



Towards an understanding of fatigue in Parkinson disease

P Hagell,^{1,2} L Brundin³

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¹ Department of Health Sciences, Lund University, Lund, Sweden; ² Department of Neurology, University Hospital, Lund, Sweden; ³ Department of Clinical Sciences, Section of Psychiatry, Lund University, Lund, Sweden

Correspondence to: Dr P Hagell, Department of Health Sciences, Lund University, PO Box 157, SE-221 00 Lund, Sweden; peter.hagell@med.lu.se

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ABSTRACT

Objectives: To gain an improved understanding of fatigue in Parkinson disease (PD) by exploring possible predictors among a wide range of motor and non-motor aspects of PD.

Methods: 118 consecutive PD patients (54% men; mean age 64 years) were assessed regarding fatigue, demographics and a range of non-motor and motor symptoms. Variables significantly associated with fatigue scores in bivariate analyses were used in multiple regression analyses with fatigue as the dependent variable.

Results: Fatigue was associated with increasing Hoehn & Yahr stages, specifically the transition from stages I–II to stages III–V. Regression analysis identified five significant independent variables explaining 48% of the variance in fatigue scores: anxiety, depression, lack of motivation, Unified PD Rating Scale (UPDRS) motor score and pain. Gender, age, body mass index, PD duration, motor fluctuations, dyskinesias, symptomatic orthostatism, thought disorder, cognition, drug treatment, sleep quality and daytime sleepiness were not significantly associated with fatigue scores. When considering individual motor symptom clusters instead of the UPDRS motor score, only axial/postural/gait impairment was associated with fatigue.

Conclusions: This study found fatigue to be primarily associated with symptoms of depression and anxiety, and with compromised motivation, parkinsonism (particularly axial/postural/gait impairment) and pain. These results are in agreement with findings in other disorders and imply that fatigue should be considered a separate PD entity differing from, for example, excessive daytime sleepiness. Fatigue may have a distinguished neurobiological background, possibly related to neuroinflammatory mechanisms. This implies that novel treatment options, including anti-inflammatory therapies, could be effective.

Fatigue can be defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion.¹ It is a common symptom in chronic conditions, including many brain disorders.^{1,2} In Parkinson disease (PD), fatigue has been reported in up to two-thirds of patients, of whom many consider it one of their most disabling symptoms; yet it often goes undetected, has an unclear cause and lacks specific therapy.³ Studies have shown partly conflicting results regarding the association between fatigue and other disease aspects, such as parkinsonian and depressive symptoms.^{4–6} However, no such study to date has taken a broader range of motor and non-motor aspects of PD into consideration, and most rely on bivariate analyses. Here we sought to gain an improved understanding of fatigue by exploring possible predictors among a wide range of motor and non-motor aspects of PD.

METHODS

Patients

A total of 118 consecutive people with PD were included (for details, see Hagell *et al*).⁷ Exclusion criteria were participation in other ongoing studies, ongoing infections, psychiatric adverse drug reactions and other clinically significant comorbidities (eg, depression, cognitive impairment, arthritis), as determined by patients' attending neurologist and the study assessor. This was done to avoid cases with fatigue of alternate aetiologies. All participants provided signed informed consent.

Procedures and data collection

Patients were assessed during the "on" phase using the Unified PD Rating Scale (UPDRS), the Hoehn & Yahr (HY) staging of PD and the Mini-Mental State Exam (MMSE). HY stages were also estimated for the "off" phase from patient-reported history and medical records. The inter-rater concordance (Kendall W) among study assessors for UPDRS and HY ratings was ≥ 0.85 . UPDRS part III (motor score) was used as an overall measure of parkinsonism. In addition, the following symptomatic profile scores were calculated: axial/postural/gait impairments (items 18, 19, 27–31), rest tremor (item 20), postural tremor (item 21), rigidity (item 22) and limb bradykinesia (items 23–26).⁸

The Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F)⁹ scale was used to measure fatigue. To ease interpretation relative to other variables, FACIT-F scores (range 0–52) were reversed in this study (0 = less fatigue). Sleep quality was assessed with the Pittsburgh Sleep Quality Index, daytime sleepiness by the Epworth Sleepiness Scale, depression and anxiety with the Hospital Depression and Anxiety Scale, and pain by the Pain scale of the Nottingham Health Profile (NHP). All patient-reported scales were completed during the "on" phase, and their reliabilities (coefficient alpha) were ≥ 0.71 .

