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ABSTRACT

Background: Nonmotor symptoms (NMS) have a great impact on patients with Parkinson disease (PD). The Non-Motor Symptoms Scale (NMSS) is an instrument specifically designed for the comprehensive assessment of NMS in patients with PD. NMSS psychometric properties have been tested in this study.

Methods: Data were collected in 12 centers across 10 countries in America, Asia, and Europe. In addition to the NMSS, the following measures were applied: Scales for Outcomes in Parkinson's Disease (SCOPA)-Motor, SCOPA-Psychiatric Complications (SCOPA-PC), SCOPA-Cognition, Hoehn and Yahr Staging (HY), Clinical Impression of Severity Index for Parkinson's Disease (CISI-PD), SCOPA-Autonomic, Parkinson's Disease Sleep Scale (PDSS), Parkinson's Disease Questionnaire–39 items (PDQ-39), and EuroQol–5 dimensions (EQ-5D). NMSS acceptability, reliability, validity, and precision were analyzed.

Results: Four hundred eleven patients with PD, 61.3% men, were recruited. The mean age was 64.5 ± 9.9 years, and mean disease duration was 8.1 ± 5.7 years. The NMSS score was 57.1 ± 44.0 points. The scale was free of floor or ceiling effects. For domains, the Cronbach α coefficient ranged from 0.44 to 0.85. The intraclass correlation coefficient (0.90 for the total score, 0.67–0.91 for domains) and Lin concordance coefficient (0.88) suggested satisfactory reproducibility. The NMSS total score correlated significantly with SCOPA-Autonomic, PDQ-39, and EQ-5D (r_S = 0.57–0.70). Association was close between NMSS domains and the corresponding SCOPA-Autonomic domains (r_S = 0.51–0.65) and also with scales measuring related constructs (PDSS, SCOPA-PC) (all $p < 0.0001$). The NMSS total score was higher for women ($p < 0.02$) and for increasing disease duration, HY, and CISI-PD severity level ($p < 0.001$). The SEM was 13.91 for total score and 1.71 to 4.73 for domains.

Conclusion: The Non-Motor Symptoms Scale is an acceptable, reproducible, valid, and precise assessment instrument for nonmotor symptoms in Parkinson disease. ***Neurology*® 2009;73: 1584–1591**

GLOSSARY

CCC = concordance correlation coefficient; **CISI-PD** = Clinical Impression of Severity Index for Parkinson's Disease; **EQ-5D** = EuroQol-5 dimensions; **HRQL** = health-related quality of life; **HY** = Hoehn and Yahr Staging; **ICC** = intraclass correlation coefficient; **IRB** = institutional review board; **MDS-UPDRS** = Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale; **NMS** = nonmotor symptoms; **NMSQuest** = Non-Motor Symptoms Questionnaire; **NMSS** = Non-Motor Symptoms Scale; **PD** = Parkinson disease; **PDQ-39** = Parkinson's Disease Questionnaire–39 items; **PDSS** = Parkinson's Disease Sleep Scale; **SCOPA** = Scales for Outcomes in Parkinson's Disease; **SCOPA-AUT** = Scales for Outcomes in Parkinson's Disease–Autonomic; **SCOPA-COG** = Scales for Outcomes in Parkinson's Disease–Cognition; **SCOPA-M** = Scales for Outcomes in Parkinson's Disease–Motor; **SCOPA-PC** = Scales for Outcomes in Parkinson's Disease–Psychiatric Complications; **SEM** = standard error of measurement; **UPDRS** = Unified Parkinson's Disease Rating Scale; **VAS** = visual analog scale.

Nonmotor symptoms (NMS) are common in Parkinson disease (PD). Studies have found a prevalence ranging from 21% at the diagnosis of PD[1] to 88% after 7 years of disease duration.[2] In a large international sample, the average number of declared NMS was more than 10 symptoms, and less than 2% of patients did not experience any of the explored NMS.[3]

NMS include autonomic dysfunction, mood disorders, fatigue, sleep disturbances, and neuropsychiatric symptoms. Patients experience an increasing number of NMS as the disease progresses,

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but some of these symptoms (olfactory problems, constipation, depression, and REM behavior disorder) may be present in the premotor phase of the disease.[4] These NMS may contribute to identify the population at risk and help in the early detection of PD, but they may lead also to misdiagnosis.[1]

NMS have a great impact on patients' quality of life and psychosocial functioning, and they cause institutionalization and increasing costs of care.[4] Nevertheless, more than 50% of existing NMS may be neglected in clinical practice,[4,5] a fact that can be explained, in part, by the lack of comprehensive and valid specific instruments to identify and assess NMS. Before 2006, several rating scales were used to assess some NMS, but there were no practical and reliable instruments for evaluating the whole range of NMS. Two instruments have been recently developed to address this unmet need: the Non-Motor Symptoms Questionnaire (NMSQuest),[6] for screening purposes, and the Non-Motor Symptoms Scale (NMSS),[7] for NMS assessment. Both tools, NMSQuest and NMSS, have been object of pilot studies by the PD NMS Group, an academic organization.

