MOTOR FLUCTUATIONS EVALUATED BY CLINICAL ASSESSMENTS AND SELF-REPORTS IN PARKINSON'S DISEASE. A WAKING-DAY MONITORING STUDY

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INTRODUCTION

L-dopa represents the most efficacious treatment for Parkinson's disease (PD). With disease progression, patients start to experience a range of L-dopa- induced complications (L-dopa induced motor fluctuations) (1-5). L-dopa induced complications occur because of a number of factors, including the peripheral and central pharmacokinetics as well as pharmacodynamics of L-dopa, resulting in pulsatile dopamine receptor stimulation and altered basal ganglia signaling pathways (3,5-7). Wearing-off (WO), defined by some authors as a generally predictable recurrence of motor symptoms preceding scheduled doses of antiparkinsonian medication that usually improve post-dosing (8-9), represents the earliest and most common manifestations of motor fluctuations (3). Proper identification of WO leads to optimal treatment in PD patients and several clinical tools have been proposed to detect wearing-off only or, in general, the different types of motor fluctuations. The Movement Disorder Society task force conducted a systematic review to identify wearing-off scales that have either been validated or used in Parkinson's patients (9). The Unified Parkinson's Disease Rating Scale section IV (UPDRS-IV) is the most used screening tool to detect motor fluctuations in both clinical practice and research and, despite the Movement Disorders lack of clinimetric validation, is considered a "suggested" tool for the rating of severity of wearing-off according to this systematic review (9).

AIMS

The aim of this study was to assess sensitivity and specificity of UPDRS-IV (items 36-38) as screening tool for motor fluctuations and wearing-off, using a 12- hours waking-day motor assessment as gold standard.

MATERIALS AND METHODS

Clinical Assessment: PD patients, according to the UK Brain Bank criteria (10), who underwent a 12-hours waking-day motor assessment were consecutively enrolled in the study. To objectively assess motor fluctuations due to dopaminergic therapy a diurnal 12- hours waking day motor assessment (WDMA) was performed.
Patients were evaluated from 8 am at baseline condition (in "practical-off" motor state, before taking the first daily dose of the dopaminergic drug after an overnight wash-out) and every 2 hours until 8 pm. At each time-interval the motor impairment was evaluated using the motor section of the UPDRS (UPDRS-III) (12). The UPDRS-IV was administered in order to assess the presence of predictable and unpredictable motor fluctuation according to the items 36-38. Motor scores were reported as line graph, as shown in fig 1. To detect motor (MF) and non-motor fluctuations (NMF), the Italian version of the Wearing Off Questionnaire-19 (WOQ-19, 13) was performed by patients under optimal clinical conditions. Six blinded raters classified patients as having or not motor fluctuations.
Statistical analysis:. We evaluated the sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) considering all types of predictable and unpredictable motor fluctuations (at least one positive item among the items 36-38) and also considering only the wearing-off that represents the most frequent type of motor fluctuation (a positive answer at the item 36 specific for predictable motor fluctuation). The waking day monitoring was used as gold standard. 95% Confidence Intervals (CI) have been also computed.

RESULTS

Sixty-two PD patients underwent a 12- hours waking-day motor assessment and were enrolled in the study. Baseline characteristics of PD patients are shown on table 1.
According to the raters evaluation 39 (62.9 %) out of the 62 patients were classified as having a motor fluctuation during the 12-hours waking-day motor assessment. Presence of motor fluctuations was associated with disease duration, UPDRS-III score, L-dopa duration of treatment, presence and severity of l-dopa induced dyskinesias as shown on table 1.

According to the raters evaluation wearing-off was the most common motor fluctuation recorded in 37 (94.9 %) out of the 39 PD fluctuating patients. On the other hand according to the items 36-38 of the UPDRS section IV, 48 PD patients (77.4%) were classified as having a motor fluctuation (predictable or unpredictable). Sensitivity and specificity of the UPDRS-IV are shown on table 2.

Thirty-three patients also completed the WOQ-19 and sensitivity was 84.2 % (95% CI 60.4-96.6) and specificity was 28.6% (CI 95% 8.93-58.1).

