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Non-motor symptoms in PD evaluated during pharmacological ON state by a new tool: The NoMoS-ON scale. Is always the "ON" state beneficial?

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ABSTRACT

Objectives: To evaluate non-motor symptoms (NMS) occurring during ON pharmacological state and validate a new questionnaire, the Non-motor symptoms-ON scale (NoMoS-ON), exploring ON NMS in Parkinson's disease (PD).

Material and methods: Patients with PD were evaluated by a new questionnaire, the NoMoS-ON scale, evaluating 17 items related to the main symptoms experienced during the ON state. PD patients who experienced at least one symptom in ON were defined ON-NMS+. Internal consistency and test-retest reliability of NoMoS-ON scale were also assessed.

Results: One-hundred and thirty-seven PD patients were consecutively enrolled (79 men and 58 women, age 69.4 ± 9.5 years (mean ± SD)). Seventy-seven patients were ON-NMS+ (56.6 %). PD patients with short disease duration (<7 years) showed the presence of unpleasant NMS: "sleepiness", "light-headedness", "nausea/vomiting". PD patients with longer disease duration experienced pleasant non-motor features including "feel lot of energy", "feel physical well-being". ON-NMS+ were also associated with female gender (OR 2.81, 95%CI 1.37–5.77, p-value 0.005) and with motor fluctuations (OR 2.41, 95%CI 1.20–4.83, p-value 0.013). Cronbach's alpha was 0.61 and 5 items had adequate item-to-total correlations ($r \geq 0.40$). Test–retest reliability was acceptable (intraclass correlation coefficient, ICC = 0.77).

Conclusions: The NoMoS-ON scale is a valid, reproducible and reliable questionnaire capturing the ON NMS in PD. PD patients with disease duration shorter than 7 years showed the presence of unpleasant NMS whereas those with longer disease duration experienced pleasant non-motor features. This could help the physician in the therapy management of PD patients in different phases of their disease.

1. Introduction

Non-motor symptoms (NMS) are very common in Parkinson's disease (PD) and may be present from the PD premotor stage, and involving several domains, leading to increased disability and poor quality of life for both patients and caregivers [1]. NMS may also present fluctuations, when occurring during the OFF or ON pharmacological state, and indeed, non-motor fluctuations (NMF) are highly prevalent in PD patients determining a major impact on disease-related disability [2,3].

A simple clinical interview can be insufficient to correctly identify NMS and NMF, and during the last few years, reliable questionnaires trying to capture and to quantify these phenomena have been proposed. The Movement Disorder Society Non-Motor Rating Scale (MDS-NMS) allows specific evaluation of NMF in PD, but only asking the patients if symptoms are present or worsen during OFF period [4]. The Neuropsychiatric Fluctuations Scale (NFS), composed by 20 items (ten items for the ON neuropsychiatric state and ten items for the OFF neuropsychiatric state) allows detecting neuropsychiatric fluctuations and capturing only acute neuropsychiatric conditions during ON and OFF state [5]. Recently, Kleiner and coll (2021) developed the Non-motor Fluctuations Assessment (NoMoFA) Questionnaire in order to quantify the entire spectrum of NMF in both the ON and the OFF-medication conditions [6].

Although the reliability of the NoMoFA questionnaire in the detection of the NMS and NMF has been demonstrated exploring both the OFF and ON condition, it did not include some of the main symptoms that PD

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patients could experience during the ON state, such as nausea, vomiting, light-headedness or dizziness.

Aim of our study was to evaluate NMS occurring during ON pharmacological state in a large cohort of PD patients evaluated during their ON motor state and validate a new specific questionnaire exploring this specific aspect, the Non-motor Symptoms ON (the NoMoS-ON) scale.

2. Materials and methods

2.1. Study population

Patients with diagnosis of clinically established PD according to the Movement Disorder Society (MDS)-PD diagnostic criteria [7] on dopaminergic treatment with levodopa for at least 6 months, attending the "Parkinson's Disease and Movement Disorders Centre" of the University of Catania, were consecutively enrolled during their regular follow-up visits. All PD patients underwent a complete neurological examination and motor disability was evaluated according to the Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) and the Hoehn and Yahr (HY) scale. Presence of motor complications, motor fluctuations and dyskinesia, was assessed using the items 32–39 of the UPDRS part IV. Levodopa Equivalent Daily Dose (LEDD) was reported together with pharmacological history. The presence of atypical parkinsonism, drug-naïve PD patients as well as the treatment with dopamine-agonists or MAO-B inhibitor alone were considered exclusion criteria.

