Prevalence of non-motor symptoms and non-motor fluctuations in Parkinson's disease using the MDS-NMS

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ABSTRACT

Background: Non-motor symptoms (NMS) are frequent in Parkinson's disease (PD).

Objectives: To estimate the prevalence of NMS and of non-motor fluctuations (NMF) using the Movement Disorders Society-Non-Motor Rating Scale (MDS-NMS) and other scales assessing NMS, and their relationship with sex and PD severity.

Methods: Cross-sectional study with a sample of 402 PD patients. The Hoehn and Yahr staging system (HY), Clinical Impression of Severity Index for PD (CISI-PD), MDS-NMS (including NMF-subscale), Non-Motor Symptoms scale (NMSS), and MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were applied. A NMS was considered present when scored ≥1. Differences in scores by sex and HY, CISI-PD, and MDS-UPDRS severity levels were calculated using Fisher's exact and chi-squared tests.

Results: Using the MDS-NMS, NMS were present in 99.7% of patients and the mean number of NMS was 16.13 (SD: 9.36). The most prevalent NMS was muscle, joint or back pain (67.4% of the sample) and the least prevalent was dopamine dysregulation syndrome (2.2%). Feeling sad or depressed was significantly more prevalent in women. Using the MDS-NMS revealed more NMS than the other scales assessing NMS. NMF were present in 41% of the sample, with fatigue being the most prevalent symptom (68.5% patients with NMF), and no differences by sex. Patients with greater PD severity had higher prevalence of NMS than patients with lower severity

Conclusions: Almost all patients with PD experience NMS, and many experience NMF. Prevalence rates for NMS using the MDS-NMS are higher than on other scales used and increase with higher disease severity.

Parkinson's disease (PD) is now recognized to comprise a wide range of motor and non-motor symptoms (NMS), spanning the prodromal phase to the palliative stage [1–4]. NMS are frequent, may precede the onset of motor symptoms, correlate variably with the severity of the motor impairment, and become increasingly prevalent with advancing disease [1,5,6]. NMS in PD cause a significant disease burden and quality of life deterioration [7,8] and are a predictor of mortality [9].

In recent years, several rating scales and questionnaires have been developed to assess NMS [10], such as the Scales for Outcomes in Parkinson's Disease (SCOPA) set of instruments [11–15]. The Non-Motor Symptoms Scale (NMSS) [16] and Questionnaire (NMSQuest) [17] were the only dedicated comprehensive NMS assessment tools (self- and investigator completed). The Movement Disorders Society-Unified Parkinson's Rating Scale (MDS-UPDRS) Part I (Non-Motor Experiences of Daily Living) [18,19], is also a comprehensive tool (part of a multi domain scale) specifically designed to quantify the severity and frequency of NMS in PD. They have been thoroughly validated and have significantly contributed to the knowledge of the impact caused by NMS in PD.

The newly developed and validated Movement Disorders Society-Nonmotor Rating Scale (MDS-NMS) is an updated version of the NMSS and has been shown to be a reliable and valid instrument for assessing the burden of a broad variety of NMS, including non-motor fluctuations (NMF) [20]. This rating scale is likely to serve as a global tool in clinical trials, global clinical registries, and epidemiological cohort studies in PD.

The aims of this study were to: (1) analyze the prevalence of NMS in PD patients using the MDS-NMS and, secondary, to compare the prevalence data with the NMSS and MDS-UPDRS Part I; (2) analyze the prevalence of NMF according to the MDS-NMS NMF section; and (3) to ascertain whether there are differences in NMS and NMF prevalence by sex and disease severity.

METHODS

Design

International, multicenter, cross-sectional validation study of the MDS-NMS in a sample of English-speaking PD patients [20].

Participants

The sample was derived from the original MDS NMS international validation study [20]. Patients were recruited from five movement disorders clinics in England and one in the United States from October 2016 to September 2018. Inclusion criterion was having a diagnosis of PD based on MDS criteria [21]. Exclusion criteria were parkinsonism due to other neurodegenerative diseases or secondary causes, moderate or severe cognitive impairment (i.e., Montreal Cognitive Assessment (MoCA) score < 21 [22,23]), and active medical or psychiatric disorders or treatment that hampered accurate assessments (e.g., active psychosis symptoms that would prevent participant from paying adequate attention to the interview).

