	Social support	40.8±19.8
	Cognition	59.0±19.6
	Communication	50.8±21.6
	Bodily discomfort	74.4±23.3
	Summary index	57.7±15.6

UPDRS Unified Parkinson's Disease Rating Scale, total score; H&Y Hoehn and Yahr staging; S&E Schwab and England disability scale. MFI Multidimensional Fatigue Inventory, PDQ-39 Parkinson's Disease Quality of Life Questionnaire.

Correlations

Table 3 presents the correlations between sociodemographic variables and PDQ-39 and functional status and PDQ-39. Higher age significantly correlated with worse Mobility, Activities of daily living, Cognition ($p < .01$) and Communication ($p < .05$); female gender showed significant correlation only with Bodily discomfort ($p < .05$). Longer disease duration had significant correlations with all QoL domains. Lower level of education correlated with Mobility, Activities of daily living, Emotional well-being and Bodily discomfort. Worse UPDRS had significant correlations with all QoL domains.

All QoL domains (except Social support) positively correlated with all fatigue dimensions ($p < .01$). The Social support domain significantly correlated only with general fatigue, reduced motivation and mental fatigue ($p < .05$).

We did an analysis of possible multicollinearity of the fatigue subscales; its results gave us additional information on the independence of the physical and mental components of fatigue.

Multiple regression analysis of PDQ-39 scores

Only variables with significant correlation to QoL domains were entered into the multiple linear regression model. Table 4 shows that mental fatigue and higher UPDRS scores were the two determinants related to overall quality of life.

Mobility was predicted by reduced activity and higher UPDRS. This model explained 56% of the variance. Activities of daily living was predicted by reduced activity and by higher UPDRS. This model explained 65% of the variance. Emotional well-being was affected by general fatigue and mental fatigue, by longer disease duration and higher UPDRS score. The model explained 27% of the variance. The Stigma domain was associated with reduced activity, reduced motivation, and worse disease severity. This model explained 12% of the variance. Social support was related to reduced motivation, with 5% of the explained variance. Higher score in Cognition was predicted by mental fatigue and higher age. The model explained 40% of the variance. Communication was predicted by mental fatigue and by higher UPDRS. The model explained 20% of the variance. Bodily discomfort was predicted by general fatigue, by higher UPDRS and female gender. The model explained 21% of the variance.

Table 3 Fatigue as predictor of quality of life for each of the eight domains of PDQ-39; controlled for age, gender, level of education, disease duration and functional status

PDQ-39	Mobility	ADL	Emotional Well-being	Stigma	Social support	Cognition	Communication	Bodily discomfort	Summary Index
Age	.03	-.05	NE	NE	NE	.26***	.14	NE	NE
Gender	NE	NE	NE	NE	NE	NE	NE	.25**	NE
Education	-.02	-.03	.12	NE	NE	NE	NE	-.09	-.06
Disease duration	-.02	.07	.17*	.12	.06	.10	.05	.04	.12
UPDRS	.50***	.75***	.25***	.28**	-.02	.13	.37***	.27**	.46***
Adjusted R2#	.48	.64	.20	.06	.01	.24	.18	.18	.43
MFI									
General fatigue	-.01	-.01	.34**	.11	.09	.05	-.06	.29*	.14
Physical fatigue	-.03	.03	-.11	.05	NE	.02	-.09	-.15	-.04
Reduced activity	.34***	.28*	-.14	.24*	NE	-.02	-.06	.12	-.06
Reduced motivation	.01	.06	.03	.33**	.27*	.01	.12	-.10	.12
Mental fatigue	.02	.10	.25*	.15	.02	.46***	.26*	-.01	.32***
Adjusted R2&	.56	.65	.27	.12	.05	.40	.20	.21	.48

Linear regression analysis entered in 2 blocks – the first block contains variables that are controlled for, the second block contains the fatigue domains, only the variables with significant correlations were entered, a stepwise method was used, only significant contributors remained in the model. Displayed results are betas, representing the analysis of all the variables.

PDQ-39 Parkinson's Disease Quality of Life Questionnaire, UPDRS Unified Parkinson's Disease Rating Scale. NE: not entered. # Adjusted R2 for the linear regression analysis of variables controlled for. & Adjusted R2 of all variables. Displayed are beta coefficients. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$

Discussion

Research involving populations with chronic neurological disease has shown fatigue to be associated with lower levels of QoL [25,26]. Until now, little research has been performed into the association between fatigue and QoL for PD patients

The presence of fatigue in PD patients predicts worsening of all QoL domains. The most affected were the domains Bodily Discomfort, Mobility and Emotional well-being. Focusing on the different components of fatigue, mental domains (especially mental fatigue) were predictors of psychological QoL domains (Emotional well-being, Stigma, Social support, Cognition, Communication). Physical dimensions of fatigue (reduced activity) were predictors of Mobility, ADL and Stigma domains. Fatigue in general appeared to be a predictor of the Emotional well-being and Bodily Discomfort domains.