The collection of data was approved by our local Ethical Committee (Code 316/2015).

2.2. ON symptoms assessment

Considering literature data about the main symptoms reported by PD patients during the ON state [2,8], but also NMS reported by PD patients in our clinical real-life experience during ON state, a new questionnaire was developed, namely NoMoS-ON scale (appendix I). It was composed of 17 items exploring different domains, including dysautonomic, mood, sensory/pain and cognitive/neuropsychiatric symptoms. We considered both pleasant non-motor features (meaning features associated to a condition of well-being and relief not affecting quality of life) and unpleasant NMS (i.e. NMS causing dysfunction and impairment in quality of life). The scale was in Italian language and administered to Italian PD patients. An English version of the NoMoS-ON scale was also developed (appendix II). PD patients were evaluated during their motor ON state, about 90–120' after the first morning dose of dopaminergic therapy and were asked if the symptoms were present only during the ON state, with a binary answer – yes or not. The score was calculated as the sum of each reported symptom (appendix I). Patients who experienced at least one symptom only in ON state were defined ON-NMS+. Moreover, a subgroup of PD patients underwent also a NoMoFA questionnaire assessment to evaluate diagnostic ability of the new NoMoS-ON scale and the correlation between the two scales.

2.3. Sample size

As previously considered [6], based on a sample size of 5–10 subjects for each scale item it was determined that a sample size of between 80 and 180 was necessary for examining the 17 items of the ON questionnaire.

2.4. Basic clinimetric properties

The clinimetric properties of this scale were examined including internal consistency (Cronbach's alpha), and item-to-total correlation. The value of Cronbach's alpha >0.6 was considered acceptable [9], while the threshold for acceptable item-to-total correlation was ≥0.20, indicating good discrimination [10].

Reproducibility (test-retest reliability) was tested by interclass correlation coefficient (ICC) for the whole scale score. ICC values of 0.70 or higher were considered acceptable [11]. Additionally, concurrent validity was assessed using Spearman's correlation coefficient for assessing relationship between the new ON scale and the NoMoFA score considering total score, ON sub-score and number of ON items.

2.5. Statistical analysis

Data were analyzed using STATA 16 software packages (StataCorp, College Station, TX, USA). Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed as number and percentage. The Shapiro-Wilk normality test was performed. Differences between means were evaluated with the unpaired *t*-test in case of normal distribution and the Mann-Whitney *U* test for not-normal distribution. The differences between proportions were evaluated by the Chi-square test. When needed, variables have been dichotomized according to the median value.

Univariate logistic regression analysis was performed to evaluate possible associations between ON-NMS+ (outcome of the study) and demographic and clinical characteristics. Additionally, in order to assess different pattern of ON response, the whole group was stratified according to the median value of the disease duration in order to have an equally distributed sample.

The significance level was set at 0.05 and the 95 % confidence intervals (CI) were calculated.

3. Results

3.1. Study population

One-hundred and thirty-seven PD patients were enrolled [79 men and 58 women, age 69.4 ± 9.5 years (mean ± SD), disease duration 8.0 ± 4.6 years]. Seventy-two PD patients (52.5 %), according to the items 32–39 of the UPDRS part IV, experienced motor fluctuations (MF), including dyskinesia (n = 47, 34.3 %) and wearing-off (n = 61, 44.5 %) (Table 1).

Table 1
Demographics and clinical characteristics of Parkinson's disease patients, stratified by ON Non-Motor response.

	Whole PD patients, n = 137	PD patients ON-NMS+, n = 78	PD patients ON-NMS-, n = 59	p-value
Gender, M/F	79/58	36/42	43/16	**0.002**
Age, years	69.4 ± 9.5	68.2 ± 10.1	71.0 ± 8.4	0.09*
Disease duration, years	8.0 ± 4.6	7.6 ± 4.3	8.6 ± 4.8	0.21*
UPDRS-ME score	33.6 ± 13.5	33.2 ± 14.0	34.1 ± 12.9	0.52*
Hoehn Yahr stage	2.4 ± 0.8	2.4 ± 0.7	2.4 ± 0.8	0.63*
LEDD, mg	564.4 ± 360.4	596.7 ± 387.3	523.7 ± 322.1	0.38*
Motor Complications, n (%)	72 (52.5)	48 (61.5)	24 (40.5)	**0.009**
Dyskinesia, n (%)	47 (34.3)	33 (42.3)	14 (23.7)	**0.01**
Motor Fluctuations, n (%)	61 (44.5)	43 (55.1)	18 (30.5)	**0.003**
Benzodiazepines, *n (%)*	36 (26.3)	20 (25.6)	16 (27.1)	0.92
Antidepressants, *n (%)*	45 (32.8)	20 (25.6)	25 (42.3)	0.91
Antipsychotics, *n (%)*	14 (10.2)	7 (8.9)	7 (11.8)	0.62