Ethical aspects

The study was approved by the institutional review boards or ethics committees of the participating centers, and the study was conducted according to Good Clinical Practice [24]. All patients gave their informed consent to participate in the study.

Assessments

Socio-demographic and PD historical data were obtained through an *ad hoc* questionnaire. In addition, the following rating scales were applied:

The MDS-NMS, a comprehensive rating scale assessing NMS and NMF in PD [25]. The section on NMS contains 52 items grouped into 13 domains: depression (5 items), anxiety (4 items), apathy (3 items), psychosis (4 items), impulse control and related disorders (4 items), cognition (6 items), orthostatic hypotension (2 items), urinary (3 items), sexual (2 items), gastrointestinal (4 items), sleep and wakefulness (6 items), pain (4 items), and other (5 items on unintentional weight loss, decreased smell, physical fatigue, mental fatigue, and excessive sweating). Items are scored for frequency (from 0, never, to 4 majority of time) and severity (from 0, not present, to 4 severe), which are multiplied to generate the item total score. Scores for each domain and for the total rating scale are calculated by summing the corresponding items, with a maximum total score of 832 points.

The NMF subscale, with 8 items (depression, anxiety, thinking or cognitive abilities, bladder symptoms, restlessness, pain, fatigue, and excessive sweating) scored from 0 (no change) to 4 (large) for typical degree of change from “on” to “off” periods. These items are summed and then multiplied by the amount of time spent in the “off” state with NMS, which ranges from 1 (rarely) to 4 (majority of time). Maximum possible score is 128.

The NMSS, consisting of 30 items, grouped into nine domains (cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous) [16]. Items are scored for severity (from 0 to 3) and frequency (from 1 to 4), which are multiplied reaching a maximum item score of 12. Total score for domains and the full scale are obtained by sum of the corresponding items, with a maximum of 360 points for total score.

The MDS-UPDRS, comprising four parts [18,19]: Part I, Nonmotor Experiences of Daily Living (nMEDL), with six rater-based items and seven for patient self-assessment; part II, motor experiences of daily living (MEDL), including 13 patient-based items; Part III, motor examination (ME), with 18 items (33 scores); and part IV, motor complications (MCompl), containing six items. In addition, it includes the Hoehn and Yahr staging system (HY).

Finally, the Clinical Impression of Severity Index for PD (CISI-PD) [26], an instrument of four items rating motor signs, disability, motor complications and cognition. The maximum total score is 24 points, with higher scores indicating more severe disease.

Data analysis

Data did not fit normal distribution (Shapiro-Francia test, all <0.001); consequently, non-parametric statistics were used. Descriptive statistics (mean, median, standard deviation, range, percentage) were calculated to characterize the sample. Prevalence of NMS was based on scores ≥ 1 in each MDS-NMS item, domain, and total scale, denoting the presence of a symptom (0 = no symptom present). For comparison, prevalence of NMS assessed with the NMSS and MDS-UPDRS was obtained by the same method.

The sample was grouped according to the following variables of interest: sex, HY severity levels (1-2, mild; 3, moderate; 4-5 severe); CISI-PD (1-7, mild; 8-14 moderate; and 15-24 points, severe), and MDS-UPDRS severity levels (for Part I: 1-10, mild; 11-21, moderate; and ≥22 points, severe; for Part II: 1-12, mild; 13-29, moderate; and ≥30 points, severe; for Part III, 1-32, mild; 33-58, moderate; and ≥59 points, severe; and for Part IV: 1-4, mild; 5-12, moderate; and ≥13 points, severe) [28]. Differences in NMS prevalence between groups was determined calculating Fisher's exact and chi-squared tests.

Data were analyzed using IBM SPSS Statistics 22.