The objective of the present study is to test the NMSS[7] in a multicenter international setting to confirm and expand the information available about the NMSS psychometric attributes.

METHODS

Design. This was an international, multicenter, cross-sectional study with retest.

Sample. Consecutive patients with PD, older than 30 years at onset of PD and at any stage of disease, diagnosed by a neurologist with competence in movement disorders according to UK PD Brain Bank criteria,[8] participated in the study. Exclusion criteria were the inability to read, understand, or answer written questionnaires, and the presence of comorbidity, sequelae, or any disorder that interferes with or impedes assessment of PD manifestations.

Patients were recruited in 12 centers across 10 countries—Brazil, India, Italy, Japan, The Netherlands, Romania, Spain, United Kingdom, United States, and Venezuela—from November 2007 to September 2008.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Carlos III Institute of Health institutional review board (IRB) and by local IRBs. Patients gave their informed consent before their participation in the study.

Assessments. In addition to sociodemographic and historic data, the following instruments were applied:

Neurologist-based. Scales for Outcomes in Parkinson's Disease–Motor (SCOPA-M),[9] SCOPA–Psychiatric Complications (SCOPA-PC),[10] SCOPA–Cognition (SCOPA-COG),[11] Hoehn and Yahr Staging (HY),[12] Clinical Impression of Severity Index for Parkinson's Disease (CISI-PD; a global clinical impression of severity),[13] and the NMSS.[7]

Patient self-assessments. SCOPA–Autonomic (SCOPA-AUT),[14] Parkinson's Disease Sleep Scale (PDSS),[15] and EuroQol–5 dimensions (EQ-5D)[16] and Parkinson's Disease Questionnaire–39 items (PDQ-39),[17] for health-related quality of life (HRQL) assessment.

These assessments were chosen to examine areas not explored in the pilot study[7] or to offer alternative information (e.g., SCOPA-M instead of Unified Parkinson's Disease Rating Scale [UPDRS]). A balance between observer-rated and self-assessments, minimizing administrative and respondent burden, was sought.

The NMSS is a specific scale developed to assess MNS in PD over the past month. It is composed of 9 domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/apathy (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary (3 items), sexual function (2 items), and miscellaneous (4 items). Items are scored for severity (from 0 to 3) and frequency (from 1 to 4), to capture symptoms that are severe but relatively infrequent or that are less severe but persistent. The theoretical maximum total score is 360 points.

For all rating scales except SCOPA-COG, PDSS, and EQ visual analog scale (VAS), higher scores reflect higher severity in the construct being measured. All scales were cross-culturally adapted, if needed, following a protocol for translation, back-translation, and consensus by bilingual persons, and participation of experts and patients when appropriate.

To evaluate the stability of the NMSS (test-retest reliability), a group of patients in each participant center ($n \geq 10$) repeated the NMSS and CISI-PD assessment 1 to 2 weeks after the first evaluation. In patients with fluctuations, the assessments were performed during "on" state.

Data analysis. Data were analyzed at the National Center of Epidemiology, Carlos III Institute of Health, Madrid, Spain. Because data did not fit normal distribution, nonparametric statistics were used. In addition to descriptive statistics, the following NMSS psychometric properties were explored.

Acceptability. Quality of data were considered satisfactory if more than 95% of NMSS data were fully computable. The range of scores, the difference between mean and median (arbitrary limit, 10% of the maximum possible score), the floor and ceiling effect (maximum acceptable for both, 15%),[18] and the skewness (limits, -1 to $+1$) were calculated.

Reliability. Internal consistency was tested by the Cronbach α coefficient (criterion value, ≥ 0.70), item-total correlation (corrected for overlap; criterion value, $r_S > 0.30$), and item homogeneity (criterion value, ≥ 0.30). The intraclass correlation coefficient (ICC, 2-way random effects model) was used to determine the test-retest reliability of NMSS. The Lin concordance correlation coefficient (CCC) was also calculated for the total NMSS.[19,20] ICC and CCC values ≥ 0.70 were considered satisfactory.[21] Standard values for acceptability and reliability were according to previous studies.[7,22,23]

Construct validity. For convergent validity, a strong relationship ($r_S \geq 0.50$)[24,25] was hypothesized between NMSS and SCOPA-AUT (for total scores and corresponding subscales) and, according to previous results,[7] between NMSS total score and HRQL measures (PDQ-39 and EQ-5D). Low to moderate association ($r_S < 0.50$) was predicted for NMSS and other PD-

related instruments. Internal validity was determined on the basis of intercorrelations of NMSS domains (standard, r_S = 0.30–0.70).[26] Known-groups validity was explored for grouping of patients by disease duration (<5 years, 5–9 years, ≥10 years), age at onset (<50 years, 51–65 years, >65 years), disease stage (HY), and disease severity levels based on CISI-PD scores.[27] At this aim, Mann-Whitney and Kruskal-Wallis tests were used to compare groups.