Patients classified as fatigued according to the Energy scale of the NHP⁷ were asked whether their fatigue typically was worse when "on" or "off," if their motor symptoms were worse when they experienced fatigue, and whether they had experienced fatigue prior to the onset of motor PD symptoms.

Analyses

Data were checked regarding underlying assumptions, and described and analysed accordingly using SPSS version 14 (SPSS, Chicago). The alpha-level for significance was set at 0.05 (two-tailed). Variables significantly associated with fatigue

scores in bivariate analyses were entered as independent variables in regression models with fatigue (FACIT-F) as the dependent variable. First, the total UPDRS motor score was entered as an independent variable to assess the association between parkinsonism and fatigue. Second, the five UPDRS motor symptom profile scores were entered instead to explore whether fatigue appears associated with any particular aspect(s) of parkinsonism.

RESULTS

The sample consisted of 64 (54%) men; the mean (SD) age and PD duration were 63.9 (9.6) and 8.4 (5.7) years, respectively (see supplementary table S1 online). Among 57 (48%) fatigued participants, 42 (74%) experienced worsening of motor symptoms while fatigued. Thirty (53%) of the 57 fatigued patients experienced motor fluctuations. Of these, 25 (83%) reported that their fatigue was worse during “off.” Eighteen patients (32%) reported that their fatigue had begun prior to motor symptom onset. Fatigue scores increased across “off” phase HY stages (fig 1).

The first regression model constructed based on bivariate analyses of associations between fatigue and other variables (see supplementary tables S2 and S3 online) identified five variables explaining 48.2% of the variance in fatigue scores (table 1). The strongest predictors were symptoms of anxiety, depression and impaired motivation. When the total UPDRS motor score was substituted with the five motor symptom profile scores (model 2), only axial/postural/gait impairment was associated with fatigue (table 1).

DISCUSSION

This study sought to improve the understanding of fatigue in PD by exploring potential predictors of fatigue among a range of motor and non-motor aspects of PD. We found fatigue to be

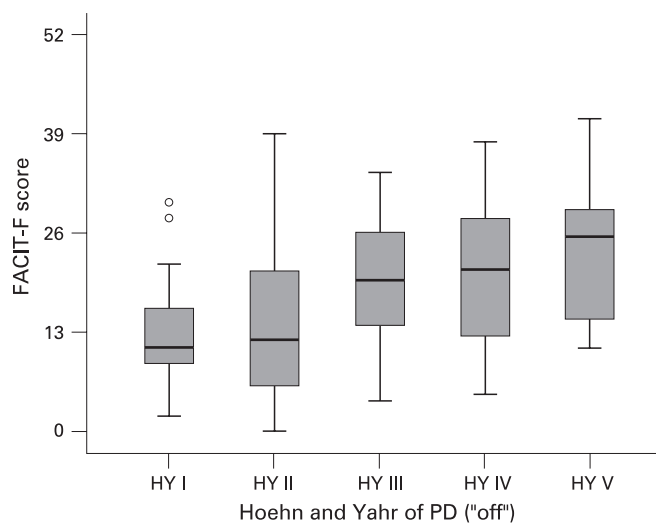


Figure 1 Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) scores across “off” phase Hoehn & Yahr (HY) stages (higher scores = more fatigue). The Kruskal–Wallis test showed significant differences across HY stages ($p = 0.005$), and post-hoc Mann–Whitney U tests indicated a significant difference between HY stages II and III ($p = 0.04$ following Bonferroni correction) but not between other stages. Solid horizontal lines are median values, boxes are interquartile ranges (25th to 75th percentiles), and error bars are ranges. Open circles are outliers, defined as values >1.5 box lengths from the 75th percentile. PD, Parkinson disease.

associated with symptoms of depression, anxiety, compromised motivation, parkinsonism and pain. When considering individual motor symptom clusters, axial/postural/gait impairment (but not tremor, rigidity or bradykinesia) was found to be associated with fatigue.