RESULTS

The sample comprised 402 PD patients (62.2% male), with a mean disease duration of 8.2 (standard deviation, SD: 5.9; median: 7, inter-quartile range, IQR: 4-12) years and in Hoehn and Yahr stages 1 to 4 (median: 2, IQR: 2-3). Main characteristics of the sample have been previously published [25] and are displayed in the Supplementary Table 1.

Using the MDS-NMS, 99.7% of the sample showed at least one NMS, while the NMSS identified NMS in 97.6%, and the MDS-UPDRS Part I in 98.5%. Patients had a mean of 16.13 NMS (SD: 9.36; range: 0-46; median: 14; IQR: 9-22) using the MDS-NMS, a mean of 9.55 (SD: 5.64; range: 0-25; median: 9; IQR: 5-13) using the NMSS and a mean of 5.96 NMS (SD: 2.76; range: 0-12; median: 6; IQR: 4-8) using the MDS-UPDRS Part I.

The most prevalent symptom using the MDS-NMS was muscle, joint or back pain (item L1, 67.4% of the sample) (Table 1). The least prevalent NMS was dopamine dysregulation syndrome (item E4, 2.2%). For comparison, using the NMSS, the most frequent symptom was forgetting things (item 17, 52.5%), and the least frequent were the items related to hallucinations and delusions (item 14, 3.7%; and item 13, 14.1%) (Table 1). Using the Part I of the MDS-UPDRS, daytime sleepiness (item 1.8, 72.3%) was the most endorsed item, while features of dopamine dysregulation syndrome (item 1.6, 7.0%) was the least frequent. Overall, corresponding items showed higher prevalence rates using the MDS-NMS than on the NMSS and MDS-UPDRS part 1 (Table 1).

In general, all items were similarly prevalent in both sexes, except item A1. Felt sad or depressed, which was significantly more prevalent in women, and items H2. Urinary frequency, H3. Nocturia, I2. Difficulty with sexual arousal, and J1. Drooling of saliva, significantly more frequent in men (Supplementary Table 2). The prevalence of individual NMS in both sexes is displayed in Supplementary Table 2.

At the domain level the most prevalent on the MDS-NMS was domain K. Sleep and wakefulness (86.5%) (Table 2). The least prevalent domain was E. Impulse control and related disorders (16.5%) in the total sample and in both sexes. Women more commonly reported symptoms in domain A. Depression (65.1%) than men (55.0%), while men showed more symptoms in domains H. Urinary and I. Sexual (78.0% and 47.7%) than women (67.8% and 27.1%).

In general, patients in moderate and severe HY, CISI-PD and MDS-UPDRS Parts II, III and IV severity levels presented higher frequency of NMS in most MDS-NMS domains than patients in the mild

level (Table 3). All MDS-NMS domains presented significantly increasing prevalence as MDS-UPDRS Part I severity levels increased.

Using the NMF subscale, 165 (41%) patients presented NMF, of whom 68.5% presented fluctuations in fatigue and 62.4% in anxiety (Table 4). In this sub-sample of patients with NMF, men represented 59.4%, with significant between-sex differences in NMF only for pain (37.6% men vs 49.3% women). Fluctuations in bladder symptoms significantly increased in prevalence by HY severity levels, while fluctuations in anxiety, thinking and cognitive abilities and excessive sweating were more common as CISI-PD severity levels increased. Table 5 presents the results in the sub-sample with NMF. Results referred to the full sample are showed in Supplementary table 3.

DISCUSSION

This is the first study that uses the newly developed MDS-NMS for reporting the prevalence of NMS and NMF in PD. The results and can lead to a better understanding on the patterns of occurrence and profiles of NMS in PD.

The study revealed a high frequency of NMS using all three scales, yielding the highest prevalence rates with the MDS-NMS. This scale is the most comprehensive tool, and includes NMS that are missing in the other scales, such as impulse control disorders and different types of pain [25]. This is also reflected in the different mean number of NMS measured by each instrument indicating that this rating scale is able to capture more comprehensively the full range of important and prevalent NMS or to differentiate several specific non-motor symptoms. Our prevalence figures are overall in line with previous studies that have shown the great frequency and burden of NMS in PD [17,29]. For example, using the NMSQuest, PD patients have 8.3 NMS in average (range: 4-19), while healthy controls show a mean of 3.5 NMS (range: 2-12) [6,30].