Data are given as means ± standard deviation or frequencies (%). PD, Parkinson's Disease; ON-NMS+, PD patients reporting at least 1 NMS in ON; ON-NMS- PD patients not reporting NMS in ON.; UPDRS-ME, Unified Parkinson's Disease Rating Scale-Motor Exam; LEDD, Levodopa equivalent daily dose. *Mann-Whitney *U* test.

3.2. ON assessment

Seventy-eight PD patients (56.9 %) reported at least one NMS during ON state and were defined ON-NMS+. Among the ON-NMS+ patients, min-max range of reported ON items was 1–7 (mean 1.6 ± 0.9). Frequency of the number of reported ON items is showed in Fig. 1. Interestingly, out of the 78 patients with PD reporting ON-NMS+, 48 (61.5 %) had also MF. There were no differences between ON-NMS+ and ON-NMS-, except for gender distribution, with higher prevalence of women with PD among ON-NMS+ and the presence of motor complications, with ON-NMS+ patients showing higher frequencies of MF and dyskinesia (Table 1).

The most reported symptoms were "sensazione di benessere fisico/feel physical well-being" (30.7 %), followed by "sonnolenza/sleepiness" (12.4 %) and "sentirsi pieno di energie/feel lot of energy" (10.9 %). The item "cefalea/headache" has never been reported in our sample.

Regarding the disease duration, PD patients with short disease duration (<7 years, considering the median value) in comparison with PD patients with longer disease duration (>7 years) reported a statistically significant higher frequency of unpleasant NMS causing dysfunction and impairment in quality of life, including "sonnolenza/sleepiness" (20.0 % *versus* 4.5 %, p-value 0.006), "sensazione di testa vuota/light-headedness" and "nausea/vomito/nausea/vomiting" (4.3 % *versus* 0 %, p-value 0.08). On the other hand, PD patients with longer disease duration (>7 years) experienced a statistically higher frequency of pleasant non-motor features, indicating condition of well-being and relief, such as "sentirsi pieno di energie/feel lot of energy" (26.4 % *versus* 5.7 % p-value 0.04) and "sensazione di benessere fisico/feel physical well-being" (41.8 % *versus* 20.0 %, p-value 0.006) (Table 2). Disease duration >7 years was strongly associated with the presence of MF (OR 4.23, 95%CI 2.06–8.65, p-value<0.001), also adjusting for age, gender, and UPDRS-ME (adjOR 5.37; 95%CI 2.45–11.78).

Finally, the presence of ON-NMS+ was associated with female gender (OR 2.81, 95%CI 1.37–5.77, p-value 0.005) and with MF (OR 2.41, 95%CI 1.20–4.83, p-value 0.013).

3.3. Clinimetric properties

Examination of internal consistency indicated an acceptable level of reliability (Cronbach's alpha = 0.61) and 5 items (difficoltà nel linguaggio/word finding difficulty, eccessiva irrequietezza/agitazione/ansia/excessive restlessness/agitation/anxiety, disturbi visivi (offuscamento, visione doppia)/changes in vision (blurring vision/double vision), sensazioni dolorose/crampi/formicolii/abnormal sensations/pain//cramps/tingling, disturbi urinari (urgenza, incontinenza)/urinary problems) had adequate item-to-total correlations (r ≥ 0.40), while the other items showed a value ≥ 0.20 indicating a sufficient discrimination (Supplementary Table 1).