Fatigue is often reported as one of the major complaints in PD patients. Its impact on their QoL is not fully understood [13,27,28]. In a community-based study of 245 PD patients compared to 100 healthy individuals and 100 patients with diabetes mellitus, Larsen et al. found more fatigue and poorer QoL among PD patients than in healthy individuals or in diabetes patients [27]. In a more recent study, Herlofson and Larsen compared 66 PD patients with and without fatigue. They reported fatigued patients as having significantly worse QoL in Emotional well-being and Mobility. No difference was observed in Cognition, Communication and Stigma [29]. Our results show in addition that mental fatigue significantly influences the Emotional well-being, Cognition and Communication domains.

Other factors also had a significant influence on QoL. Disease severity measured by UPDRS was a significant predictor for all domains except Social support and Cognition. The influence of functional status on QoL had conflicting results in previous studies. In a community-based sample of 111 patients Karlsen et al. did not find that motor complications significantly influenced QoL scores measured with the Nottingham Health Profile [2]. In contrast, Chapuis et al. using a disease-specific questionnaire on a sample of 143 PD patients, found worse motor scores were connected with worse scores for Mobility and ADL [5].

In our study the influence of fatigue on QoL was controlled for demographic variables, as their influence was confirmed by previous studies. We found higher age to be a significant predictor of worse Cognition. Karlsen et al. found a significant relationship of higher age with the physical mobility domain of the NHP questionnaire [1], but other studies did not report the influence of age on QoL [2,9]. Female gender was found to have a significant influence on the Bodily Discomfort domain in our study. Chapuis et al. found male gender significantly worsened the

ADL [5]. Behari et al. found female gender had the most influence on QoL [10]. Longer disease duration was a significant predictor of the Emotional well-being domain. Chapuis et al. showed an influence of longer disease duration on worse scores for Mobility, Activities of daily living, Stigma, Social Support and Communication [5].

For the purposes of measuring fatigue we decided to use a generic measure, as its advantage is the possibility of using a generic instrument for different patient groups and consequently, to compare them. Fatigue is a frequent complaint of PD patients. The developers of the MFI did not propose cut-off scores, but statistical rules allow the possibility of using the upper 2/3 of the scores as a cut-off. In our sample 49.5% of patients complained of general fatigue, 53.7% of physical fatigue, 37.7% of reduced activity, 39.0% of reduced motivation and 37.2% of mental fatigue. These figures are consistent with the studies reporting the frequency of fatigue in 40-56% of PD patients [12].

There were limitations in our 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. Differences in gender between responders and non-responders showed men to be more likely to participate in our study, meaning that our sample is not fully representative, though gender proved not to be a significant variable affecting QoL except Bodily discomfort. Despite the rather low response rate, fatigue is already a serious problem worsening patients' quality of life, so we expect this to be even worse in the total PD patients group. The present study was not controlled for depression and sleep disorders, as there is an overlap in symptomatology – sleep problems and fatigue are among the diagnostic criteria for depression and vice versa. Future studies are to be performed to understand their contribution to QoL as well.

To our knowledge this is the first study separately evaluating different fatigue domains and their influence on quality of life. The strength of our study is the use of a disease-specific instrument, as it better reflects the consequences of the disease for individuals, and is more sensitive compared to generic instruments that contain more general items and therefore lack specificity.

While clinicians are mostly concerned with physical manifestations, the affected persons tend to identify other problems also related to their quality of life. We stress the importance of recognizing different aspects of fatigue in PD patients because of their negative effect on different quality of life domains. Improvement of physical fatigue by proper antiparkinsonian drug therapy may improve Mobility and ADL, and improvement of mental fatigue by psychological interventions or patient education may improve Emotional well-being, ADL or Cognition domains. The frequency, severity

and impact of fatigue on QoL suggest that new research should be done in this area. Identifying a more effective approach to managing this problem should be one of the current challenges in PD treatment.

Conclusion

Fatigue is frequent and important in the lives of PD patients. It is multidimensional, with physical and mental aspects, having significant negative effects on all QoL domains, especially Bodily Discomfort, Mobility and Emotional well-being. It is important to identify its presence, and its proper management to improve quality of life for PD patients.

