Prevalence of fatigue in Parkinson disease and its clinical correlates

Fabrizio Stocchi, MD
Giovanni Abbruzzese, MD
Roberto Ceravolo, MD
Pietro Cortelli, MD, PhD
Marco D'Amelio, MD
Maria F. De Pandis, MD, PhD
Giovanni Fabbrini, MD
Claudio Pacchetti, MD
Gianni Pezzoli, MD
Alessandro Tessitore, MD, PhD
Margherita Canesi, MD
Claudio Iannacone
Mario Zappia, MD
For the FORTE Study Group

Correspondence to Dr. Stocchi: fabrizio.stocchi@sanraffaele.it

ABSTRACT

Objective: To assess in a noninterventional setting the prevalence and severity of fatigue in patients with Parkinson disease (PD).

Methods: This was a cross-sectional study conducted in Italian patients with PD. Objectives included the evaluation of the current prevalence and severity of fatigue in patients with PD measured using the 16-item Parkinson Fatigue Scale (PFS-16), distressing fatigue (defined as a PFS-16 mean score ≥3.3), and assessment of its clinical correlates.

Results: A total of 402 patients were enrolled and 394 patients completed the PFS-16 questionnaire with a PFS-16 mean (±SD) score of 2.87 ± 0.99. Of these, 136 patients (33.8%) reported distressing fatigue (PFS-16 mean score ≥3.3). Patients with distressing fatigue were older ($p = 0.044$) and had a longer duration of PD ($p < 0.0001$) than those without distressing fatigue. The presence of distressing fatigue was associated with higher total Unified Parkinson's Disease Rating Scale (UPDRS) scores, poorer quality of life (39-item Parkinson's Disease Questionnaire [PDQ-39]), worse social and psychological behaviors, a higher severity of depressive symptoms, and a higher prevalence of sleep disorders (all $p < 0.001$). Logistic regression analyses revealed that higher total UPDRS scores, female sex, depression, sleep disorders, as well as higher UPDRS activities of daily living scores and PDQ-39 mobility scores increase the likelihood of distressing fatigue in patients with PD.

Conclusions: Approximately one-third of patients with PD have distressing fatigue, which is significantly associated with depression and sleep disorders. The fact that the presence of fatigue worsens patient quality of life supports the need to better diagnose and treat this debilitating symptom. ***Neurology*® 2014;83:215–220**

GLOSSARY

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; ***ICD-10*** = *International Classification of Diseases, 10th revision*; **MAO-B** = monoamine oxidase B; **MS** = multiple sclerosis; **PD** = Parkinson disease; **PDQ-39** = 39-item Parkinson's Disease Questionnaire; **PDSS** = Parkinson's Disease Sleep Scale; **PFS-16** = 16-item Parkinson Fatigue Scale; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Fatigue is a nonspecific symptom common to several CNS disorders. According to *ICD-10*, signs and symptoms of fatigue include asthenia, debility, general physical deterioration, lethargy, and tiredness.[1] Although previously overlooked in Parkinson disease (PD), fatigue is now accepted to be one of the most common PD symptoms with a reported prevalence between 33% and 58%.[2] Not only is the prevalence of fatigue higher than the age-matched population,[3] the fatigue experienced in PD seems to be qualitatively different from that experienced by the general population.[2,4] Fatigue is often considered by patients with PD to be one of the most disabling symptoms affecting daily activities[5,6] and quality of life.[7–10]

