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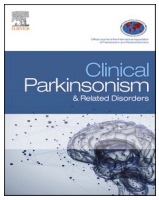

Short Communications

Screening cut-off scores for clinically significant fatigue in early Parkinson's disease

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ABSTRACT

Background: Fatigue is one of the most disabling non-motor symptoms in PD. Researchers have previously used cut-offs validated in non-PD conditions when using the Fatigue Severity Scale (FSS) or the Multidimensional Fatigue Inventory (MFI) scores to evaluate fatigue in PD.
Objective: We used a set of criteria for diagnosing clinically significant fatigue in PD to identify the proper cut-offs of the FSS and MFI.
Methods: One hundred thirty-one PD patients (59F; age 67.3 ± 7.6 y; H&Y 1.6 ± 0.7) were assessed for clinically significant fatigue, followed by the FSS, MFI, Center for Epidemiologic Studies Depression Scale (CES-D), and Montreal Cognitive Assessment (MOCA). Mean scores were compared between 17 patients who met diagnostic criteria (significant fatigue group, SFG) and 114 who did not (non-significant fatigue group, NSFG).
Results: The SFG had significantly higher scores in the 9-item FSS (p <.0001), total MFI score (p <.0001), and every MFI dimension except reduced motivation (p =.1) than the NSFG. Using area under the curve (AUC) of receiver operating characteristic (ROC) analyses, we recommend the following cut-offs: 9-item FSS 37; total MFI 60; general fatigue 11; reduced activity 10; physical fatigue 9; mental fatigue 9; and reduced motivation 9.
Conclusions: The recommended cut-offs for clinically significant fatigue in the FSS, MFI, and MFI dimensions will be valuable for diagnosing clinically significant fatigue and for future studies in investigating pathophysiology and potential treatments of fatigue in PD.

1. Introduction

Fatigue is one of the most common non-motor symptoms reported in Parkinson's disease (PD), ranging from 33 to 70 % of the PD population [1]. Patients report that the fatigue experienced with PD differs from what was experienced before PD, making diagnosis of clinically significant fatigue challenging.

An international task force for PD-related fatigue proposed a set of diagnostic criteria to identify clinically significant fatigue in PD [2]. This diagnostic criteria has been recently validated in an Italian sample, recommending its use for clinical and research applications [3]. However, the authors noted that by using the diagnostic criteria, only 7 % of PD participants met criteria for significant fatigue (compared to 20 % in a similar study by the authors [4]). The discrepancy between PD subjects identified as having significant fatigue using the diagnostic criteria versus rating scales warrants further evaluation.

There are approximately eight possible rating scales used to evaluate fatigue in PD, which further complicates measuring fatigue in clinical and research applications. The FSS and MFI are most commonly used [5]. The FSS is a single-dimensional 9-item inventory scored on a 7-point Likert scale to assess perceptions of fatigue [6]. In various clinical samples, recommended cut-off scores are mean scores between 4 and 5 (total scores of 36 – 45) [4,6,7]. We predicted that in our fatigued PD patients, the cut-off for the FSS will be consistent with previous research in PD patients [4] and will be higher than that which is found with other clinical conditions.

The MFI is a 20-item inventory scored on a 5-point Likert scale and measures five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity [8]. The MFI dimension scores range from 4 to 20 (most severe) and have been credited with reliably measuring fatigue severity in each dimension. However, no MFI cut-off scores have been validated to discriminate between fatigued and non-fatigued PD patients. In various clinical samples, a general score of 13 has been used across all dimensions [9], or

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the medians for the two highest scoring dimensions have been used (e.g., 13 for general fatigue and 10 for reduced activity) [10]. Due to the complexity and independence of fatigue domains in PD [1], we believe that the same cut-off score should not be applied across all domains assessed by the MFI. Rather, it is necessary to determine appropriate cut-off scores for each domain, based on PD patient perceptions.