Precision for each NMSS domain and total score was estimated by means of the standard error of measurement (SEM = SD × $\sqrt{[1 - r_{xx}]}$).[22,28] An SEM value <½ SD was used as criterion for precision, and both SEM and ½ SD were used as estimates of minimally detectable change.[29]

RESULTS In the study, 411 patients with PD were included (median 40 per center, range 20–60). Mean age (±SD) was 64.5 ± 9.9 (range 34–89) years, and they were predominantly men (61.3%), married (75.4%) or widowed (10%), retired (56.4%) or employee (25.3%), with 10.9 ± 4.4 years of education. The age at onset of PD was 56.4 ± 10.3 years, the duration of disease was 8.1 ± 5.7 years, and the HY distribution was as follows: stage 1, 15.1%; stage 2, 40.4%; stage 3, 32.1%; stage 4, 10.5%; and stage 5, 1.7%. More than two-thirds of the sample (68.6%) were treated with a combination of antiparkinsonian drugs, whereas 28.5% were in monotherapy (levodopa, 16.6%; dopamine agonist, 8.8%; other, 3.1%) and 2.9% were drug naive.

Descriptive statistics of the applied measures are shown in table 1. NMSS data were fully computable for 99.5% of the sample. The NMSS total mean score was 57.1 ± 44.0 (median = 43, difference mean − median = 14.1 points, 3.9% and 6.1% of the maximum theoretical and observed score; table 2). The difference between NMSS scores from English-speaking and non–English-speaking countries was not significant. The NMSS total score was higher for women (64.5 ± 48.6) than for men (52.4 ± 40.3) ($p < 0.02$). Two patients (0.50%) declared no NMS, whereas 1 patient (0.24%) reached the maximum score in the study (233 points). Regarding NMSS domains, all of them showed a floor effect, and 2 (perceptual problems/hallucinations and miscellaneous) did not cover the full possible range of scores (table 2). Skewness was 1.2 for the total score.

Cronbach α coefficients ranged from 0.44 (miscellaneous) to 0.85 (mood/apathy) (table 3). Item-total correlation reached values from 0.20 to 0.73 (table 3), and item homogeneity reached values from 0.16 (miscellaneous) to 0.54 (attention/memory). Regarding test-retest reliability (n = 127), the ICC for items reached values between 0.56 (item 15, double vision) to 0.89 (item 10, seem sad or depressed). For domains, the ICC ranged from 0.67 (sexual function domain) to 0.91 (mood/apathy domain) (table 3). The ICC was 0.90 and the CCC was 0.88 for the NMSS total score.

Table 1 Score distribution of the applied rating scales

	Mean	SD	Min	Max
SCOPA-M	22.0	12.4	2	72
Motor examination	11.9	6.9	0	41
ADL	7.2	4.0	0	21
Motor complications	2.7	3.1	0	12
SCOPA-PC	1.9	2.5	0	16
SCOPA-COG	25.4	8.6	2	43
CISI-PD	8.5	4.8	1	24
Motor status	2.8	1.2	0	6
Disability	2.4	1.4	0	6
Motor complications	1.7	1.7	0	6
Cognitive status	1.6	1.4	0	6
SCOPA-AUT	18.0	10.4	0	51
PDSS	96.5	29.6	3	150
EQ-5D index	0.56	0.34	−0.65	1
EQ-5D VAS	63.6	22.3	0	100
PDQ-39	28.7	17.5	0	87.3

Min = minimum; Max = maximum; SCOPA = Scales for Outcomes in Parkinson's Disease; M = Motor; ADL = activities of daily living; PC = Psychiatric Complications; COG = Cognition; CISI-PD = Clinical Impression of Severity Index for Parkinson's Disease; AUT = Autonomic; PDSS = Parkinson's Disease Sleep Scale; EQ-5D = EuroQoL-5 dimensions; VAS = visual analog scale; PDQ-39 = Parkinson's Disease Questionnaire-39 items.

As hypothesized, the NMSS total score reached the highest correlation coefficients with SCOPA-AUT (r_S = 0.64), PDQ-39 (r_S = 0.70), and—at a lower level—EQ-5D Index (r_S = 0.57). Correlation coefficient values with other measures were as follows: HY, 0.38; SCOPA-M, 0.44; SCOPA-PC, 0.51; SCOPA-COG, 0.44; CISI-PD, 0.49; PDSS, 0.53; and EQ-VAS, −0.37. NMSS domains showed a tight relationship with measures for similar constructs: sleep/fatigue with PDSS (r_S = 0.56), perceptual problems/hallucinations with SCOPA-PC (r_S = 0.53), and attention/memory with CISI-PD cognition (r_S = 0.51). Just under the statistical threshold for a high association was the correlation between attention/memory and SCOPA-PC (r_S = 0.49).

