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Motor and non-motor wearing-off and its impact in the quality of life of patients with Parkinson's disease

Flutuações motoras e não-motoras e seu impacto na qualidade de vida de pacientes com doença de Parkinson

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ABSTRACT

The wearing-off phenomenon is common in patients with Parkinson's disease. Motor and non-motor symptoms can fluctuate in relation to the "on/off" periods. **Objective:** To assess the impact of motor and non-motor wearing-off on activities of daily living and quality of life of patients with PD. **Methods:** A cross-sectional study was carried out. All patients were evaluated using the Movement Disorders Society Unified Parkinson's Disease Rating Scale. Wearing-off was assessed using the Wearing-Off Questionnaire-19, and quality of life was assessed using the Parkinson's Disease Questionnaire-8. **Results:** A total of 271 patients were included; 73.4% had wearing-off; 46.8% had both motor and non-motor fluctuations. Patients with both motor and non-motor wearing-off had a worst quality of life compared with those with only motor fluctuations (p = 0.047). **Conclusions:** Motor and non-motor fluctuations have an impact on activities of daily living and quality of life. Non-motor wearing-off may have a higher impact.

Keywords: Parkinson disease; quality of life; activities of daily living.

RESUMO

O fenômeno de encurtamento do fim de dose é comum em pacientes com doença de Parkinson. Tanto os sintomas motores quanto os não motores podem flutuar em relação aos períodos de "on/off". **Objetivo:** Avaliar o impacto das flutuações motoras e não-motoras nas atividades da vida diária e qualidade de vida em pacientes com doença de Parkinson. **Métodos:** Um estudo transversal foi realizado. Todos os sujeitos foram avaliados utilizando a escala unificada para a doença de Parkinson da Sociedade de Distúrbios do Movimento. O encurtamento do fim de dose foi avaliado através do questionário WOQ-19 e a qualidade de vida foi avaliada através do PDQ-8. **Resultados:** Um total de 271 pacientes foram incluídos, 73,4% tiveram deterioração de fim de dose. A maioria dos pacientes tiveram tanto flutuações motoras quanto não-motoras (46,8%). Os pacientes com ambos os tipos de flutuações motoras e não-motoras tiveram pior qualidade de vida do que pacientes apenas com flutuações motoras (p = 0.047). **Conclusões:** Pacientes com flutuações motoras e não-motoras tiveram impacto significativo nas atividades da vida diária e na qualidade de vida. As flutuações não-motoras parecem ter um impacto maior que as flutuações motoras sobre a qualidade de vida.

Palavras-chave: doença de Parkinson; qualidade de vida; atividades cotidianas.

Motor fluctuations in Parkinson's disease (PD) have been extensively studied[1,2]. Conversely, less is known about the behavior of non-motor symptoms in relation to the "on" and "off" periods. While some authors have suggested that these non-motor fluctuations correlate closely with motor fluctuations[3,4,5], the heterogeneity of study designs and differences in sample populations complicate the generalization of these results. In addition, non-motor symptoms have an important impact on quality of life[6] and, in some cases, their burden can be more disabling when compared with motor symptoms[7].

Wearing-off is defined as a predictable recurrence of motor and non-motor symptoms preceding scheduled doses of antiparkinsonian medication[8]. The underlying pathophysiology of wearing-off is thought to be multi-factorial[9].

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Motor wearing-off includes the recurrence of motor symptoms like tremor, rigidity, and bradykinesia; while non-motor wearing-off includes the recurrence of symptoms such as anxiety, fatigue, or depressed mood[10].

Different scales have been specifically developed to assess wearing-off in patients with PD[11]. The Wearing-Off Questionnaire (WOQ-19) has been used in several studies as a screening tool to identify patients with wearing-off phenomena[12].

The objective of this study was to assess the impact of motor and non-motor wearing-off on activities of daily living and quality of life of patients with PD.

METHODS

A cross-sectional study was performed on consecutive patients with PD, based on the UK Parkinson's Disease Society Brain Bank Criteria[13], attending the Movement Disorders outpatient clinic at the National Institute of Neurology and Neurosurgery in Mexico City. All the participating patients agreed to take part in the study and gave full consent as dictated by the National Institute of Neurology and Neurosurgery local ethics committee. Since the study included several self-administered questionnaires to be completed by a respondent without intervention of the researchers, patients with cognitive decline (Montreal Cognitive Assessment < 26) or any medical or psychiatric comorbidity that would hinder an adequate assessment were not included.