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From the Institute of Neurology (F.S.), IRCCS San Raffaele Pisana, Rome; Section of Neurology (G.A.), DINOGMI, University of Genoa; Department of Neuroscience (R.C.), University of Pisa; IRCCS Institute of Neurological Sciences of Boulogne (P.C.), Department of Biomedical and Neuromotor Sciences (DIBINEM), Alma Mater Studiorum, University of Boulogne; Department of Experimental Biomedicine and Clinical Neurosciences (M.D.), University of Palermo; Parkinson Operative Unit (M.F.D.P.), San Raffaele Institute, Cassino (FR); Department of Neurology and Psychiatry (G.F.), and IRCSS Neuromed, La Sapienza University of Rome; Parkinson's Disease and Movement Disorders Unit (C.P.), IRCCS Neurological National Institute C. Mondino, Pavia; Parkinson Institute (G.P., M.C.), I.C.P., Milan; Department of Neurology (A.T.), Second University of Naples; LB Research (C.I.), Cantù (CO); and Department G.F. Ingrassia (M.Z.), Neurosciences Area, University of Catania, Italy.

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Despite the advances made in our understanding of fatigue in PD, several important questions remain. First, what is the prevalence of this symptom in patients with PD treated in routine clinical practice? Most studies have been limited in size and inclusion criteria, and have not had fatigue as the focus of the investigation. Moreover, previous studies have not consistently evaluated the severity of the fatigue. Second, little is known about whether there are any clinical correlates that may be associated with the presence of fatigue. For example, whereas a number of studies did not find any direct relationship between disease severity and fatigue,[11,12] others indicate that the severity of the fatigue increases with disease progression.[13,14] The aims of this study were to assess, in a noninterventional epidemiologic setting, the prevalence and severity of fatigue in patients with PD and its clinical correlates.

METHODS

Standard protocol approvals, registrations, and patient consents. This was an observational, cross-sectional, multicenter study, conducted in 27 sites in Italy between March and June 2011. The study protocol was approved by the ethics committee of the coordinating center (Comitato Etico dell IRCCS San Raffaele Pisana, Rome, Italy) and by the reference local ethic committees of each of the participating sites. The study was undertaken in accordance with Good Clinical Practice and the provisions of the International Conference on Harmonization, with all patients providing written informed consent.

Patients. To emulate the real-world general PD population, this study recruited outpatients (male or female, aged 18 years or older) with a confirmed diagnosis of idiopathic PD according to Brain Bank diagnostic criteria,[15] attending routine neurology clinics at the participating sites. Patients could be receiving any medication for PD and comorbidities. Exclusion criteria included the following: any type of dementia (*DSM-IV* criteria), congestive heart failure, other severe cardiopathy, severe liver disease/cirrhosis, severe renal insufficiency/dialysis, severe respiratory insufficiency, and other conditions known to cause or influence fatigue, including severe anemia, severe hypothyroidism, and severe diabetes (severity according to investigator judgment, no cutoff values specified).

Assessments. The study plan included a single visit during which all information was collected. Clinical data included patient demographics, medical history (onset and duration of PD), presence of comorbidities and associated treatments, severity of PD according to the modified Hoehn and Yahr scale, severity of key motor symptoms (resting tremor, rigidity, bradykinesia, gait disturbance) as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS, version 3) during the *on* phase, total UPDRS scores (sum of parts I, II, and III), quality of life as assessed by the 39-item Parkinson's Disease Questionnaire (PDQ-39) and the Psychological Well-being Scale, depression assessed by the Beck Depression Inventory, and sleep disorders assessed by the Parkinson's Disease Sleep Scale (PDSS).

Fatigue was assessed using the 16-item Parkinson's Fatigue Scale (PFS-16), which was developed for use in routine clinical practice and has been recommended for screening and suggested for rating the severity of fatigue.[16,17] The PFS is a 16-item, patient-rated scale that encompasses the physical aspects of fatigue and their impact on patients' daily functioning. Item scores range from 1 (strongly disagree) to 5 (strongly agree), with the PFS-16 mean score being calculated as the mean of all individual item scores (range: 1.0–5.0).[16] During the development process, the scale developers found that a threshold PFS-16 mean score $\geq$3.3 was able to differentiate between patients who perceived their fatigue to be distressing (patients were asked if they found their fatigue to be a problem) and those who did not find their fatigue to be distressing with a sensitivity of 84.7% and a specificity of 82.1%.[17] In accordance with this finding, we used a threshold PFS-16 mean score of 3.3 to define the presence of distressing fatigue in our study.