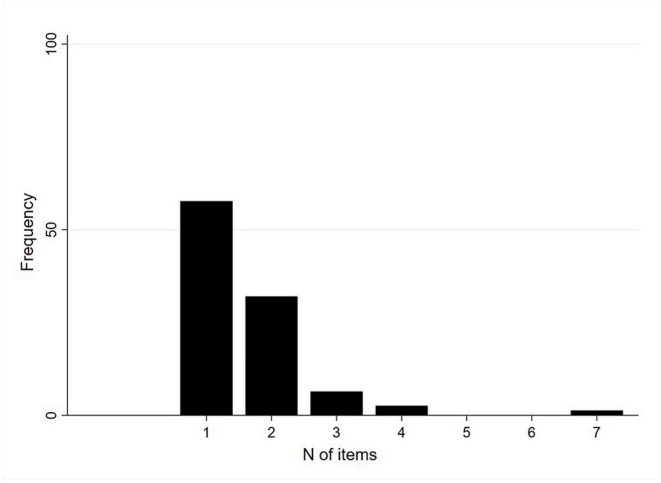

Fig. 1. Number of reported ON items in the ON-NMS+ subgroup.

Table 2
Frequency of reported items in the whole PD sample and stratified by disease duration (median value = 7).

ON questionnaire items, n (%)	Whole PD patients, n = 137	Disease duration ≤7 years (n = 70)	Disease duration >7 years (n = 67)	p-value
Sensazione di confusione mentale/ feel mentally tired	6 (4.4)	5 (7.1)	1 (1.5)	0.1
Sensazione di testa vuota/light-headedness	3 (2.2)	3 (4.3)	0	0.08
Nausea/vomito/ nausea/vomiting	3 (2.2)	3 (4.3)	0	0.08
Capogiri/vertigini/ dizziness	1 (0.7)	0	1 (1.5)	0.3
Sonnolenza/sleepiness	18 (13.1)	15 (21.4)	3 (4.5)	**0.006**
Palpitazioni/ palpitations	2 (1.5)	0	2 (2.9)	0.1
Eccessiva sudorazione/ excessive sweating	4 (2.9)	3 (4.3)	1 (1.5)	0.3
Difficoltà nel linguaggio/words finding difficulty	2 (1.5)	1 (1.4)	1 (1.5)	0.9
Cefalea/headache	0	0	0	/
Eccessiva irrequietezza/ agitazione/ansia/ excessive restlessness/ agitation/anxiety	5 (3.6)	3 (4.3)	2 (2.9)	0.7
Incontrollabile necessità di fare determinate cose/ compulsions/ uncontrollable urges	9 (6.6)	5 (7.1)	4 (6.0)	0.8
Sentirsi pieno di energie/feel lot of energy	15 (10.9)	4 (5.7)	11 (26.4)	**0.04**
Sensazione di benessere fisico/feel physical well-being	42 (30.7)	14 (20.0)	28 (41.8)	**0.006**
Allucinazioni/ hallucinations	4 (2.9)	2 (2.9)	2 (2.9)	0.9
Disturbi visivi (offuscamento, visione doppia)/ changes in vision (blurring vision/ double vision)	2 (1.5)	1 (1.4)	1 (1.5)	0.9
Sensazioni dolorose/ crampi/formicolii/ abnormal sensations/ pain//cramps/ tingling	3 (2.2)	1 (1.4)	2 (2.9)	0.5
Disturbi urinari (urgenza, incontinenza)/ urinary problems	7 (5.1)	5 (7.1)	2 (2.9)	0.3

Data are given as frequencies (%). PD, Parkinson's Disease.

Test–retest reliability was assessed in a sample of 41 stable PD patients tested over 3 months (±1 months) showing adequate values (ICC = 0.77 [95 % CI 0.58–0.88]).

3.4. Diagnostic ability

One-hundred and eleven PD patients were evaluated also with the NoMoFA questionnaire. Spearman's correlation coefficient comparing the NoMoS-ON scale and the NoMoFA scores showed statistically significant correlation values between NoMoS-ON scale total score and

NoMoFA total ON subscores and number of ON items reported in the NoMoFA questionnaire ($r = 0.798$, $p < 0.001$ and $r = 0.794$, $p < 0.001$ respectively) and no correlation with NoMoFA total OFF subscores ($r = 0.180$, $p = 0.06$) and NoMoFA total score ($r = 0.02$, $p = 0.77$). Out of 111 PD patients, 44 (39.6 %) were ON-NMS+ considering the NoMoFA assessment, while 64 (57.6 %) were ON-NMS+ assessed with the new NoMoS-ON scale.

4. Discussion

The new developed NoMoS-ON scale was found to be valid, consistent and reliable in capturing NMS during the ON pharmacological state in a large cohort of PD patients.