Clinical and demographic data collected included age, gender, years of education and disease duration. In addition, the levodopa equivalent daily dose (LEDD) was calculated[14].

Patients were evaluated in their "on" state by a neurologist with expertise in movement disorders using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part IA (non-motor experiences of daily living), Part III (motor examination) and Part IV (treatment complications)[15]. Part IV was not included in the analysis as it mainly evaluates the presence of fluctuations along with dyskinesia. Disease severity was assessed using the Hoehn and Yahr (HY) staging.

Patient-reported outcomes, including activities of daily living and quality of life, were evaluated using the Spanish version of the MDS-UPDRS Part IB (non-motor experiences of daily living) and Part II (motor experiences of daily living). These two parts are designed as self-administered questionnaires and could be completed either alone or with their caregivers.

For the study purposes, it is important to highlight that in the MDS-UPDRS Part IA the patient had to choose the best answer that describes how he/she had felt "most of the time during the past week". On the other hand, Parts IB and II required the patient to mark the answer that best describes what he/she could do "most of the time".

Quality of life was assessed using the Parkinson's Disease Questionnaire-8 (PDQ-8). The PDQ-8 is a disease-specific and self-administered instrument addressing aspects of functioning and well-being in the past month. The scale comprises eight questions, scored by frequency of problems (0 = never to 4 = always). A PDQ-8 single index is calculated resulting in a score ranging from 0 to 100 (0 = no problem at all; 100 = maximum level of problem)[16].

In addition, the WOQ-19 was applied. The WOQ-19 is a disease-specific and self-administered instrument addressing aspects of motor and non-motor symptoms related to the wearing-off phenomenon. The WOQ-19 assesses the following motor symptoms: tremor, difficulty with speech, weakness, problems with balance, slowness, reduced dexterity, general stiffness and difficulty getting out of the chair. On the other hand, non-motor features assessed include: anxiety, sweating, mood changes, numbness, panic attacks, cloudy mind/dullness of thinking, abdominal discomfort, muscle cramping, experiencing hot and cold, pain and aching.

Patients marked the presence/absence of selected symptoms as well as the improvement after the next dose of medication. The presence of wearing-off was considered if the symptom is reported to improve after the following dose of medication[12]. For the study purposes, patients were classified in the following groups: patients without wearing-off (Non-WO), patients with exclusively motor wearing-off symptoms (M-WO), patients with exclusively non-motor wearing-off symptoms (NMS-WO), and patients with both with motor and non-motor wearing-off symptoms (Mixed-WO).

Statistical analysis

Demographic data were reported in terms of percentage, mean and standard deviation. Data distribution was assessed using the Shapiro-Wilk test.

The analysis of quantitative variables between the groups was performed using one-way ANOVA with Tukey's Honest Significant Difference *post hoc* test for normally distributed data. If nonparametric comparison was needed, a Kruskal-Wallis test with pairwise comparisons using the Dunn-Bonferroni approach were performed. Differences in proportions of categorical variables were analyzed using Chi-square or Fisher's test as needed. The 95% confidence interval is reported through-out. A level of $p < 0.05$ was set for statistical significance. All statistical analyses were performed with SPSS software version 17.

RESULTS

A total of 271 patients (148 males and 123 females) with PD were included. The mean age was 65.4 ± 12.4 years, and the mean disease duration was 9.0 ± 5.5 years. According to the HY stage, 60.4% had mild disease (HY stages 1–2), 25.9% had moderate disease (HY stage 3), and 13.7% had severe disease (HY stage 4–5). Two hundred and forty-six patients (90.8%) were on levodopa in monotherapy or

polytherapy, and 166 patients were treated with a dopaminergic agonist (61.3%).

The complete sociodemographic characteristics of the study sample are summarized in Table 1.

A total of 199 patients (73.4%) had a wearing-off phenomenon. After categorizing patients according to the type of wearing-off phenomena, 63.8% had Mixed-WO, 32.7% had M-WO, and 3.5% had NMS-WO. The comparison of the main demographic and clinical variables between groups is shown in Table 2.

Statistically significant differences between groups were found for the MDS-UPDRS I total score (p = 0.004), MDS-UPDRS II total score (p = 0.043), use of levodopa (p = 0.007), use of dopamine agonists (p = 0.019), LEDD (p < 0.001), and the PDQ-8 score (p = 0.016).