Regarding the correlation between NMSS domains and the corresponding SCOPA-AUT dimensions, the following coefficient values were found: cardiovascular, r_S = 0.62; gastrointestinal, r_S = 0.65; urinary, r_S = 0.65; and sexual function, r_S = 0.51. NMSS item 30 (excessive sweating) correlated at a high level with the SCOPA-AUT thermoregulatory domain (r_S = 0.51). In addition, some NMSS domains reached high correlations with the PDQ-

Table 2 Data quality and acceptability of the Non-Motor Symptoms Scale

	Fully computable, %	Mean	SD	Median	Min	Max	Floor effect, %	Ceiling effect, %
Item/domain								
1. Light-headedness	100	1.4	2.4	0.0	0	12	59.4	1.0
2. Fainting	100	0.3	1.3	0.0	0	12	90.8	0.5
D1. Cardiovascular	100	1.8	3.2	0.0	0	24	57.9	0.2
3. Daytime sleepiness	100	2.0	2.9	0.0	0	12	52.6	2.9
4. Fatigue	100	3.5	3.9	2.0	0	12	34.1	8.8
5. Difficulty falling asleep	100	2.7	3.8	1.0	0	12	49.6	8.5
6. Restless legs	99.8	1.4	2.7	0.0	0	12	68.0	1.5
D2. Sleep/Fatigue	99.8	9.6	9.0	7.0	0	48	13.2	0.2
7. Lost interest in surroundings	100	1.5	2.7	0.0	0	12	65.7	1.9
8. Lack motivation	100	1.9	3.2	0.0	0	12	56.4	4.4
9. Feel nervous	99.8	2.3	3.4	1.0	0	12	49.3	5.6
10. Seem sad	100	2.5	3.6	0.0	0	12	50.4	7.1
11. Flat mood	100	1.4	2.8	0.0	0	12	67.9	2.7
12. Difficulty experiencing pleasure	100	1.4	3.0	0.0	0	12	70.6	3.6
D3. Mood/Apathy	99.8	11.2	14.3	6.0	0	72	24.4	0.5
13. Hallucinations	100	0.6	1.9	0.0	0	12	82.5	1.0
14. Delusions	100	0.5	1.9	0.0	0	12	90.3	1.0
15. Double vision	100	0.7	2.1	0.0	0	12	82.5	1.5
D4. Perceptual problems/ Hallucinations	100	1.9	4.1	0.0	0	25	70.1	0.2
16. Concentration	100	2.3	3.1	1.0	0	12	46.0	3.2
17. Forget things or events	100	2.0	2.9	1.0	0	12	49.1	2.9
18. Forget to do things	100	1.6	2.8	0.0	0	12	58.2	2.9
D5. Attention/Memory	100	5.8	7.3	3.0	0	36	28.0	0.2
19. Saliva	100	2.2	3.5	0.0	0	12	56.7	6.3
20. Swallowing	100	1.3	2.6	0.0	0	12	70.6	1.7
21. Constipation	100	2.9	4.0	0.0	0	12	50.9	9.7
D6. Gastrointestinal	100	6.3	7.3	4.0	0	36	26.5	0.5
22. Urgency	100	2.6	3.4	1.0	0	12	45.5	4.4
23. Frequency	100	2.8	3.6	1.0	0	12	45.5	5.8
24. Nocturia	100	3.6	3.8	2.0	0	12	31.6	10.0
D7. Urinary	100	9.0	8.7	7.0	0	36	17.8	1.2
25. Interest in sex	100	1.9	3.6	0.0	0	12	67.2	7.5
26. Problems having sex	100	1.8	3.5	0.0	0	12	72.0	6.3
D8. Sexual dysfunction	100	3.7	5.8	0.0	0	24	56.9	2.4
27. Pain	100	2.0	3.4	0.0	0	12	60.6	5.1
28. Taste or smell	100	2.6	3.8	0.0	0	12	58.4	7.3
29. Weight change	100	1.4	2.8	0.0	0	12	70.3	2.7
30. Excessive sweating	100	1.6	3.2	0.0	0	12	69.6	4.1
D9. Miscellaneous	100	7.6	8.1	5.0	0	37	24.1	0.2
NMSS total	99.5	57.1	44.0	43.0	0	233	0.5	0.2

Min = minimum; Max = maximum; NMSS = Non-Motor Symptoms Scale.

39: sleep/fatigue, 0.58; and mood/apathy, 0.57 (all $p < 0.0001$).

Regarding internal validity, 53% of the interdomain correlations were between 0.30 and 0.42, and the rest were <0.30 (range: 0.06, perceptual problems/hallucinations with sexual function, to 0.42, sleep/fatigue with miscellaneous).