Due to the differences between the rating scales applied in this study, their components are not equivalent and therefore the most and least prevalent NMS are not the same across instruments. For example, the NMSS does not have an item on dopamine dysregulation syndrome. Nonetheless, items pertaining to the cognitive, urinary and pain domains were the most endorsed in all three instruments, while those pertaining to impulse control disorders and psychosis domains were the least prevalent. Cognitive decline, including mild cognitive impairment, may

occur even in early stages of the disease, and is related to lower quality of life and higher caregiver burden [31]. Regarding urinary problems, 62% patients had nocturia and 56% urinary urgency in a previous study using the NMSQuest [30]. These symptoms are frequently reported as one of the main sources of disease burden and impairment of quality of life in PD patients [32–34]. Pain is also a complex and common symptom in PD as seen in the PRIAMO study [29], with a considerable impact on quality of life [35]. Specifically, musculoskeletal pain has been found to be highly prevalent in different studies, with abnormal nociceptive input processing in the central nervous system as a possible explicative factor [36,37]. Given the frequency and impact of these NMS, it is essential that clinicians are aware of their high frequency to fully assess and manage them [38].

The differences in frequency of some NMS between men and women have been described in previous studies [39,40]. In our study, women showed higher prevalence of depression on the MDS-NMS, similar to what is seen in the general population, while men presented more urinary and sexual problems and drooling of saliva, in line with the results of other studies [39]. Gender-related differences in PD have been also seen in age at PD onset, in some motor features and motor fluctuations and with levodopa-induced dyskinesia which have been reported to be more severe and of earlier appearance in women [41,42]. In this study, some differences were also observed between sexes in NMF. Women showed significantly more fluctuations only in pain than men, but according to previous studies, being female is a risk factor for NMF overall [43,44]. Differences between sexes in PD may be explained by variances in gene expression in human dopaminergic neurons in the central nervous system, the protective role of estrogens in women, different profiles of risk factors between men and women and the influence of environmental factors [42]. More studies are however needed to elucidate the basic physiological mechanisms that underlies the sex-related differences in NMS and NMF in PD.

In general, the prevalence of NMS and some NMF increased as PD severity increased, as seen in other studies [45]. Some NMS are common in prodromal or early stages of PD (sleep disorders, constipation and depression) and have been proposed as a clinical biomarkers of PD, while others clearly are more frequent in advanced stages of the disease (dementia, apathy) [4,46]. Different profiles of NMS can be also identified in early- and late-stage- PD patients [47]. In our study, depression, apathy, psychosis, orthostatic hypotension, and urinary and gastrointestinal problems were significantly more prevalent in moderate-severe HY stages than in mild patients. In general, NMS were also less prevalent in mild than in more severe levels using CISI-PD and MDS-UPDRS

severity levels. The existence of non-motor subtypes or phenotypes in PD and their correlation with PD motor subtypes is an emerging line of research [48], and the differences in NMS prevalence across the PD stages may shed a light on this topic. In line with this, severity of motor and cognitive features combined with disease duration has been proposed as one of the aspects for defining a benign vs malignant (or a slow vs fast) PD course [49]. According to previous studies, disease duration is also a determinant of the appearance of NMF, along with levodopa treatment, motor fluctuations and autonomic symptoms [50].

As an advantage, the MDS-NMS is the first comprehensive and global instrument that includes the assessment of the NMF. NMF appear simultaneously with or later than motor fluctuations, and can be a marker of severe neurodegeneration [51]. Despite its impact on the patients' quality of life and disease burden, NMF have been largely underestimated in clinical practice and research [52].