Acknowledgements

This work was supported by the Slovak Research and Development Agency under Contract No. APVV-20-038305.

References

- (1) Karlsen KH, Larsen JP, Tandberg E, Maeland JG. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 1999; **66**:431-435.
- (2) Karlsen KH, Tandberg E, Arslan D, Larsen JP. Health related quality of life in Parkinson's disease: a prospective longitudinal study. *Journal of Neurology, Neurosurgery, and Psychiatry* 2000; **69**:584-589.
- (3) Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. *Movement Disorders* 2000; **15**:1112-1118.
- (4) The Global Parkinson's Disease Survey (GPDS) Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Movement Disorders* 2002; **17**:60-67.
- (5) Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Movement Disorders* 2005; **20**:224-230.
- (6) Pechevis M, Clarke CE, Vieregge P, *et al.* Effects of dyskinesias in Parkinson's disease on quality of life and health-related costs: a prospective European study. *European Journal of Neurology* 2005; **12**:956-963.
- (7) Scaravilli T, Gasparoli E, Rinaldi F, Polesello G, Bracco F. Health-related quality of life and sleep disorders in Parkinson's disease. *Neurological Sciences* 2003; **24**:209-210.
- (8) Quittenbaum BH, Grahn B. Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. *Parkinsonism & Related Disorders* 2004; **10**:129-136.
- (9) Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life

- in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery, and Psychiatry* 2000; **69**:308-312.
- (10) Behari M, Srivastava AK, Pandey RM. Quality of life in patients with Parkinson's disease. *Parkinsonism & Related Disorders* 2005; **11**:221-226.
 - (11) van Hilten JJ, Weggeman M, van der Velde EA, Kerkhof GA, van Dijk JG, Roos RA. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. *Journal of Neural Transmission. Parkinson's Disease and Dementia Section* 1993; **5**:235-244.
 - (12) Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. *Movement Disorders* 1999; **14**:237-241.
 - (13) Herlofson K, Larsen JP. Measuring fatigue in patients with Parkinson's disease - the Fatigue Severity Scale. *European Journal of Neurology* 2002; **9**:595-600.
 - (14) Brown RG, Dittner A, Findley L, Wessely SC. The Parkinson fatigue scale. *Parkinsonism & Related Disorders* 2005; **11**:49-55.
 - (15) Zenzola A, Masi G, De Mari M, Defazio G, Livrea P, Lamberti P. Fatigue in Parkinson's disease. *Neurological Sciences* 2003; **24**:225-226.
 - (16) Lou JS, Kearns G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Movement Disorders* 2001; **16**:190-196.
 - (17) Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Psychiatry* 1992; **55**:181-184.
 - (18) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975; **12**:189-198.
 - (19) Fahn S, Elton RL, members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Lieberman A, editors. *Recent developments in Parkinson's disease, vol. 2*. Florham Park, NJ: MacMillan Healthcare Information, 1987: 153-163.
 - (20) Hoehn MM, Yahr MD. Parkinsonism onset progression and mortality. *Neurology* 1967; **17**:427-442.
 - (21) Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IMI, editors. *Third symposium on surgery in Parkinson's disease*. Edinburg: Livingstone, 1969: 152-157.
 - (22) Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Quality of Life Research* 1995; **4**:241-248.

- (23) Marinus J, Ramaker C, van Hilten JJ, Stiggelbout AM. Health related quality of life in Parkinson's disease: a systematic review of disease specific instruments. *Journal of Neurology, Neurosurgery, and Psychiatry* 2002; **72**:241-248.
- (24) Smets EMA, Grassen B, Bonke B, De Haes JCJM. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research* 1995; **39**:315-325.
- (25) Lou JS, Reeves A, Benice T, Sexton G. Fatigue and depression are associated with poor quality of life in ALS. *Neurology* 2003; **60**:122-123.
- (26) Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Multiple Sclerosis* 2001; **7**:340-344.
- (27) Larsen JP, Karlsen K, Tandberg E. Clinical problems in non-fluctuating patients with Parkinson's disease: a community-based study. *Movement Disorders* 2000; **15**:826-829.
- (28) Martinez-Martin P, Catalan MJ, Benito-Leon J, *et al.* Impact of fatigue in Parkinson's disease: the Fatigue Impact Scale for Daily Use (D-FIS). *Quality of Life Research* 2006; **15**:597-606.
- (29) Herlofson K, Larsen JP. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. *Acta Neurologica Scandinavica* 2003; **107**:1-6.