We excluded patients with comorbidities such as depression. This may pose some limitations to the generalizability of results—for example by underestimating the role of depression. Since fatigue is common in major depression, and depression is common in PD, including depressed patients could have increased the predictive value of depression for fatigue. It should also be kept in mind that several of our variables were coarse single item ratings, and no laboratory measures were included. However, a major strength of this study is its comprehensiveness in terms of the number of variables considered. As such, this appears to be the first study of its kind in PD.

In contrast to what has been documented before in PD, we found that anxiety was a stronger predictor of fatigue than depression. Lack of motivation was also identified as a significant predictor of fatigue. This is in accordance with previous hypotheses suggesting that central motivational processes are important contributors to the experience of fatigue in neurological disorders.² Taken together, anxiety, depressive symptoms and lack of motivation could predict about 42% of the variation in fatigue scores.

We found an association between fatigue and the underlying severity of parkinsonism. However, when considering individual symptom clusters, only axial/postural/gait impairment was associated with fatigue (despite no overt signs of multicollinearity). Accordingly, fatigue scores primarily appear to worsen in HY stages III (ie, when postural symptoms appear) and above. Similarly, Alves *et al* found fatigued PD patients to exhibit worse UPDRS motor scores and have more postural instability and gait difficulties than non-fatigued patients.⁵ Together with the observed lack of association with dopaminergic drug treatment and indications of more dysautonomy in fatigued patients, this could suggest involvement of extrastriatal pathology in the development of fatigue. Accordingly, a recent study among people with dopa-naïve PD found fatigued patients to have more severe parkinsonism but similar striatal dopamine transporter uptake compared with non-fatigued patients.¹⁰ Interestingly, we found that parkinsonism was associated with fatigue but only explained an additional 3.6% of its variance once the influence of anxiety, depressive symptoms and reduced motivation had been taken into account. Furthermore, while dopaminergic drugs can help improve fatigue,¹⁰ we failed to see any association between fatigue and dosages of antiparkinsonian medications. Taken together, fatigue does therefore not seem to be a direct consequence of the nigrostriatal dopaminergic pathology in PD.

We found indications that fatigue cannot be explained by excessive daytime sleepiness (EDS) or poor sleep. This is in accordance with previous work in PD,³ and other populations.¹¹ The wake-promoting agent modafinil has been used for both fatigue and EDS.¹² However, randomised controlled trials (RCTs) using the substance to treat fatigue have largely yielded negative or inconclusive results.^{12–15} However, when used to treat EDS in PD, results have appeared more encouraging.¹⁶ The distinction between fatigue and sleepiness may therefore have important implications, neurobiologically as well as in terms of symptom management.

Fatigue is common in inflammatory and infectious conditions. The combination of symptoms such as fatigue, depressed

Table 1 Multiple linear regression with fatigue (Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) score) as the dependent variable*