Since the release of the recommended set of diagnostic criteria [2], one study has sought to use this tool to establish cut-off scores on fatigue assessments [4]. An Italian sample of Parkinson's patients was tested on the 9-item FSS and the Parkinson Fatigue Scale (PFS-16). In the current study, we did not use the PFS-16 because it had less sensitivity to measure the severity of fatigue. The authors found that 20 % of their sample met diagnostic criteria for clinically significant fatigue. The prevalence of significant fatigue using diagnostic criteria was lower compared to rates determined using rating scales.

The purpose of this study was to use these criteria to identify appropriate cut-offs of the Fatigue Severity Scale (FSS) and Multidimensional Fatigue Inventory (MFI) for clinically significant fatigue in PD. We predicted that we would find that by using the new set of diagnostic criteria to determine significant fatigue in PD, cut-off scores for rating scales FSS and MFI will be equal to or more restrictive compared to general standards (predicted cut-off scores: FSS $\geq$ 4; MFI domain $\geq$ 13). Improving methods for defining the threshold upon which PD-related fatigue symptoms become clinically significant will improve both clinical and research applications of current recommended rating scales.

2. Methods

2.1. Participants

We recruited PD patients from the Movement Disorders Clinic at Sanford Health in Fargo, ND. All patients met at least two of the four diagnostic criteria for PD: bradykinesia, tremor, rigidity, and postural instability and were DOPA responders. We excluded participants with comorbid conditions which might cause fatigue. Exclusionary conditions included obstructive sleep apnea, multiple sclerosis, stroke, epilepsy, or severe medical illnesses such as COPD, congestive heart failure, cancer, or renal failure. We also excluded those PD patients with dementia (MOCA $<$ 21) or high depressive symptoms (CES-D $>$ 15). The Sanford Health IRB approved the protocol, and we obtained written informed consent from all patients.

2.2. Experimental protocols

The diagnostic criteria for Parkinson's disease-related fatigue [2] was verbally administered to each participant. Participants who met the diagnostic criteria were designated as the 'significant fatigue group (SFG)'. Those patients who did not meet the diagnostic criteria were designated as the 'non-significant fatigue group (NSFG)'.

We used Hoehn and Yahr staging to assess disease severity. Participants maintained their regular schedule for PD medications. We calculated the levodopa equivalent daily dosage (LEDD) using the conversion formula proposed by Tomlinson and colleagues (e.g., Sinemet: 1 * 600 mg = 600 LEDD) [11]. We measured subjective fatigue using the FSS and MFI. We evaluated depressive symptoms using the Center for Epidemiological Studies-Depression Scale (CES-D) [12], a 20-item validated assessment for depression screening (cut-off: $>$ 15).

2.3. Statistical analysis

We performed the statistical analysis using SPSS version 29.0.1.0 for Mac (IBM SPSS Statistics). All statistical tests were done with alpha = 0.05. Demographic and endpoint means were compared between the groups. Tests for qualitative variables were compared using the chi-square test, and tests for quantitative variables were done using a *t*-test (first testing for equality of variance).

Receiver operating characteristic (ROC) analyses were performed for the SFG and NSFG for MFI Total, five MFI dimensions, and FSS Total. The area under a ROC curve (AUC) quantifies the overall ability of the test to discriminate between those individuals who are fatigued and who are not fatigued and ranges from 0.50 (no diagnostic ability) to 1.0 (perfect diagnostic ability). The ROC curve is created by plotting the true positive rate (sensitivity) as a function of the true negative rate (1-specificity) at various threshold settings. Overall classification was evaluated using the area under the curve and cut-off values were determined using Youden's index, which maximizes the summation of the sensitivity and specificity (sensitivity + specificity – 1).

Table 1
Characteristics of 131 patients with PD.