Some limitations in this study should be acknowledged. The sample was limited to English-speaking patients attending movement disorders clinics in United States and United Kingdom. Moreover, it was a convenience sample and whilst efforts were made to include patients from all stages, advanced stages were underrepresented, and the prevalence is likely to be even higher in more advanced samples. On the other hand, although the inclusion of patients with mild cognitive impairment could lead to some difficulties in the application of the instrument, cognitive impairment is common in PD and it is likely that the prevalence of cognitive features is an underestimate. These weaknesses could restrict external validity of the study, but the main characteristics of the sample (mean age, sex distribution, HY stages) are coincident with most studies on clinical characteristics of PD patients. Although it is not an epidemiological study, it is the first study reporting frequencies of NMS and NMF using the newly developed MDS-NMS.

In conclusion, the prevalence of NMS and NMF in our sample was high. The use of the MDS-NMS provides a greater range and higher prevalence rates of NMS, and its routine administration can help lead to a better recognition and management of all NMS in PD.

Supplemental tables

Table 1. Descriptive statistics of the sample.

Table 2. Frequency and percentage of non-motor symptoms (scores ≥1) by sex

Table 3. Percentage of patients with NMF by severity levels in the total sample

Authors Roles

1. Research project: A. Conception, B. Organization, C. Execution;

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

C.R.-B.: 2A, 2B, 3A.

A.S.: 1A, 1B, 1C, 2C, 3B.

A.R.: 1B, 1C, 2C, 3B.

K.R.C.: 1A, 1B, 1C, 2C, 3B.

P.M.-M.: 1A, 1B, 1C, 2C, 3B.

D.W.: 1A, 1B, 1C, 2C, 3B.

Data Access and Responsibility

C.R.-B. takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Compliance Statement

The study was approved by the institutional review boards or ethics committees of the participating centers, and the study was conducted according to Good Clinical Practice [24]. All patients gave their informed consent to participate in the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

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PMM is Co-Chair of the Program on Rating Scales of the IPMDS.

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Table 1. Percentage of symptoms measured by MDS-NMS, NMSS and MDS-UPDRS Part I.

MDS-NMS	%[a]	NMSS	%[a]	MDS-UPDRS Part I	%[a]
A1. Sad or depressed	47.9	10. Sad or depressed	39.9	1.3 Depressed mood	38.9
		11. Flat moods	28.4		
A2. Difficulty pleasure	25.4	12. Difficulty pleasure	22.1		
A3. Hopeless	21.0				
A4. Negative thoughts	26.4				
A5. Felt life is not worth	12.0				
B1. Worried	54.5	9. Nervous, worried	31.1	1.4 Anxious mood	46.8
B2. Nervous	44.3	9. Nervous, worried	31.1		
B3. Panic or anxiety attacks	15.2				
B4. Worried about in public	32.1	9. Nervous, worried	31.1		
C1. Reduced motivation	38.3	7. Lost interest in surroundings	20.2	1.5 Apathy	28.7
		8. Lost interest in doing things	33.3		
C2. Reduced interest talking	28.4	8. Lost interest in doing things	33.3		
C3. Reduction in emotions	18.7	11. Flat moods	28.4		
D1. Passage or presence	21.9			1.2 Hallucinations and psychosis	17.7
D2. Illusions	15.4	13. Sees things that are not there	14.1		
D3. Hallucinations	10.7	13. Sees things that are not there	14.1		
D4. Delusions, misidentification	4.5	14. Beliefs that are not true	3.7		
E1. Increase in gambling, sex,	8.2				
E2. Increase other behaviours	6.5				
E3. Punding	4.0				
E4. Dopamine dysregulation	2.2			1.6 Features of DDS	7.0
F1. Difficulty remembering	59.0	17. Forget things	52.5	1.1 Cognitive impairment	48.0
		18. Forget to do things	36.8		
F2. Difficulty learning new	34.6				
F3. Difficulty keeping focus	45.8	16. Problems sustaining concentration	40.8		
F4. Difficulty finding words	54.0				
F5. Executive abilities	28.6				
F6. Visuospatial abilities	17.4				
G1. Lightheaded or fainted	29.6	1. Light-headedness, faintness	36.1	1.12 Light headedness on standing	33.1
G2. Dizziness or weakness	34.3	1. Light-headedness, faintness	36.1		