Statistical analysis. The sample size of at least 380 patients for this study was estimated according to the number of exploratory variables clinically relevant to be included in the logistic regression analysis (number of subjects = [number of variables $\times$ 10]/event rate) plus a 20% missing data rate in the covariance data matrix. There were 9 exploratory variables included in the multivariate analysis and the estimation assumed that the rate of patients with a significant correlation between the degree of fatigue (PFS-16 score) and the PD severity (Hoehn and Yahr score) would be $\geq$30%.

Data analyses were performed in the overall evaluable population defined as all patients enrolled in the study. Continuous variables were summarized by descriptive statistics and categorical variables were summarized using counts of patients and percentages. Comparisons between patients with and without fatigue were made using χ^2 test or Fisher exact test for qualitative variables and the nonparametric Mann-Whitney test for quantitative variables.

A preplanned logistic regression analysis was used to assess the factors associated with fatigue in PD; confidence intervals were derived using the Wald method. A binary dependent variable of fatigue was assigned a value of 0 when the PFS-16 mean score was $<$3.3 and value of 1 when the score was $\geq$3.3. The following preplanned covariates were included in the logistic model: age, sex, marital status (married vs other status), duration of PD, total UPDRS score, severity of PD (Hoehn and Yahr stages 1–2 vs stages 3–4), depression (presence vs absence), sleep disorders (presence vs absence), and daytime sleepiness (item 15 of the PDSS; presence vs absence). In addition, a second post hoc logistic regression analysis was performed that included all of the variables of the first model plus PDSS, UPDRS, PDQ-39, and Beck Depression Inventory questionnaire scores, age at PD diagnosis, and geographical area. A backward procedure with a cutoff of $p = 0{\cdot}10$ was applied to select the variables that were to be removed from the model.

No missing data were replaced. All statistical tests were performed at the $p \leq 0.05$ level (2-sided). Statistical analyses were performed using the SAS System version 9.2 (SAS Institute, Cary, NC).

RESULTS

Total population. A total of 402 patients were screened and all were eligible for inclusion into the study; the main patient demographic and clinical characteristics are summarized in table 1. The study cohort included more men than women (60.9% vs 39.1%) and a large proportion of patients (37.6%) were older than 70 years. Approximately three-quarters

Table 1 Demographic and clinical characteristics of the total sample

Characteristic	Value
Age, y (n = 402), mean ± SD (range)	66.9 ± 8.9 (37–89)
Duration of PD, y (n = 394), mean ± SD (range)	7.5 ± 5.6 (1–40)
PFS-16 score (n = 394), mean ± SD (range)	2.87 ± 0.99 (1–5)
Sex (n = 402), women; men, n (%)	157 (39.1); 245 (60.9)
Hoehn and Yahr stage (n = 402), n (%)	
1	94 (23.4)
2	202 (50.2)
3	96 (23.9)
4	10 (2.5)
Education, n (%)	
None/first level	116 (29.4)
Secondary level	124 (31.5)
High school	110 (27.9)
University	44 (11.2)
Current PD medications (n = 394), n (%)	
Not treated	1 (0.3)
Amantadine	21 (5.3)
Anticholinergics	13 (3.3)
COMT inhibitors	100 (25.4)
Dopamine agonists	280 (71.1)
Levodopa	306 (77.7)
MAO-B inhibitors	153 (38.8)
Comorbidities >5% of evaluable population (n = 394), n (%)	
Any	278 (70.6)
Hypertension	143 (36.3)
Depression	46 (11.7)
Benign prostatic disorder[a]	39 (15.9)
Hypercholesterolemia	29 (7.4)
Diabetes mellitus	26 (6.6)
Cardiomyopathy	21 (5.3)