Figure 1. Graphical representation of a 12- hours waking-day motor assessment

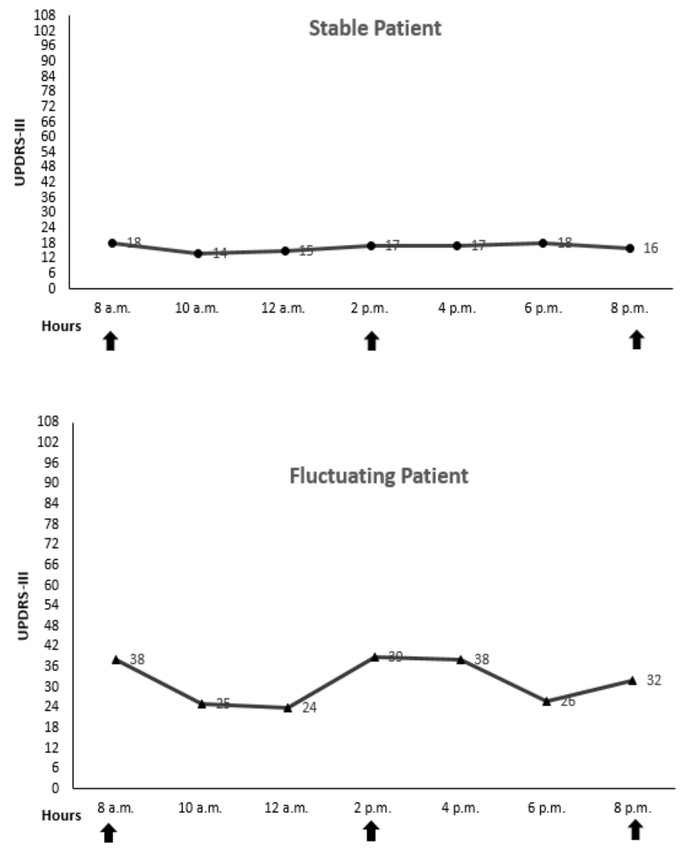

Table 1: Baseline characteristics of the enrolled PD patients

	62 Patients Mean ± SD*	Fluct (N=39) Mean ± SD	Stable (N=23) Mean ± SD	*p-value*
Age (years)	66.1 ± 8.3	66.7 ± 8.4	65.0 ± 8.1	0.4
Mean Age at onset (years)	58 ± 10.0	57.6 ± 10.2	58.8 ± 9.9	0.6
Disease Duration (years)	8.0 ± 5.1	9.1 ± 4.7	6.3 ± 5.3	**0.03**
MMSE	26.7 ± 2.6	27 ± 2	26.2 ± 3.5	0.2
L-dopa therapy duration (years)	6.6 ± 4.8	7.56 ± 4.5	4.91 ± 5.1	**0.04**
LED(mg)**	578.5 ± 279.2	622.1 ± 304.8	504.6 ± 216.0	0.1
Hoehn-Yahr	2.5 ± 0.7	2.6 ± 0.7	2.3± 0.6	**0.05**
UPDRS-I	2.8 ± 2.0	2.8 ± 2.0	2.65 ± 2.1	0.7
UPDRS-II	12.9 ± 5.3	14.3 ± 5.6	10.6 ± 3.9	**0.007**
UPDRS-IV	4.6 ± 2.9	5.7 ± 2.6	2.87 ± 2.4	**0.0001**
UPDRS-III (Off)	34.0 ± 11.8	37.5 ± 12.3	28.1 ± 8.2	**0.002**

*SD: Standard Deviation; **LED: levodopa equivalent dose.

Table 2. Sensitivity, specificity, PPV and NPV of the UPDRS section IV

	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
	%	95%CI	%	95%CI	%	95%CI	%	95%CI
Motor Fluctuation (Item 36-38)	87.2	72.6-95.7	43.5	23.2-65.5	72.3	57.4-84.4	66.7	38.4-88.2
Wearing-off (Item 36)	86.5	71.2-95.5	40	21.3-61.3	68.1	52.9-80.9	66.7	38.4-88.2

CONCLUSIONS

To the best of our knowledge, this is the first study carried out to evaluate the sensitivity and specificity of the UPDRS-IV to detect motor fluctuations and, for the first time, we used a 12- hours waking-day motor assessment as gold standard. It should be underlined that the waking day monitoring, even if it is a time consuming procedure, represents the only objective tool able to evaluate the presence of motor fluctuation independently by the patients reporting. Our results confirm the high level of sensitivity and the usefulness of UPDRS-IV to screen motor fluctuations in patients treated with antiparkinsonian medication. However the low specificity should be taken into account in interpreting research data because it could lead to an overestimation of the outcome.

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