H1. Urinary urgency	57.2	22. Urgency	48.0	1.10 Urinary problems	63.7
H2. Urinary frequency	42.3	23. Frequency	37.7		
H3. Nocturia	41.5	24. Nocturia	50.9		
I1. Decreased sexual drive	31.4	25. Altered interest in sex	26.9		
I2. Difficulty sexual arousal	29.3	26. Problems having sex	26.3		
J1. Drooling of saliva	46.6	19. Dribbling saliva	33.3		
J2. Difficulty swallowing	30.4	20. Difficulty swallowing	28.1		
J3. Nausea, feel sick stomach	19.7				
J4. Constipation	34.6	21. Constipation	33.1	1.11 Constipation problems	48.0
K1. Insomnia	51.4	5. Difficult falling/staying asleep	49.0	1.7 Sleep problems	62.6
K2. REM sleep behavior	46.8				
K3. Dozed off or fallen asleep	48.3	3. Doze off or fall sleep	46.0	1.8 Daytime sleepiness	72.3
K4. Restlessness	37.1	6. Restlessness	33.3		
K5. Periodic limb movements	38.3				
K6. Snoring, gasping, breathing	13.2				
L1. Muscle, joint or back pain	67.4	27. Pain	29.6	1.9 Pain and other sensations	64.9
L2. Deep or dull aching pain	28.6	27. Pain	29.6		
L3. Pain due to dystonia	20.9				
L4. Other types of pain	14.4				
M1. Weight loss	10.7	29. Change in weight	14.2		
M2. Impaired olfaction	57.0	28. Change in ability to taste/smell	54.7		
M3. Physical fatigue	55.0	4. Fatigue or lack of energy	51.2	1.13 Fatigue	64.9
M4. Mental fatigue	32.3	4. Fatigue or lack of energy	51.2		
M5. Excessive sweating	21.4	30. Excessive sweating	17.2		

[a] Percentages are computed as the proportion of scores ≥1 in each item.

Table 2. Percentage of patients with non-motor symptoms in each MDS-NMS domain and total scale in total sample and by sex

	Total sample (N=402)		Men (N=250)		Women (N=152)		
	N	%[a]	N	%[a]	N	%[a]	p[b]
A. Depression	226	56.4	127	55.0	99	65.1	**0.007**
B. Anxiety	270	67.2	162	64.8	108	71.1	0.228
C. Apathy	189	47.0	122	48.8	67	44.1	0.410
D. Psychosis	125	31.1	84	33.6	41	27.0	0.183
E. IC & related disorders	66	16.5	40	16.1	26	17.1	0.783
F. Cognition	322	80.1	203	81.2	119	78.3	0.520
G. Orthos. hypotension	166	41.3	105	42.0	61	40.1	0.754
H. Urinary	298	74.1	195	78.0	103	67.8	**0.026**
I. Sexual	150	40.0	112	47.7	38	27.1	**<0.001**
J. Gastrointestinal	289	72.1	184	73.9	105	69.1	0.304
K. Sleep & wakefulness	347	86.5	215	86.3	132	86.8	1.000
L. Pain	305	75.9	187	74.8	118	77.6	0.550
M. Other	322	80.1	197	78.8	125	82.2	0.441
MDS-NMS TOTAL	372	99.7	232	99.6	140	100.0	1.000

[a] Percentages are computed as the proportion of scores ≥1 in each domain.

[b] Fisher's test. IC: Impulse control.

Table 3. Percentage of patients with NMS in MDS-NMS domains by severity levels.