The NMSS total score was higher for patients with increased disease duration, HY stage, and CISI-PD severity level ($p < 0.001$; table 4). There were no significant differences by age at onset.

SEM ranged from 1.71 (cardiovascular) to 4.73 (mood/apathy) for domains, and was 13.91 for total score (table 5).

DISCUSSION The NMSS is an instrument specifically designed for the comprehensive measurement of NMS in patients with PD. This study was aimed to confirm and complete the information supplied by the pilot study[7] in a 70% wider sample of patients and, for the most part (85%), applied by researchers never before involved in NMSS development.

As a whole, NMSS acceptability was satisfactory. Data quality was excellent, with 99.5% of data fully computable and a difference between central tendency statistics clearly <10% of the maximum possible score. For 7 dimensions, the complete range of scoring was covered; the total NMSS score was free of a floor or ceiling effect; and the skewness value (+1.2) was slightly higher than the upper standard limit (+1.0). This asymmetry was consistent with the floor effect present in all NMSS domains, a finding already detected in the pilot study[7] and in other complex scales assessing NMS in PD.[14] Such instruments include a variety of symptoms grouped in dimensions, frequently unrelated to those included in other domains and experienced only by a proportion of the patients, so that the lower the prevalence of symptoms is, the higher the domain floor effect is. In this sense, findings are in agreement with prospective studies that showed relatively lower prevalence for hallucinations and perceptual problems (25%–60%) than for sleep disorders and fatigue (40%–98%),[3,30-33] the NMSS dimensions reaching the highest and lowest floor effect. Nonetheless, the NMSS was developed as a unified assessment for a diversity of NMS and, because of their high prevalence as a whole (only 0.50% of the patients declared no NMS, as in the pilot study),[7] its total score is exempt of a floor effect.

Regarding internal consistency, 3 domains (mood/apathy, attention/memory, and urinary) reached coefficient values over the minimal threshold for groups ($\alpha \geq 0.70$). The mean Cronbach α was 0.60, with the lowest values obtained for miscella-

Table 3 Reliability of the Non-Motor Symptoms Scale

	Item-total correlation (Cronbach α)	Intraclass correlation coefficient
Item/domain		
1. Light-headedness, dizziness	0.43*	0.68
2. Fainting or blacking out		0.84
D1. Cardiovascular	(0.53)	0.72
3. Fall asleep unintentionally	0.26	0.75
4. Fatigue or lack of energy	0.45	0.70
5. Difficulties falling/staying asleep	0.40	0.65
6. Restlessness in legs	0.34	0.62
D2. Sleep/Fatigue	(0.58)	0.77
7. Loss of interest in surroundings	0.67	0.81
8. Loss of interest in doing things	0.68	0.77
9. Feel nervous, worried, frightened	0.55	0.70
10. Seem sad or depressed	0.65	0.89
11. Flat mood	0.56	0.70
12. Difficulty in experiencing pleasure	0.70	0.63
D3. Mood/Apathy	(0.85)	0.91
13. Sees things that are not there	0.31	0.85
14. Beliefs that are not true	0.27	0.68
15. Double vision	0.25	0.56
D4. Perceptual problems/Hallucinations	(0.45)	0.71
16. Problems sustaining concentration	0.53	0.65
17. Forget things or events	0.73	0.78
18. Forget to do things	0.59	0.67
D5. Attention/Memory	(0.77)	0.83
19. Dribbling saliva	0.32	0.71
20. Difficulty swallowing	0.43	0.80
21. Constipation	0.22	0.79
D6. Gastrointestinal	(0.49)	0.78
22. Difficulty holding urine	0.53	0.81
23. Frequently voiding	0.59	0.76
24. Nocturia	0.51	0.79
D7. Urinary	(0.72)	0.83
25. Altered interest in sex	0.36*	0.69
26. Problems having sex		0.67
D8. Sexual function	(0.52)	0.67
27. Unexplained pain	0.35	0.70
28. Change in ability to taste/smell	0.23	0.73
29. Change in weight	0.20	0.71
30. Excessive sweating	0.22	0.81
D9. Miscellaneous	(0.44)	0.81

*Interitem correlation.

neous (0.44) and perceptual problems/hallucinations (0.45) (table 3). However, 23 items (77%) showed item-total correlation coefficients over the standard 0.30, and the item homogeneity was higher than the standard value for cardiovascular, mood/apathy, attention/memory, urinary, and sexual function. Internal consistency reflects the precision of a scale, "based on the homogeneity of the scale's items at one point in time."[23] The inclusion of few items for assessment of some complex domains, such as perceptual problems/hallucinations, allows for low intercorrelation among the items and low α values (a coefficient influenced by the number of items).[25] However, the need for obtaining a brief instrument for holistic evaluation of the many NMS potentially present in PD dictated that strategy.