Demographics (SD)	Overall Sample (N = 131)	Fatigue Group (N = 17)	Non-Fatigue Group (N = 114)
Gender, % Female	45 %	41.2 %	45.6 %
Age, years	67.3 (7.6)	66 (7.7)	67.6 (7.6)
LEDD	735.7 (473.1)	1015.2 (620.9)	694.0 (435.6)
PD Duration, years	5.1 (4.5)	6.4 (3.2)	5.05 (4.6)
H & Y Stage	1.6 (0.7)	1.8 (0.8)	1.6 (0.7)
1 (%)	67 (51.1)	7 (41.2)	60 (52.6)
2 (%)	48 (36.6)	6 (35.3)	42 (36.8)
3 (%)	16 (12.2)	4 (23.5)	12 (10.5)
MOCA	26.1 (2.3)	26.4 (2.3)	26 (2.3)
FSS Total		46.1 (6.1) ***	31.0 (12.2)
FSS Average		5.1 (0.7)***	3.5 (1.4)
MFI Total		61.3 (11.8)***	47 (13.7)
MFI General		13.5 (2.9)***	10.4 (3.2)
MFI Mental		11.9 (3.6)***	8.7 (3.2)
MFI Physical		13.2 (3.9)***	9.9 (3.6)
MFI Reduced Activity		12.8 (3.6)***	9.4 (4.1)
MFI Reduced Motivation		9.9 (2.7)	8.6 (3.1)
CES-D		10.3 (6.1)**	6.61 (4.2)

Abbreviations: CESD- Center for Epidemiological Studies Depression; FSS-Fatigue Severity Scale; H & Y- Hoehn and Yahr; LEDD- Levodopa Equivalent Daily Dosage (Tomlinson et al, 2010); MFI-Multidimensional Fatigue Inventory; MOCA- Montreal Cognitive Assessment.
*Denotes a significant difference between the fatigue and non-fatigue group.
* $p \leq 0.05$ ** $p \leq 0.01$ *** $p \leq 0.001$.

3. Results

3.1. Demographic data

Of the 131 participants who met inclusion criteria, 17 (13 %) met diagnostic criteria for SFG. A comparison of the two groups identified that LEDD was the only demographic which reached marginal significance, with participants in the SFG group treated with a higher LEDD (M = 1015) compared to participants in the NSFG (M = 694; p =.054). Table 1 compares participant characteristics for the two groups. The SFG and the NSFG were not significantly different in gender (p =.73), PD duration (p =.22), or H &Y disease severity (p =.30).

3.2. Determining the cut-offs in the MFI and the FSS for clinically significant fatigue in PD

Table 1 compares mean scores for the subjective assessments of FSS, five dimensions of MFI, and CES-D between the two fatigue groups. The SFG had significantly higher scores in the 9-item FSS (p $<$.0001), total MFI score (p $<$.0001), MFI-Reduced Activity (p =.001), and MFI-General, Mental, and Physical Fatigue (p $<$.0001) compared to the NSFG. The severity of depressive symptoms (CES-D; p =.002), was also greater for the SFG than the NSFG. There was no significant difference

Table 2
Receiver Operating Characteristics for Each Cut-off.

Assessments	AUC (95 % CI)	Youden's J	Sensitivity	Specificity	*p*	Cut-off
FSS Total	0.869 (0.808-0.930)	0.719	1.0	0.719	<0.0001	37
MFI Total	0.786 (0.678-0.894)	0.472	0.647	0.175	<0.0001	60
MFI General	0.754 (0.632-0.877)	0.365	0.882	0.482	0.001	11
MFI Mental	0.752 (0.631-0.872)	0.450	0.941	0.509	0.001	9
MFI Physical	0.731 (0.609-0.853)	0.336	0.941	0.395	0.002	9
MFI Reduced Activity	0.740 (0.631-0.849)	0.370	0.765	0.605	0.001	10
MFI Reduced Motivation	0.633 (0.501-0.764)	0.232	0.706	0.526	0.078	9

Abbreviations: AUC- Area under the curve; FSS-Fatigue Severity Scale; MFI-Multidimensional Fatigue Inventory.
Youden's index is used to determine optimal thresholds for diagnostic tests; the value is out of 1.
The *p*-value indicates the significance between the AUC for each assessment compared with a null hypothesis (AUC = 0.5).

between the two groups for MFI-Reduced Motivation (p =.1) or MOCA (p =.55).