Severity levels†	MDS-NMS domains													MDS-NMS
HY	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**Total**
Mild (N=270)	48.7 *	64.1	40.7 *	27.8 *	18.5	75.9 *	38.9 *	70.4	39.1	69.5 *	85.2	73.3	78.1	99.6
Moderate (N=111)	69.4 *	71.2	58.6 *	34.2 *	13.6	91.0 *	42.3 *	80.2	44.0	73.9 *	89.2	80.2	82.9	100
Severe (N=21)	85.7	85.7	66.7	57.1	4.8	76.2	66.7	90.5	31.6	95.2	90.0	85.7	90.5	100
p [a]	*<0.001*	*0.072*	*0.001*	*0.014*	*0.169*	*0.003*	*0.043*	*0.030*	*0.516*	*0.036*	*0.522*	*0.203*	*0.272*	*0.791*
CISI-PD														
Mild (N=228)	47.1 *	60.1 *	37.7 *	23.2 *	14.0	73.2 *	39.9	67.5 *	34.0 *	64.5 *	82.9	72.4	75.0 *	99.5
Moderate (N=158)	67.7 *	75.9 *	57.6 *	41.8 *	20.4	89.2 *	43.7	82.9 *	48.3 *	80.9 *	90.4	79.7	86.7 *	100
Severe (N=12)	83.3	83.3	66.7	50.0	8.3	91.7	33.3	91.7	36.4	100	100	100	100	100
p [a]	*<0.001*	*0.002*	*<0.001*	*<0.001*	*0.190*	*<0.001*	*0.650*	*0.001*	*0.022*	*<0.001*	*0.040*	*0.036*	*0.004*	*0.678*
MDS-UPDRS Part I														
Mild (N=222)	60.4 *	55.0 *	33.3 *	22.5 *	9.0 *	71.2 *	34.2	65.8 *	28.2 *	63.3 *	79.3 *	70.7 *	72.1 *	100
Moderate (N=140)	25.0 *	81.4 *	58.6 *	39.3 *	25.7 *	92.1 *	45.7	84.3 *	48.5 *	84.3 *	96.4 *	85.0 *	88.6 *	100
Severe (N=30)	0	96.7	99.7	56.7	30.0	100	80.0	96.7	82.8	86.7	100	83.3	100	100
p [a]	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.005*	*<0.001*	*0.678*
MDS-UPDRS Part II														
Mild (N=216)	43.7 *	58.8 *	34.7 *	20.8 *	12.5 *	72.7 *	31.9 *	65.7 *	32.0 *	62.5 *	84.7	70.8 *	71.8 *	99.5
Moderate (N=162)	71.0 *	79.0 *	59.9 *	43.2 *	23.6 *	90.7 *	53.7 *	84.0 *	50.0 *	85.1 *	88.2	84.0 *	90.7 *	100
Severe (N=13)	84.6	76.9	100	69.2	7.7	92.3	61.5	100	58.3	92.3	100	82.3	82.3	100
p [a]	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.012*	*<0.001*	*<0.001*	*<0.001*	*0.001*	*<0.001*	*0.219*	*0.005*	*<0.001*	*0.663*
MDS-UPDRS Part III														
Mild (N=194)	46.6 *	60.8	35.1 *	21.1 *	12.9	74.7	35.6	66.0 *	32.1	67.0	86.6	67.0 *	72.7	99.5
Moderate (N=96)	68.8 *	69.8	51.0 *	36.5 *	10.4	86.5	49.0	83.3 *	38.2	79.2	84.4	81.3 *	83.3	100
Severe (N=10)	90.0	100	70.0	40.0	20.0	90.0	50.0	70.0	33.3	60.0	100	80.0	80.0	100
p [a]	*<0.001*	*0.020*	*0.006*	*0.013*	*0.630*	*0.048*	*0.075*	*0.008*	*0.604*	*0.076*	*0.418*	*0.034*	*0.128*	*0.764*
MDS-UPDRS Part IV														
Mild (N=97)	53.6	63.9	44.3	27.8	14.6	81.4	39.2	70.1	26.4	76.3	89.7	71.1	84.5	100
Moderate (N=125)	71.2	81.7	57.9	38.1	29.4	84.1	46.0	86.5	57.7	81.6	92.1	84.1	90.5	100
Severe (N=9)	88.9	88.9	66.7	66.7	22.2	100	55.6	77.8	62.5	77.8	88.9	77.8	100	100
p [a]	*0.007*	*0.006*	*0.090*	*0.035*	*0.034*	*0.346*	*0.450*	*0.011*	*<0.001*	*0.623*	*0.809*	*0.065*	*0.211*	*1.000*

† Parkinson's disease severity levels according to Expert Rev Neurother 2018; 18: 41–50 [Ref. 28]

[a] chi-squared test; * significant differences between mild and moderate levels.