Table 4 Known-groups validity of the Non-Motor Symptoms Scale

	Mean	SEM	95% CI
Hoehn and Yahr stage			
I	34.3	3.3	27.8–40.7
II	49.1	3.0	43.1–55.1
III	61.9	3.7	54.6–69.2
IV	92.3	7.2	78.1–106.5
V	123.6	24.8	74.8–172.3
CISI-PD severity level			
Mild	41.8	2.5	36.8–46.8
Moderate	57.3	2.9	51.7–63.0
Severe	107.7	6.7	94.5–121.0
Disease duration			
<5 y	45.8	3.5	38.9–52.8
5–9 y	55.5	3.5	48.6–62.4
≥10 y	69.4	4.0	61.5–77.2

All Kruskal-Wallis test, all $p < 0.0001$.
SEM = standard error of the mean; CI = confidence interval; CISI-PD = Clinical Impression of Severity Index for Parkinson's Disease.

Table 5 Non-Motor Symptoms Scale precision and minimally detectable change

	Range of scores	SEM	SD
Cardiovascular	0–24	1.71	1.61
Sleep/Fatigue	0–48	4.31	4.50
Mood/Apathy	0–72	4.28	7.14
Perceptual problems/Hallucinations	0–36	2.19	2.03
Attention/Memory	0–36	3.02	3.66
Gastrointestinal	0–36	3.40	3.62
Urinary	0–36	3.60	4.36
Sexual function	0–24	3.35	2.92
Miscellaneous	0–48	3.62	4.05
NMSS total score	0–360	13.91	22.00

SEM = standard error of measurement; NMSS = Non-Motor Symptoms Scale.

In this study, internal consistency results were marginally lower than in the pilot study,[7] a difference probably related to the conditions of the present study. The participant field researchers were not familiar with the scale, and they received the protocol and material for the study via e-mail, without additional instructions or investigators meeting. These circumstances were intentional, to test the measure apart of any potential "favorable" bias introduced by the scale developers.

Regarding the reproducibility of the NMSS, 67% of the items and all the domains except sexual function reached ICC values at the standard level of 0.70 or higher (table 3). Again, these results are similar to the corresponding findings in the pilot study.[7] In addition, the ICC for the total score was calculated in the present study, and, to overcome some problems with the ICC assumptions (common population variance for the different measures),[20] the Lin concordance coefficient was also obtained.[19] Both coefficients (0.90 and 0.88) showed that NMSS total score possesses a satisfactory stability.

The construct validity analysis of the NMSS showed evidence favoring an appropriate interpretation of NMSS scores based on the theoretical implications associated with the construct. The convergent validity with scales measuring related constructs was moderate or high, mainly with the specific HRQL questionnaire (PDQ-39) and SCOPA-AUT. The NMSS components have been identified in a diversity of studies as sources of distress and quality of life deterioration in PD.[34-37] Therefore, a close association between NMSS and PDQ-39 scores was expected, as anticipated with the PDQ-8 in the pilot study.[7] On the other hand, 4 domains of the NMSS overlap with the SCOPA-AUT domains (cardiovascular, gastrointestinal, urinary, and sexual function), and the correlation coefficients between the corresponding components were high (r_S = 0.51–0.65), as it was between the total scores (r_S = 0.64). To be highlighted is the high association found between some NMSS subscales and specific measures for similar constructs: sleep/fatigue with PDSS, perceptual problems/hallucinations with SCOPA-PC, and attention/memory with CISI-PD cognition (r_S = 0.51–0.56). In summary, the convergent validity of the NMSS was satisfactory in the present study.

The NMSS demonstrated the ability to detect differences, at a point in time, among groups of patients. As per the results in the present study, NMSS scores are higher for increasing PD duration, HY stage, and severity level based on the CISI-PD (table 4). A proper discriminative validity was observed in the pilot study for severity levels based on HY,[7] and that result is now confirmed and expanded. Although correlation of NMSS (domains and total score) was associated at a low or moderate level with duration of disease, HY, and total CISI-PD, the analysis by groups showed that NMS increased in prevalence and severity with the progression of PD.[3,7]

The SEM represents the error associated with the measurement and remains relatively constant across samples,[22,23,38] although a variation depending on the method (reliability coefficient applied) and the scores' variance in the sample may be observed.[28] The SEM is also considered the minimally detectable change[28,29,38] and, therefore, furnishes an estimate of the scale responsiveness.[28] Six of the 9 NMSS domains showed SEM values less than 10% of their maximum theoretical score and/or less than ½ SD, whereas the rest were higher. The SEM of the NMSS total score also was 8.10 points lower than the corresponding ½ SD (table 5). The obtained values were close to those of the pilot study,[7] except for the NMSS total score SEM, which was almost double in the present study. This discrepancy may be explained by the very high reliability index (ICC = 0.97) obtained from an insufficient number of patients included in the test-retest analysis of the pilot study (n = 30),[21] recognized as a limitation of the study.[7] Taking into consideration the results of the present study, it may be concluded that NMSS is a precise and potentially responsive measure.