Abbreviations: COMT = catechol-*O*-methyltransferase; MAO-B = monoamine oxidase B; PD = Parkinson disease; PFS-16 = 16-item Parkinson's Fatigue Scale.
The total sample includes 402 patients, 394 of whom completed the PFS-16.
[a] Men only.

of patients (73.6%) were in Hoehn and Yahr stages 1–2 and all but one patient were taking antiparkinsonian medication. The majority of patients received treatment with levodopa and/or a dopamine agonist; 9 patients (3.5%) were receiving monoamine oxidase B (MAO-B) monotherapy. In addition, 30 patients received concomitant antidepressants (mostly selective serotonin reuptake inhibitors) and 21 patients were being treated with amantadine.

Presence of fatigue. Overall, 394 patients completed the PFS-16 questionnaire; of these, 136 patients (33.8%) reported distressing fatigue (PFS-16 mean score ≥3.3 points). For the total population, the mean ± SD PFS-16 score was 2.87 ± 0.99. In patients with distressing fatigue, mean scores for all PFS-16 items were higher than 3.3. The items with the highest mean score were as follows: "Because of fatigue, it takes me longer to get things done," "I get tired more quickly than other people I know," "If I was not so tired, I could do more things," and "I have to rest during the day."

Fatigue vs nonfatigue subgroup comparisons. Comparisons between patients with distressing fatigue vs those without distressing fatigue showed that patients with distressing fatigue were older (68.0 ± 9.2 vs 66.3 ± 8.7 years; $p = 0.044$) and had a longer duration of PD (9.1 ± 6.4 vs 6.6 ± 5.0 years; $p < 0.001$). However, the mean age at diagnosis did not differ between the 2 subgroups. Marital status had no significant effect on the presence of distressing fatigue; however, the distribution of educational level by category of fatigue showed that patients with lower educational status (no education or secondary school level) were more likely to have a PFS-16 mean score ≥3.3 points (35.3% and 36.0%, respectively) than a score <3.3 points (26.4% and 29.1%, respectively). Conversely, patients with a high school or university education were more predominant among those with a PFS-16 mean score <3.3 points (31.4% and 13.2%, respectively) than among those with a score ≥3.3 points (21.3% and 7.4%, respectively). The difference in the distribution of educational level between fatigue subgroups was statistically significant ($p = 0.021$).

The presence of distressing fatigue was associated with increased total UPDRS scores, a poorer quality of life, worse sensations of psychological well-being, a higher severity of depressive symptoms, and a higher prevalence of sleep disorders (nocturnal sleep problems and daytime sleepiness) (table 2). Further analysis of each of the key UPDRS motor symptoms revealed that patients with distressing fatigue had higher scores for all motor symptoms assessed ($p < 0.001$), with the exception of tremor at rest and rigidity in the lower joints. Similarly, patients with distressing fatigue were more likely to have mild to moderate or moderate to severe depressive symptoms, while patients without distressing fatigue were more likely to have absence/denial of or minimal depressive symptoms ($p < 0.001$). Patients with distressing fatigue were also more likely to have very severe, severe, or moderate daytime sleep disorders, while patients without distressing fatigue were more likely to have mild/absent daytime sleep disorders ($p < 0.001$).

There were no substantial differences in PFS-16 mean scores when comparing patients taking different antiparkinsonian medications. However, a review (descriptive data only) of the different treatment combinations indicated that there was a lower proportion

Table 2 Factors associated with distressing fatigue

	PFS-16 <3.3	PFS-16 ≥3.3	*p* Value
Total UPDRS score	28.8 ± 15.5	43.9 ± 20.6	<0.0001
PDQ-39 score	45.7 ± 12.3	64.1 ± 14.7	<0.0001
PWS score	358.1 ± 44.1	329.5 ± 44.7	<0.0001
BDI score	8.9 ± 6.8	15.6 ± 8.0	<0.0001
Total PDSS score	109.2 ± 24.9	90.8 ± 24.7	<0.0001
PDSS item 15 score (daytime sleepiness)	7.8 ± 2.8	6.5 ± 3.4	<0.001