The table shows the percentage of scores ≥1 in each domain.

MDS-NMS domains: A. Depression, B. Anxiety, C. Apathy, D. Psychosis, E. Impulse control and related disorders, F. Cognition, G. Orthostatic hypotension, H. Urinary, I. Sexual, J. Gastrointestinal, K. Sleep and wakefulness, L. Pain, M. Other.

Table 4. Percentage of patients with NMF in the total sample and by sex

		N	% Total sample[a] (N=402)	% patients with fluctuations [a] (N=165)	N	% men[a] (N=250)	% men with fluctuations [a] (N=98)	N	% women[a] (N=152)	% women with fluctuations [a] (N=67)	p[b]
1.	Depression	67	16.7	40.6	36	14.5	36.7	31	20.4	46.3	0.259
2.	Anxiety	103	25.6	62.4	59	23.6	60.2	44	28.9	65.7	0.516
3.	Thinking or cognitive abilities	93	23.1	56.4	52	20.9	53.1	41	27.0	61.2	0.339
4.	Bladder symptoms	41	10.2	24.8	27	10.8	27.6	14	9.2	20.9	0.364
5.	Restlessness	70	17.4	41.8	44	17.6	43.9	26	17.1	39.8	0.526
6.	Pain	64	15.9	38.8	31	12.4	31.6	33	21.7	49.3	0.034
7.	Fatigue	113	28.1	68.5	68	27.2	69.4	45	29.6	67.2	0.865
8.	Excessive sweating	24	6.0	14.5	14	5.6	14.3	10	6.6	14.9	1.000

[a] Percentages are computed as the proportion of scores ≥1 in each item.

[b] Fisher's test for the sample with fluctuations

Table 5. Percentage of patients with NMF by severity levels

Severity levels†	NMF items							
HY	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Mild (N=105)	36.2	59.0	52.4	23.8 [a]	42.9	37.1	69.5	9.5
Moderate (N=47)	48.9	66.0	68.1	19.1 [a]	42.6	42.6	63.8	23.4
Severe (N=13)	46.2	76.9	46.2	53.8	30.8	38.5	76.9	23.1
*p**	*0.306*	*0.382*	*0.146*	*0.035*	*0.701*	*0818*	*0.621*	*0.053*
CISI-PD								
Mild (N=59)	33.9	47.5 [a]	44.1 [a]	16.9	39.0	35.6	61.0	5.1 [a]
Moderate (N=96)	43.8	70.8 [a]	64.6 [a]	27.1	44.8	38.5	72.9	19.8 [a]
Severe (N=10)	50.0	70.0	50.0	50.0	30.0	60.0	70.0	20.0
*p**	*0.395*	*0.012*	*0.040*	*0.060*	*0.572*	*0.341*	*0.300*	*0.037*
MDS-UPDRS Part IV								
Mild (N=97)	31.3	50.0	45.8	20.8	37.5	39.6	60.4	8.3 [a]
Moderate (N=125)	45.9	68.4	60.2	25.5	42.9	38.8	75.5	16.3 [a]
Severe (N=9)	44.4	67.6	67.6	44.4	44.4	22.2	88.9	44.4
*p**	*0.235*	*0.095*	*0.209*	*0.323*	*0.810*	*0.599*	*0.082*	*0.021*

† Parkinson's disease severity levels according to Expert Rev Neurother 2018; 18: 41–50 [Ref. 28]

* chi-squared test; [a] significant differences between levels.

Percentages are computed as the proportion of scores ≥1 in each item.

NMF items: 1. Depression, 2. Anxiety, 3 Thinking or cognitive abilities, 4. Bladder symptoms, 5. Restlessness, 6. Pain, 7. Fatigue, 8. Excessive sweating.