Significant independent variables†	B (95% CI)	β	p Value	
Model 1‡				
Anxiety (HADS)	0.939 (0.407 to 1.471)	0.321	0.001	
Depression (HADS)	0.908 (0.258 to 1.558)	0.267	0.007	
Motivation (item 4, UPDRS I)	5.165 (1.779 to 8.552)	0.258	0.003	
Parkinsonism (UPDRS III total score)	0.178 (0.031 to 0.325)	0.194	0.018	Adjusted R ² , final model: 0.482
Pain (NHP-Pain)	0.076 (0.005 to 0.146)	0.175	0.035	
Model 2§				
Anxiety (HADS)	0.783 (0.375 to 1.191)	0.297	<0.001	
Axial/postural/gait impairment (UPDRS III)	0.811 (0.434 to 1.188)	0.302	<0.001	
Depression (HADS)	0.837 (0.287 to 1.387)	0.253	0.003	Adjusted R ² , final model: 0.498
Motivation (item 4, UPDRS I)	4.277 (1.505 to 7.049)	0.220	0.003	

*FACIT-F scores were reversed so that low scores indicate less fatigue. Significant predictors were identified by means of forward stepwise multiple regression (entry/removal criteria, $p < 0.05/p > 0.10$). Data were then reanalysed with only significant predictors entered as independent variables in a forced entry model.

†Listed by their relative predictive value (β).

‡Independent variables: age (years), time since Parkinson disease diagnosis (years), daily pramipexole dose (mg), UPDRS III total score, MMSE score, ESS score, HADS depression score, HADS anxiety score, NHP-Pain score, PSQI global score, symptomatic orthostasis (item 42, UPDRS IV; 0 = no, 1 = yes), thought disorder (item 2, UPDRS I, dichotomised; 0 = no signs of thought disorder, 1 = signs of thought disorder (scores 1–4)), motivation (item 4, UPDRS I, dichotomised; 0 = normal motivation, 1 = impaired motivation (scores 1–4)).

§Independent variables as in model 1 but with axial/postural/gait impairment, resting tremor, action tremor, limb bradykinesia and rigidity scores entered instead of the total UPDRS motor score (see Methods).

β, standardised regression coefficient; B, regression coefficient; FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue scale; HADS, Hospital Anxiety and Depression Scale; UPDRS, Unified Parkinson's Disease Rating Scale; NHP, Nottingham Health Profile.

mood, pain and social withdrawal experienced during severe infections is often referred to as “sickness-behaviour.”¹⁷ Interestingly, this syndrome is similar to predictors for fatigue identified here and elsewhere.^{18–19} Chronic fatigue syndrome (CFS) has been found associated with hypocortisolism and elevations of the proinflammatory cytokine IL-6.²⁰ In PD, there is evidence of neuroinflammation with activation of glial cells and elevation of cytokine levels.²¹ Whether primary or not, a sustained low-grade neuroinflammation could represent an alternative pathology in PD leading to symptoms such as fatigue. Indeed, a recent study found plasma cytokine levels to correlate with fatigue in PD.²²

It is possible that fatigue has a specific underlying pathogenesis that is common across disorders and that requires targeted therapy. Although not excluding other possibilities, one alternative could be anti-inflammatory treatment. An RCT of acetyl-salicylic acid to treat fatigue in multiple sclerosis provides tentative support for this hypothesis.²³ Moreover, cyclooxygenase-2 inhibitors have been used against treatment-resistant depression with promising results²⁴ and have been suggested for treating CFS.²⁵

Our results show that symptoms of depression and anxiety are the main predictors of fatigue in PD. Furthermore, fatigue is associated with lack of motivation, parkinsonism and pain. We propose that fatigue should be separated from sleepiness and suggest that it may have a distinct neurobiological background requiring different, non-dopaminergic treatment strategies such as anti-inflammatory therapies.

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Competing interests: None.

Ethics approval: The study was approved by the Research Ethics Committee, Faculty of Medicine, Lund University, Sweden.

Patient consent: Obtained.

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Neurological picture

Acute middle cerebral artery stroke and an innominate steal from a ruptured brachiocephalic trunk atheroma

A 59-year-old man developed sudden left hemiparesis and dysarthria 35 min before arrival at the emergency room. He was

a current smoker. He had facial palsy, hemiparesis and sensory extinction on the left side. His baseline National Institutes of Health Stroke Scale score was 9. The right radial pulse was diminished. An initial diffusion weighted image showed areas of subtle diffusion restriction in the right middle cerebral artery (MCA) territory (fig 1A). CT angiography after administration of intravenous tissue plasminogen activator demonstrated right distal MCA stem occlusion (fig 1B). Intra-arterial thrombolysis was attempted 4 h after the onset of symptoms.