The MDS-UPDRS part I score was higher in the NMS-WO group compared with the M-WO group (mean difference of 8.64 ± 2.64, 95% CI 1.82-15.45, p = 0.007). There was a trend toward significance between the NMS-WO group and Mixed-WO group (mean difference of 6.48 ± 2.57, 95% CI -0.23-13.07, p = 0.086).

The MDS-UPDRS part II score showed a trend between the M-WO and Mixed-WO groups (mean difference of 3.62 ± 1.67, 95% CI -0.70-7.93, p = 0.091), but no statistical significant differences were found after the *post hoc* analysis.

In regard to treatment, patients with NMS-WO were less frequently on a dopamine agonist compared with those in the Mixed-WO and M-WO groups (28.5% vs. 77.9%, p = 0.010 and 28.5% vs. 73.8%, p=0.025, respectively). Also, patients in the Mixed-WO group were more commonly on levodopa compared with those in the Non-WO group (96% vs. 81.9%, p = 0.001). After *post hoc* analysis, patients in the Mixed-WO group had a higher LEDD compared with the Non-WO group (mean difference of 283.75 ± 63.02, 95% CI 120.81-446.67, p < 0.001). No other statistical significant differences were found.

Regarding the quality of life, the *post hoc* analysis did show a statistically significant difference between groups. The Mixed-WO group had a worse quality of life compared with the M-WO group (mean difference of 7.96 ± 3.26, 95% CI 0.48-16.40, p = 0.047).

Table 1. Clinical and demographic data of the study sample.

Variable	Mean ± Standard deviation
Male gender*	148 (54.6%)
Current age (years)	65.41 ± 12.43
Disease duration (years)	8.98 ± 5.48
Years of education	8.98 ± 5.45
Levodopa equivalent daily dose	797.38 ± 427.29
MDS-UPDRS Part I	10.35 ± 6.74
MDS-UPDRS Part II	15.20 ± 11.03
MDS-UPDRS Part III	30.53 ± 15.85
MDS-UPDRS Part IV	2.75 ± 3.98

MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; Part I: non-motor experiences of daily living; Part II: motor experiences of daily living; Part III: motor examination; Part IV: treatment complications.

DISCUSSION

Motor and non-motor wearing-off are frequent in patients with PD receiving dopaminergic replacement therapy. Non-motor wearing-off has been less studied; consequently, this type of complication may be overlooked in clinical practice. Moreover, non-motor fluctuations may be confused with anxiety or depression.

Non-motor wearing-off prevalence varies widely between studies ranging from 17% to 100% depending on

Table 2. Comparison of the main demographic and clinical variables between different groups.

Variable	Non-WO n = 72	M-WO n = 65	NMS-WO n = 7	Mixed-WO n = 127	p-value
Male gender **	38 (52.7%)	35 (52.2%)	2 (28.5%)	73 (57.4%)	0.460
Current age (years)*	68.04 ± 11.59	66.60 ± 11.20	69.85 ± 6.96	63 ± 13.35	0.077
Disease duration*	8.78 ± 6.24	8.22 ± 4.29	6.85 ± 4.14	9.60 ± 5.57	0.131
MDS-UPDRS I*	10.71 ± 6.60	8.51 ± 6.14	17.14 ± 5.78	10.72 ± 6.90	0.004
MDS-UPDRS Item 1.3 (depressed mood)*	0.56 ± 0.85	0.49 ± 0.77	1.57 ±1.13	0.50 ± 0.80	0.214
MDS-UPDRS II*	14.13 ± 10.87	13.37 ± 10.61	11 ± 7.37	16.98 ± 11.31	0.043
MDS-UPDRS III*	31.52 ± 15.31	28.83 ± 14.65	27.71 ± 10.76	31.02 ± 17.03	0.704
MDS-UPDRS IV*	1.17 ± 2.76	2.03 ± 3.64	2.14 ± 3.38	4.02 ± 4.35	< 0.001
PDQ-8*	25.31 ± 19.57	23.32 ± 21.37	37.05 ± 15.24	31.27 ± 22.61	0.016
Use of dopamine agonist**	47 (65.2%)	48 (73.8%)	2 (28.5%)	99 (77.9%)	0.019
Use of levodopa**	59 (81.9%)	59 (90.7%)	7 (100%)	122 (96%)	0.007
LEDD (mg)*	581.66 ± 421.77	748.81 ± 445.94	502.50 ± 346.99	865.41 ± 423.97	< 0.001