Using ROC analysis, we used the diagnostic criteria for PD-related fatigue to guide cut-offs for the FSS, total MFI, and dimensions within the MFI (see Table 2). We recommend the following cut-offs: 9-item FSS 37; total MFI 60; physical fatigue 9; mental fatigue 9; reduced motivation 9; reduced activity 10, and general fatigue 11.

4. Discussion

Few studies have used the new set of diagnostic criteria [2] to evaluate clinically significant fatigue in PD. Our findings indicated that our prediction for the FSS was supported, yielding a cut-off score (≥37) that was more restrictive (≥36) than the value typically used in clinical and research applications. However, we found that our prediction was not met for the MFI, yielding cut-off scores that were less restrictive (<13) or comparable (reduced activity) compared to previous research.

Our cut-off score for PD patients on the 9-item FSS was more restrictive than what has been established in other clinical groups, but was less than the cut-off of 42 (average of 4.67) proposed by Siciliano and colleagues [4]. The 5-point difference between the current study and that by Siciliano et al. highlights the challenge of evaluating symptoms of fatigue in PD. It is important to note that the aforementioned study used an Italian sample whereas the current sample consists of PD patients from the Midwest region of the United States. The two samples show similar age, gender distribution, disease duration, and H&Y, reflecting a relatively young, newly diagnosed, predominately male sample. However, the samples did show larger differences in LEDD total (472.86 Italian sample versus 735.7 U.S. sample) and cognitive function measured using the MOCA (21.27 Italian sample versus 26.1 U. S. sample). These differences should not be ignored as levodopa and cognitive impairment have both been considered as having an association with fatigue.

Our cut-off scores for PD patients on the MFI dimensions were different from the findings in previous research on chronic fatigue syndrome (CFS) and normal controls. Reeves et al. [10] used the median for the two highest scoring dimensions of the MFI to define severe fatigue: general fatigue (≥13) and reduced activity (≥10). Recent studies have used Reeve's findings as a guide for evaluating significant fatigue in PD or have used a cut-off of 13 across all MFI dimensions [9]. Our proposed cut-offs (ranging from 9 to 11) are several points lower than 13. These findings suggest that mean scores of the MFI for a selected sample are too stringent for the evaluation of clinically significant fatigue in PD. Additionally, a single cut-off value should not be used to generalize across all MFI dimensions.

The FSS showed improved ability compared to the MFI to define the threshold in which fatigue in PD becomes clinically significant (AUC = 0.869 and 0.786, respectively). The FSS continues to be a measure *recommended* for the evaluation of fatigue severity [3–5]. The MFI was recently rated as a method *suggested* for the evaluation of fatigue severity [5]. Although the FSS had a larger AUC than the MFI, indicating improved ability to differentiate between those with significant fatigue from those without fatigue, we acknowledge that it may be more appropriate to use an assessment that addresses the multidimensional properties of fatigue. As noted in the recent review of all non-motor assessments, there is a lack of data on the reliability of the MFI in the PD population. The MFI continues to be used in research application with PD patients and therefore warrants further testing on the validity and reliability of the assessment.

In conclusion, our study evaluated appropriate cut-offs for the MFI and FSS for clinically significant fatigue in PD using a set of diagnostic criteria [2]. The patients with clinically significant fatigue had higher scores of depression, were prescribed higher LED dosages, and showed increased fatigue in all dimensions except for reduced motivation. The consequences of fatigue are great and it can affect quality of life in PD patients and can lead to the need to disability services and early retirement. Identifying the appropriate cut-offs in the MFI and FSS for clinically significant fatigue will facilitate diagnosis of significant fatigue in PD and future research in the pathophysiology and treatment of fatigue.

Author contributions

AXAH and JSL conceived the research and designed the experiment. AXAH and TP performed data acquisition and statistical analysis. AXAH drafted the manuscript. AXAH and JSL interpreted results. All authors read, edited, and approved the final manuscript for publication.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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