We demonstrated the presence of a different distribution of NMS occurring during ON response in PD patients. Indeed, PD patients with short disease duration (<7 years) showed the presence of unpleasant NMS causing dysfunction and impairment in quality of life, such as "sonnolenza/sleepiness", and "sensazione di testa vuota/light-headedness". On the other hand, PD patients with longer disease duration (>7 years) experienced more pleasant non-motor features, including "sentirsi pieno di energie/feel lot of energy" and "sensazione di benessere fisico/feel physical well-being".

Previous studies reported a great amount of data about the occurrence of NMS and NMF in patients with PD [1–3,12,13]. Nevertheless, many studies considered the presence of wearing-off, thus referring mainly to the OFF state [12–15]. Few data are present in literature about NMS and NMF occurring specifically during the ON state. Carpi and coll (2023) recently investigated the presence of NMF using the NoMoFA questionnaire, reporting in a small sample (twenty-five PD patients) a higher frequency of NMF during the ON state, with the most reported NMS including "low energy/fatigue" and "excessive daytime sleepness" [8]. Accordingly, a recent study [16] evaluated the presence of NMS and NMF in a larger cohort of PD patients (one-hundred and twenty-one) with the NoMoFA questionnaire demonstrating that the most frequent NMF experienced in ON state were "Feel excessively sleepy during the day" (22.1 %), and "Act quickly without thinking things through" (19.4 %). In this context, features such as impulsivity, hyperactivity, and a feeling of euphoria are observed more frequently and exclusively in the ON motor condition. However, only few validated questionnaires allow to detect NMS specifically occurring in ON condition [2].

Storch and coll (2013), by means of a standardized interview including NMS Questionnaire, the 9-item Wearing-off Questionnaire (WOQ-9), Beck Depression Inventory (BDI-1A), and Parkinson's Disease Questionnaire-8 (PDQ-8), evaluated NMS both in OFF and ON state. Authors demonstrated that all NMS except dysphagia, excessive sweating, and bladder urgency were more frequent in OFF compared to ON state, whereas only happiness was the NMS more frequent in ON state [3]. It should be noted that the questionnaires used in that cohort of patients evaluated a pattern of NMS mainly affecting the OFF condition, thus underestimating the NMS that could occur in the ON state. The same Authors, by means of a modified version of the Non-Motor Symptoms Scale (NMSS) did not find a significant NMS profile occurring only in the ON state [17]. Recently, Del Prete and coll (2022) in a small sample of PD patients (N = 18) clearly showed different neuropsychiatric NMS occurring during OFF and ON condition [18]. These data suggest that probably the best moment to evaluate a PD patient's condition is during the specific pharmacological state (i.e. ON or OFF) using specific tools tailored for those symptoms. Indeed, it should be considered that the pharmacological condition in which PD patients answer these questionnaires could influence their subjective perception of the NMS and NMF, under- or overestimating the degree of these symptoms [18].

Our new questionnaire, the NoMoS-ON scale, has been developed in order to assess all the NMS that could occur during the ON state, representing a fluctuation from OFF to ON state, considering also those experienced by PD patients in the early stage of the disease. Main finding of our paper was the presence of a different profile of NMS during the ON state between PD patients with short disease duration compared to those with longer disease duration, thus suggesting a sort of "pharmacological sensitivity switch" across the disease. Concerning the presence of NMS regardless the pharmacological state, Guo and coll (2013) evaluating a large cohort of PD patients (n = 616) by means of NMSS, reported that the burden of NMS increases with disease duration. Symptoms including "falls because of fainting", "daytime sleepiness", "fatigue", "difficulty falling asleep", "restless legs", "hallucinations", "delusions", "double vision", "dribbling saliva", "swallowing", "constipation", "nocturia", "weight change", and "excessive sweating" were more severe in patients with disease duration of more than 5 years than in those with duration of less than 5 years [19]. Even in this case Authors have not specifically stated if PD patients were evaluated in OFF or ON state, and as mentioned above, NMSS include a variety of symptoms affecting mainly the OFF condition. Similarly, a 6-year longitudinal study highlighted the presence of different rate of progression of the NMS in PD patients, being subtle during the first 2-year and becoming faster and more severe at the sixth year [20]. Interestingly, Storch and coll (2019), evaluated a cohort of PD patients (n = 101) demonstrating that NMF decreased in amplitude with disease progression [21].