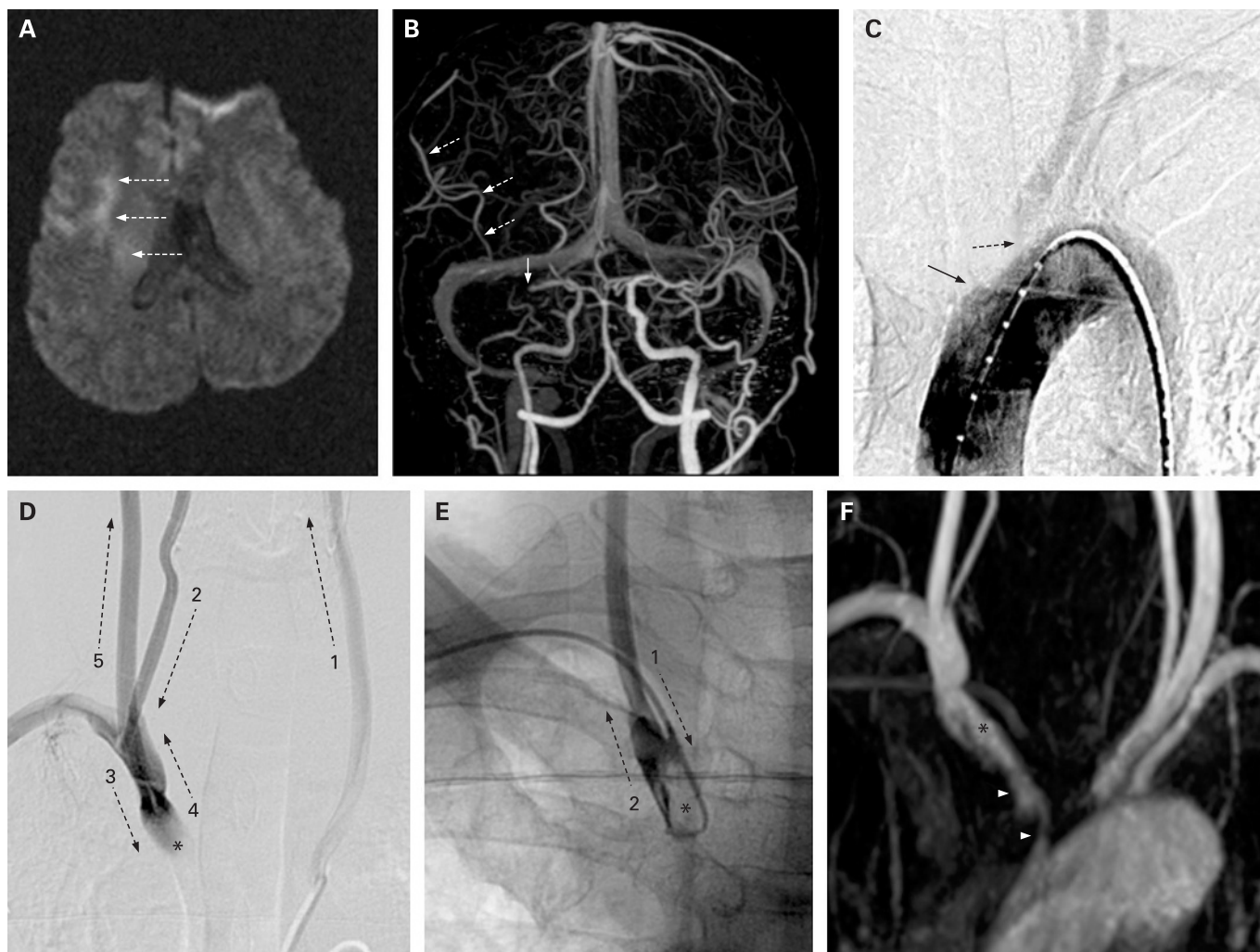


Figure 1 (A) An initial diffusion weighted image shows areas of subtle diffusion restriction at the right insular cortex and corona radiata (broken arrows). (B) CT angiography shows right distal middle cerebral artery stem occlusion (arrow) and leptomeningeal collaterals (broken arrows). (C) There was complete obstruction of the right brachiocephalic trunk at its origin (arrow), and tight stenosis at the left common carotid artery origin (broken arrow). (D) Contrast agent filled (in order) the left vertebral artery (arrow 1), the right vertebral artery (arrow 2), the right subclavian artery (arrow 3), the right brachiocephalic trunk (*) and the right common carotid artery (arrows 4, 5). (E) Angiography via brachial access (arrow 1) showed a thrombus of an innominate artery origin (*) and flow into the right common carotid artery (arrow 2). (F) The thrombus lodged at the right brachiocephalic trunk disappeared (*) and the underlying atheroma (white arrowheads) was detected at the right brachiocephalic trunk on magnetic resonance angiography 4 days after symptom onset.

Supplementary Table S1 Patient characteristics (n=118)

Gender (men / women)	64 (54%) / 54 (46%) ^a
Age (years)	63.9 (9.6; 41-82) ^b
Body Mass Index	24.8 (3.7; 15.6-36.8) ^b
Time since PD diagnosis (years)	8.4 (5.7; 0.4-30.7) ^b