Limitations of the present study are related to the aforementioned organizational aspects, without extra instructions or training with the scale. However, this strategy was chosen to simulate a scenario whereby real-life use of the scales are replicated, avoiding a potentially artificial and favorable use for a validation study. An additional limitation is depending on the sample and related to the low representation of patients in the most advanced stages of disease. A high proportion of patients in that situation will fit with the exclusion criteria for this kind of study, this way retaining a gap in knowledge about NMS assessment in those patients. On the other hand, all the problems associated with summative scales[39] are operative with the NMSS total score, which—at any rate—may represent the burden of NMS.

The most relevant NMS are also covered by the Movement Disorder Society–sponsored revision of the UPDRS (MDS-UPDRS), each symptom being represented by 1 item with 5 options of response. Therefore, the information it provides on severity is limited.[40] The NMS Scale includes 2 to 6 items per domain, each item scoring severity and frequency (0–12 points), this way providing a more detailed assessment. Furthermore, some relevant NMS not mentioned in the MDS-UPDRS are addressed in the

NMS Scale. Prevalence studies have shown that these NMS, such as sexual dysfunction, visual problems, and sweating, are important items for a holistic assessment of PD.

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DISCLOSURE

Dr. Martinez-Martin served on a scientific advisory board for Novartis; serves on the editorial boards of *Neurologia*, the Spanish Society of Neurology, *Revista de Neurologia*, and Societies of Neurology of the Spanish autonomous regions; has received speaker honoraria from Sanofi-aventis and Novartis; and receives research support from Novartis and the Carlos III Institute of Health. Ms. Rodriguez-Blazquez, Dr. Abe, and Dr. Bhattacharyya report no disclosures. Dr. Bloem has served on scientific advisory boards for Boehringer Ingelheim, GlaxoSmithKline, UCB, and Teva Pharmaceutical Industries, Ltd.; serves on the editorial boards of *Movement Disorders* and *Physiotherapy Canada* and as Editor-in-Chief of *Tijdschrift voor Neurologie & Neurochirurgie*; receives research support from the Michael J. Fox Foundation, the National Parkinson Foundation, and the Internationaal Parkinson Fonds, ZonMw and The Netherlands Organisation for Scientific Research Smart Mix Program. Dr. Carod-Artal, Dr. Esselink, Dr. Falup-Pecurariu, and Dr. Gallardo report no disclosures. Dr. Mir receives research support from Ministerio de Educación y Ciencia de España, Consejería de Innovación, Ciencia y Empresa de la Junta de Andalucía, Consejería de Salud de la Junta de Andalucía, and Sociedad Andaluza de Neurología. Mr. Naidu, Dr. Nicoletti, and Dr. Prakash report no disclosures. Dr. Sethi serves on a scientific advisory board for the International Essential Tremor Foundation; serves on the editorial boards of *Current Neurology and Neuroscience Reports* and *Medscape Neurology & Neurosurgery*; receives royalties from publishing *Drug Induced Movement Disorders* (Marcel Dekker, Inc.,2005); has served as a consultant and/or on speakers' bureaus for GlaxoSmithKline, Boehringer Ingelheim, Novartis, Ipsen, Teva Pharmaceutical Industries, Ltd., Solvay Pharmaceuticals, Inc., and Allergan, Inc.; receives research support from Boehringer Ingelheim, GlaxoSmithKline, Solvay Pharmaceuticals, Inc., Teva Pharmaceutical Industries, Ltd., ACADIA Pharmaceuticals Inc., the NIH [5 U10 NS044464-07 (Site PI)], and the National Parkinson Foundation; holds stock in Elan Corporation and Pfizer Inc; and has given expert testimony in welding litigation. Dr. Tsuboi reports no disclosures. Dr. van Hilten has served on scientific advisory boards for Novartis and GlaxoSmithKline; serves on the editorial board of *Movement Disorders*; and receives research support from the Dutch consortium TREND. Dr. Visser receives research support from the Dutch Parkinson's Disease Society, the Princes Beatrix Foundation, the van Alkemdade-Keuls Foundation, and the Michael J. Fox Foundation. Dr. Zappia served on a scientific advisory board for Novartis Italia; has received research support from AXA, Pfizer Inc, Sanofi-aventis, Merck Serono, Boehringer Ingelheim, and from the Italian Government (Ministry of Education, University and Research grant 2006065350_004; Ministry of Health grant PS-NEURO_56/2005/17). Dr. Chaudhuri serves on scientific advisory boards for Solvay Pharmaceuticals, Inc., Boehringer Ingelheim, GlaxoSmithKline, Merck Serono, and Teva Pharmaceutical Industries, Ltd.; has received speaker honoraria from the European Federation of Neurological Societies, the Swedish Movement Disorders Society, and LIMPE Italy; and receives research support for a clinical research nurse from UCB.