Abbreviations: BDI = Beck Depression Inventory; PDQ-39 = 39-item Parkinson's Disease Questionnaire; PDSS = Parkinson's Disease Sleep Scale; PFS-16 = 16-item Parkinson's Fatigue Scale; PWS = Psychological Well-being Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
Data are mean ± SD.

of patients taking levodopa plus an MAO-B inhibitor (n = 100) in the fatigued vs nonfatigued subgroup (19.9% vs 28.4%) and also of patients taking a dopamine agonist plus an MAO-B inhibitor (n = 103) (18.4% vs 31.1%). There was no substantial difference in the proportion of patients with or without distressing fatigue taking levodopa plus a dopamine agonist (n = 194) (52.9% vs 47.5%), but the proportion of patients taking levodopa plus the COMT (catechol-*O*-methyltransferase) inhibitor entacapone (n = 100) appeared to be higher in the fatigued vs nonfatigued group (33.1% vs 21.4%).

The proportion of patients with concomitant diseases was slightly higher in patients with distressing fatigue vs those without distressing fatigue (73.5% vs 69.0%), but this difference was not significant (p = 0.416). However, the 2 most common diseases—arterial hypertension and depression—were more prevalent in patients with distressing fatigue than in those without distressing fatigue (44.1% vs 32.2% for hypertension, and 16.2% vs 9.3% for depression, respectively).

Factors associated with fatigue. Preplanned logistic regression analysis (n = 343) showed that total UPDRS scores, female sex, the presence of depression, and the presence of sleep disorders significantly increased the odds of having distressing fatigue in patients with PD (table 3). In the second analysis, performed post hoc (n = 319), higher UPDRS activities of daily living and worse PDQ-39 mobility scores (and none of the other factors analyzed) were found to be predictive of fatigue in PD.

Table 3 Logistic regression analysis of factors associated with fatigue

Covariate	OR	95% Wald confidence limits	*p* Value
Preplanned analyses (n = 343)			
Sex (women)	1.781	1.026-3.092	0.040
Depression (yes)	3.137	1.228-8.012	0.017
Sleep disorders (yes)	1.833	1.050-3.199	0.033
Total UPDRS score[a]	1.039	1.018-1.059	0.0002
Post hoc analyses (n = 319)			
UPDRS, activities of daily living[a]	1.06	1.008-1.124	0.0237
PDQ-39, mobility[a]	1.05	1.034-1.064	<0.0001

Abbreviations: OR = odds ratio; PDQ-39 = 39-item Parkinson's Disease Questionnaire; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] OR can be interpreted as the odds of having fatigue for every 1-unit increase in the predictive factor.

DISCUSSION The results of this large Italian study confirm that fatigue is common in outpatients with PD being treated in routine practice and is considered distressing (defined as PFS-16 mean score ≥3.3 points) in approximately one-third of them. Subgroup comparisons showed that the presence of distressing fatigue was associated with increased disease severity, a poorer quality of life, worse social and psychological behaviors, a higher severity of depressive symptoms, and a higher prevalence of nocturnal sleep disorders and daytime sleepiness.

The prevalence of fatigue in patients with PD in this study appears somewhat lower than that observed in most other studies.[4,8,11,18] However, the literature shows a wide range of prevalence of fatigue in PD according to the different definitions of fatigue and the populations tested. Unlike other surveys, which simply looked for the presence and absence of this symptom, our study purposefully used a higher cutoff score (PFS-16 mean score of 3.3) to better identify the prevalence of fatigue that patients with PD find "distressing."[17] This probably lowered the percentage measured. Fatigue is a subjective experience; what one person finds difficult to live with, another might better cope with. In this respect, it is pertinent to note that the PFS-16 mean score for the total population was 2.87, indicating that while one-third of patients (33.8%) reported distressing fatigue (score >3.3), a higher percentage probably had some fatigue present but believed that they could cope with it. In addition, we also acknowledge that the PFS-16 focuses on the physical aspects of fatigue and therefore may have

underestimated clinically relevant emotional, cognitive, or social aspects of fatigue.[16]