Daily dopaminergic anti-PD medication ^{d, e}	780 (518, 1110; 0-5580) ^c
Hoehn & Yahr stage of PD during "on" (I-V) ^f	II (II, III; I-IV) ^c
Hoehn & Yahr stage of PD during "off" (I-V) ^f	III (II, III; I-V) ^c
MMSE score (0-30) ^g	29 (28, 30; 23-30) ^c
UPDRS III, motor score during "on" (0-108) ^h	17 (10.5, 27; 1-50) ^c
UPDRS IV, dyskinesia score (0-13) ^h	1 (0, 3; 0-10) ^c
UPDRS IV, fluctuation score (0-7) ^h	1 (0, 2; 0-5) ^c
Thought disorder (item 2, UPDRS I) (0-4) ^h	0 (0, 1; 0-3) ^c
Motivation (item 4, UPDRS I) (0-4) ^h	0 (0, 1; 0-3) ^c
Symptomatic orthostasis (item 42, UPDRS IV)	41 (35%) ^a
ESS (0-24) ^h	10 (6, 13; 0-21) ^c
HADS depression (0-21) ^h	5 (3, 7; 0-12) ^c
HADS anxiety (0-21) ^h	5 (3, 8; 0-15) ^c
NHP-Pain (0-100) ^h	14.3 (0, 28.6; 0-100) ^c
PSQI (0-21) ^h	7 (4, 10; 1-18) ^c
Fatigue (FACIT-F) score (0-52) ^h	17.7 (9.9; 0-41) ^b

^a n (%).

^b Mean (standard deviation; min-max).

^c Median (q1, q3; min-max).

^d Expressed as total levodopa equivalent dose: 100 levodopa equivalents = 100 mg standard levodopa = 133 mg controlled-release levodopa = 10 mg bromocriptine = 5 mg ropinirole = 1 mg pramipexole = 1 mg cabergoline = 2 mg apomorphine. For patients who received a COMT-inhibitor, the sum of standard levodopa and 0.75 times the dose of controlled-release levodopa was multiplied by 1.3.