In our sample, the different pattern of NMS experienced in ON could be explained by pharmacodynamic and pharmacokinetics mechanisms. In the early stages of PD, the unpleasant NMS occurring during the ON state, such as nausea, light-headedness, sleepiness, could be driven by dopaminergic effects for which tolerance has not yet been developed, including also peripheral mechanisms; as the disease progresses a switch of effects, due to tolerance mechanisms, could be observed with an improvement of the adverse events and a gain of pleasant non-motor features, including feel lot of energy and well-being. It is well-known that in PD, compensatory changes in dopamine receptors could emerge as a consequence of the loss of dopamine nerve terminals or due to the dopaminergic therapy itself. A recent meta-analysis including nuclear imaging studies, demonstrated that a dopamine receptor upregulation in early PD followed by a downregulation in advanced PD (mean disease duration 4.4 years after motor symptoms onset) is present [22]. Authors also suggested that the receptor downregulation could be a consequence of both disease progression and pharmacological treatment considering that disease duration and dopaminergic therapy were associated to lower D2 receptor binding in PD patients [22]. Furthermore, another nuclear imaging study showed that the dopamine receptor downregulation demonstrated by decreased PET D2 receptor ligand binding, seems to disappear in PD patients whose medications are withdrawn after DBS implantation [23], linking receptor changes to pharmacological treatment. From a clinical point of view, levodopa effects related to disease duration still need to be deeply investigated. Fabbri and coll (2017) showed that levodopa administration as an acute test challenge in a group of late-stage PD patients significantly improved NMS, including anxiety and pain, in absence of severe adverse events [24]. Thus, we could hypothesize that during the disease course, changes in dopaminergic receptor modulated by dopaminergic treatment itself, could lead to a different response to levodopa, also involving the NMS manifestations. On this background, considering the most reported unpleasant NMS in our PD sample (i.e. sleepiness, nausea and light-headedness), these could be due both to peripheral action of dopaminergic therapy and to hypersensitivity of dopaminergic receptor; on the other hand, the most reported pleasant non-motor features in ON state by PD patients with longer disease duration (i.e. feel lot of energy and well-being) could be determined by the receptor downregulation together with changes in the mesocorticolimbic dopaminergic pathway predisposing to hyperdopaminergic behavior [2].

Our findings raise another important issue related to the therapeutic management in PD patients. The presence of NMS such as nausea, sleepiness, dizziness at the beginning of the dopaminergic treatment and the persistence of these symptoms overtime, could lead to a suboptimal therapy adherence, determining early discontinuation, underuse, and

irregular drug intake [25]. Regularity in medication intake is very important in order to achieve control of symptoms, therefore, it is essential to identify and recognize NMS as soon as possible for effective management strategies [26]. Alongside, in accordance with previous data [12,16,27], we found that the presence of ON-NMS+ was more frequent and associated with female gender. Although there is not a clear explanation for the higher frequency of ON-NMS+ among women, female gender has commonly considered a risk factor for the development of motor- and non-motor fluctuations in PD. Women with PD may present a different response to dopaminergic therapy due to difference in bioavailability and pharmacokinetics [28]. Furthermore, neuroimaging studies demonstrated the presence of a preserved presynaptic system and a higher striatal dopaminergic level in women with PD [29]. These features, together with a possible role of estrogens hormones [30], may have a role in the occurrence of these clinical features in women with PD.

Finally, considering the clinimetric properties, data about internal consistency (Cronbach's alpha = 0.61), ICC value (0.77) and diagnostic accuracy (76.6 %) indicate a sufficient reliability of the new NoMoS-ON scale suggesting the usefulness in the clinical practice and further validation in larger sample size.

In conclusion, we develop a new and reliable questionnaire exploring NMS occurring specifically in the ON state of PD patients evaluated in their ON condition. The NoMoS-ON scale is proposed as an easy, fast, and suitable tool for routine clinical use and tailored for assessing this condition. Finally, we underline the importance of consider the pharmacological state of the patients during the clinical evaluation, in order to better recognize and manage NMS and NMF and to ensure adherence to the pharmacological treatment.

Ethical approval

The study has been approved by the local ethics review board, and conducted according to the Declaration of Helsinki.

Data availability

The data supporting the findings of this study are available on request from the corresponding author.

CRediT authorship contribution statement

G. Donzuso: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A. Luca:** Writing – review & editing, Data curation. **C.E. Cicero:** Writing – review & editing, Data curation. **G. Mostile:** Writing – review & editing, Data curation. **A. Nicoletti:** Writing – review & editing, Supervision, Data curation. **M. Zappia:** Writing – review & editing, Supervision, Data curation, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2024.107036.

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