While it is generally held that there is no relationship between the severity of motor dysfunction and fatigue,[2] the results of this study showed that higher total UPDRS, UPDRS activities of daily living, and PDQ-39 mobility scores were all associated with fatigue, and that scores for individual motor items were consistently higher in patients with distressing fatigue compared to those without. These findings indicate that fatigue worsens with the underlying disease progression, and are in agreement with recent studies conducted in Italy[19] and in Norway.[3] This study did not specifically assess whether the presence of motor complications increased the likelihood of distressing fatigue, but it might be expected because the prevalence of motor complications also increases with disease duration and severity.[20] Notably, the Norwegian study also found that female sex is predictive of fatigue.[3] It is not clear why women might be more prone to fatigue than men; however, studies conducted in patients affected by psychiatric disorders have also found that the prevalence of fatigue is higher in women.[21] Similarly, while it is unclear why patients with PD who have a lower educational status may be more likely to have distressing fatigue, studies of fatigue in multiple sclerosis (MS) have also reported a strong correlation.[22]

This study serves to highlight the need to identify and treat fatigue in PD. However, the management of fatigue in PD still poses a significant problem in clinical practice. For example, a study conducted in a movement disorders center found that neurologists failed to identify fatigue in more than half of the cases and that the diagnostic accuracy for this symptom was only 25%.[23] The pharmacologic treatment of fatigue in PD is also difficult, but clinical studies have shown that treatment with levodopa[24] and methylphenidate[25] can improve fatigue. Results for the MAO-B inhibitor rasagiline have been mixed, with one randomized trial showing a benefit[26] whereas another smaller study failed to find a significant effect.[27] Other studies in patients with PD have found that fatigue is not influenced by dopamine agonists.[28] In our study, there were no substantial differences in PFS-16 mean scores when grouping patients according to their current antiparkinsonian medications. This is in line with previous studies that have found that the level of fatigue between drug-naive patients and those treated with antiparkinsonian agents was similar.[29] However, in our study, proportionately more patients without distressing fatigue (n = 153) were taking an MAO-B inhibitor with either levodopa or a dopamine agonist than in the fatigued group (n = 52). By contrast, the proportion of patients taking levodopa plus entacapone was higher in the group of patients with fatigue compared with the group without distressing fatigue. It is important to note, however, that the levodopa plus entacapone combination was used more frequently in patients with more severe PD, while the rate of patients treated with levodopa and an MAO-B inhibitor did not substantially differ between PD severity grades.

Despite the reported strong correlation of distressing fatigue with depression and sleep disturbances, most studies agree that all 3 are independent symptoms,[2] and there is currently much interest in whether they share pathophysiologic mechanisms. Similar associations are known in patients with MS,[30–32] and the treatment of depression has been shown to improve the symptoms of fatigue in patients with MS.[31] Whether the treatment of fatigue improves depressive symptoms has not been well studied. It is therefore of considerable interest whether management of these common nonmotor symptoms will improve the symptoms of fatigue in patients with PD. Notably, in MS and other diseases, fatigue, sleep disturbances, and depression have also been shown to "symptom cluster" with cognitive impairment,[32] and a limitation of the present study is that it does not address fatigue in patients with PD who have dementia and might have had difficulty in reporting their symptoms of fatigue.

AUTHOR CONTRIBUTIONS

All authors were involved with the study design and data acquisition, analysis and interpretation of the results (steering committee meetings), and all authors critically reviewed drafts and gave approval to the final version of this article. Fabrizio Stocchi produced the first draft of the manuscript and also participated in literature searches and revision of the manuscript. Anita Chadha-Patel (medical writer) assisted with the systematic literature search and editing of the manuscript.

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