^e Oral levodopa (n=114), oral dopamine agonists (n=77), COMT-inhibitors (n=56), selegiline (n=16), amantadine (n=11), anticholinergics (n=1), intraduodenal levodopa infusion (n=1), and subcutaneous apomorphine infusion (n=3). Three people not receiving levodopa therapy were treated with subcutaneous apomorphine infusion monotherapy, subthalamic nucleus deep-brain stimulation, and pramipexole, respectively; the fourth person was not yet on any medical anti-parkinsonian therapy. Eight people had undergone neurosurgical interventions for their PD.

^f Range, I-V (I = mild unilateral disease; II = Bilateral disease without postural impairment; III = Bilateral disease with postural impairment, moderate disability; IV = Severe disability, still able to walk and stand unassisted; V = Confined to bed or wheelchair unless aided).

^g High scores = less problems.

^h High scores = more problems.

PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; NHP, Nottingham Health Profile; PSQI, Pittsburgh Sleep Quality Index; MMSE, Mini-Mental State Exam; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue scale.

Supplementary Table S2Bivariate associations between fatigue (FACIT-F scores) and other variables (n=118)^a

	Spearman correlations with fatigue	
	r_s	P-value
Age	0.227	0.013
Body Mass Index	0.049	0.601
Time since PD diagnosis	0.231	0.012
Daily levodopa equivalent dose ^b	-0.002	0.986
Daily levodopa dose	0.105	0.259
Daily bromocriptine dose	-0.035	0.707
Daily ropinirole dose	0.130	0.160
Daily cabergoline dose	-0.061	0.512
Daily pramipexole dose	-0.257	0.005
Daily entacapone dose	0.025	0.786
Daily selegiline dose	0.152	0.099
Daily amantadine dose	-0.137	0.141
MMSE score (0-30) ^c	-0.192	0.038
UPDRS III, motor score (0-108) ^d	0.311	0.002
UPDRS IV, dyskinesia score (0-13) ^d	0.164	0.078
UPDRS IV, fluctuation score (0-7) ^d	0.156	0.095
ESS (0-24) ^d	0.302	0.001
HADS depression (0-21) ^d	0.545	<0.001
HADS anxiety (0-21) ^d	0.536	<0.001
NHP-Pain (0-100) ^d	0.343	<0.001
PSQI (0-21) ^d	0.347	<0.001

^a FACIT-F scores were reversed so that low scores indicate less fatigue.^b Expressed as: 100 levodopa equivalents = 100 mg standard levodopa = 133 mg controlled-release levodopa = 10 mg bromocriptine = 5 mg ropinirole = 1 mg pramipexole = 1 mg cabergoline = 2 mg apomorphine. For patients who received a COMT-inhibitor, the sum of standard levodopa and 0.75 times the dose of controlled-release levodopa was multiplied by 1.3.^c High scores = less problems.^d High scores = more problems.

FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue scale; PD, Parkinson's disease; MMSE, Mini-Mental State Exam; UPDRS, Unified Parkinson's Disease Rating Scale; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale; NHP, Nottingham Health Profile; PSQI, Pittsburgh Sleep Quality Index.

Supplementary Table S3 Group wise comparisons of fatigue (FACIT-F scores)

		Mean (SD) FACIT-F score	P-value ^a
Gender	Female (n=54)	33.4 (10.2)	0.374
	Male (n=64)	35.0 (9.6)	
Sleep medicine	Yes (n=18)	30.8 (10.1)	0.110
	No (n=100)	34.9 (9.7)	
Thought disorder (UPDRS I, item 2)	Score 0 (n=63)	37.2 (9.9)	0.001
	Score >0 (n=53)	31.3 (8.6)	
Motivation (UPDRS I, item 4)	Score 0 (n=62)	37.9 (8.7)	<0.001
	Score >0 (n=54)	30.6 (9.5)	
Symptomatic orthostatism (UPDRS IV, item 42)	Yes (n=41)	31.9 (10.3)	0.031
	No (n=75)	35.9 (9.2)	

^a Independent samples t-test.

FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue scale;
UPDRS, Unified Parkinson's Disease Rating Scale.