Non-WO: Non-wearing-off; M-WO: Motor wearing-off; NMS-WO: Non-motor wearing-off; Mixed-WO: Mixed wearing-off; MDS-UPDRS: Movement Disorder Society – Unified Parkinson's Disease Rating Scale; PDQ-8: Parkinson's Disease Quality of Life; LEDD: Levodopa Equivalent Daily Dose. * Kruskal-Wallis test. Mean ± standard deviation. ** Fisher's test.

the clinical tools used for assessment[3,4,10,16,17]. In our study, a prevalence of 49.4% was found (127 patients with mixed wearing-off and seven patients with non-motor wearing-off). This finding can be explained by the relatively long disease duration of almost nine years, due to the fact that a longer disease duration has been clearly associated with a higher prevalence of treatment complications[18].

It has been reported that motor and non-motor fluctuations tend to be present concomitantly, although the latter can appear without motor fluctuations[19]. Brun et al.[4] found that the presence of motor fluctuations was an independent predictor for non-motor fluctuations, while Witjas et al.[10] reported that all patients with motor wearing-off in their cohort also had non-motor fluctuations. In our study, the prevalence of non-motor wearing-off in combination with motor fluctuations was 46.8%. In fact, only seven patients with exclusively non-motor wearing-off were found. On the other hand, less than 27% of the patients had no wearing-off phenomena. This group had less exposure to levodopa than the patients with motor or mixed wearing-off, which is in line with previous reports[10,16]. It should also be noted that patients in the NMS-WO group received a lower LEDD compared with those groups with motor fluctuation (M-WO and Mixed-WO). Overall, patients in the Mixed-WO group were more frequently on a dopamine agonist and levodopa, as well as on a higher dose. This may suggest that motor wearing-off is more related to the dopaminergic treatment dosage than the non-motor fluctuations.

The MDS-UPDRS part I total score, assessing non-motor aspects of daily living, was higher in the NMS-WO group compared with patients in the M-WO group. No difference was found between patients with mixed wearing-off and those patients without the wearing-off phenomenon. This finding suggests that patients with motor wearing-off may have a lower overall burden of non-motor symptoms; while patients with mixed or no wearing-off have similar burdens, as measured by the MDS-UPDRS part I. Conversely, patients with non-motor fluctuations also have a higher burden of non-motor symptoms.

On the other hand, no differences were found between groups in the MDS-UPDRS part II scores (motor experiences of daily living). Lack of statistical difference in the MDS-UPDRS part II may suggest that the total score of this subscale does not relate to the presence of motor and non-motor wearing-off symptoms.

Regarding the motor state, Seki et al.[16] reported that patients with both motor and non-motor wearing-off had more severe motor symptoms as assessed by the MDS-UPDRS part III. In our sample, we did not find any differences between groups. While the management of motor symptoms as measured by motor evaluation was not related to the wearing-off phenomena, the type of dopaminergic replacement treatment and its dose did show some association, as mentioned before. The MDS-UPDRS part IV score was higher in the Mixed-WO group; this finding was expected since three of the six items comprising this part address motor fluctuations.

Wearing-off symptoms have implications in health-related quality of life. Non-motor symptoms have been clearly associated with a decrease in the quality of life[20,21]. Nonetheless, there is less evidence regarding the impact of non-motor fluctuations and quality of life. In our study, PD patients in the NMS-WO group had the worst score in the PDQ-8, followed by patients in the Mixed-WO group. On the other hand, patients with no wearing-off and those with only motor wearing-off had a better quality of life. This finding suggests that, in fact, non-motor fluctuations may yield a higher impact on the quality of life than motor wearing-off symptoms.

Our study has several limitations. First, by study design, we did not analyze individual non-motor fluctuations. Nonetheless, the objective of our study was to assess the overall impact of non-motor wearing-off phenomena. Second, we evaluated only the frequencies of motor and non-motor fluctuations, but we did not assess their severity. Lastly, due to the small size of the NMS-WO group, our results should be interpreted with caution; other independent studies confirming our findings are required.

In conclusion, the present study shows that both motor and non-motor fluctuations have an impact on activities of daily living and quality of life. However, the presence of non-motor fluctuations did significantly worsen the quality of life. The identification and assessment of non-motor fluctuations in the day-to-day clinical practice could result in the improvement of the quality of life of patients with PD.

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