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REFERENCES

1. O'Sullivan SS, Williams DR, Gallagher DA, Massey LA, Silveira-Moriyama L, Lees AJ. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord 2008;23:101–106.
2. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov Disord 2001;16:507–510.
3. Martinez-Martin P, Schapira AH, Stocchi F, et al. Prevalence of nonmotor symptoms in Parkinson's disease in an international setting: study using nonmotor symptoms questionnaire in 545 patients. Mov Disord 2007;22:1623–1629.
4. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5:235–245.
5. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord 2002;8:193–197.
6. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. Mov Disord 2006;21:916–923.
7. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. Mov Disord 2007;22:1901–1911.
8. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.
9. Marinus J, Visser M, Stiggelbout AM, et al. A short scale for the assessment of motor impairments and disabilities in Parkinson's disease: the SPES/SCOPA. J Neurol Neurosurg Psychiatry 2004;75:388–395.
10. Visser M, Verbaan D, van Rooden SM, Stiggelbout AM, Marinus J, van Hilten JJ. Assessment of psychiatric complications in Parkinson's disease: the SCOPA-PC. Mov Disord 2007;22:2221–2228.
11. Marinus J, Visser M, Verwey NA, et al. Assessment of cognition in Parkinson's disease. Neurology 2003;61:1222–1228.
12. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.

13. Martinez-Martin P, Forjaz MJ, Cubo E, Frades B, de Pedro CJ. Global versus factor-related impression of severity in Parkinson's disease: a new clinimetric index (CISI-PD). Mov Disord 2006;21:208–214.
14. Visser M, Marinus J, Stiggelbout AM, van Hilten JJ. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov Disord 2004;19:1306–1312.
15. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:629–635.
16. EuroQol: a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199–208.
17. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. Age Ageing 1997;26:353–357.
18. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res 1995;4:293–307.
19. Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989;45:255–268.
20. Schuck P. Assessing reproducibility for interval data in health-related quality of life questionnaires: which coefficient should be used? Qual Life Res 2004;13:571–586.
21. Terwee CB, Bot SD, de Boer MR, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol 2007;60:34–42.
22. McHorney CA, Tarlov AR. Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res 1995;4:293–307.
23. Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002;11:193–205.
24. Juniper EF, Guyatt GH, Jaeschke R. How to develop and validate a new health-related quality of life instrument. In: Spilker B, editor. Quality of Life and Pharmacoeconomics in Clinical Trials, 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1996:49–56.
25. Feeny D, Farris K, Côté I, Johnson JA, Tsuyuki RT, Eng K. A cohort study found the RAND-12 and Health Utilities Index Mark 3 demonstrated construct validity in high-risk primary care patients. J Clin Epidemiol 2005;58:138–141.
26. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain 2001;124:962–973.
27. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, de Pedro J; on behalf of the Spanish-American Longitudinal PD Patient Study Group. The Clinical Impression of Severity Index for Parkinson's disease: international validation study. Mov Disord 2009;24:211–217.
28. Beaton DE, Bombardier C, Katz JN, Wright JG. A taxonomy for responsiveness. J Clin Epidemiol 2001;54:1204–1217.
29. de Vet HC, Terwee CB, Ostelo RW, Beckerman H, Knol DL, Bouter LM. Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. Health Qual Life Outcomes 2006;4:54.
30. Fenelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 2000;123:733–745.
31. Goetz CG, Leurgans S, Pappert EJ, Raman R, Stemer AB. Prospective longitudinal assessment of hallucinations in Parkinson's disease. Neurology 2001;57:2078–2082.
32. Garcia-Borreguero D, Larrosa O, Bravo M. Parkinson's disease and sleep. Sleep Med Rev 2003;7:115–129.
33. Friedman JH, Brown RG, Comella C, et al. Fatigue in Parkinson's disease: a review. Mov Disord 2007;22:297–308.
34. Martinez-Martin P. An introduction to the concept of "quality of life in Parkinson's disease." J Neurol 1998;245(suppl 1):S2–S6.
35. Damiano AM, Snyder C, Strausser B, Willian MK. A review of health-related quality-of-life concepts and measures for Parkinson's disease. Qual Life Res 1999;8:235–243.
36. Kuopio AM, Marttila RJ, Helenius H, Toivonen M, Rinne UK. The quality of life in Parkinson's disease. Mov Disord 2000;15:216–223.
37. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;69:308–312.
38. Wyrwich KW, Wolinsky FD. Identifying meaningful intra-individual change standards for health-related quality of life measures. J Eval Clin Pract 2000;6:39–49.
39. Hobart JC, Cano SJ, Zajicek JP, Thompson AJ. Rating scales as outcome measures for clinical trials in neurology: problems, solutions, and recommendations. Lancet Neurol 2007;6:1094–1105.
40. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 2008;23:2129–2170.

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