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Validation of the Italian version of the Non Motor Symptoms Scale for Parkinson's disease

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ABSTRACT

Objective: To validate the adapted Italian version of the Non-Motor Symptoms Scale (NMSS), a tool to assess non-motor symptoms (NMS) in Parkinson's disease (PD).
Methods: A cross cultural adaptation of the NMSS into Italian and a psychometric analysis of the translated version of the NMSS was carried out in patients with PD from two university centres –affiliated hospitals. The quality of data and the acceptability, reliability and construct validity of NMSS were analyzed. The following standard scales were also applied: Hoehn and Yahr staging, Unified Parkinson's Disease Rating Scale (UPDRS) part III, Montreal Cognitive Assessment, Beck Depression Inventory, Neuropsychiatric Inventory, Epworth Sleepiness Scale, Autonomic Scale for Outcomes in Parkinson's disease-Motor, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part I and Modified Cumulative Illness Rating Scale (CIRS). Levodopa equivalent daily dose (LEDD) was calculated.
Results: Seventy-one patients with PD were assessed (mean age years 69.8 ± 9.6 SD; 31% women; mean length of disease 6.3 ± 4.6 years; H&Y median: 2). Mean NMSS was 39.76 (SD 31.9; skewness 0.95). The total score of NMSS was free of floor or ceiling effects and showed a satisfactory reliability (Cronbach's alpha coefficient on total score was 0.72 [range for domains: 0.64–0.73], SEM value was 3.88 [½ SD = 31.90]). Significant positive correlations were found among total NMSS and other NMS standard tests, but no significant correlation appeared with UPDRS part III, CIRS and LEDD.
Conclusions: The Italian NMSS is a comprehensive and helpful measure for NMS in native Italian patients with PD.

1. Introduction

Parkinson's disease (PD) is a progressive neurological condition, characterized by a dopamine deficiency causing tremor, rigidity, bradykinesia and gait problems mainly arising from dopamine deficiency. During the last decade, PD has been increasingly recognized as also implying non-dopaminergic dysfunction and non-motor symptoms (NMS) that can appear at all stages of the disease [1] and have a relevant impact on patients' health and quality of life [2–5].

Non-motor symptoms mainly include neuropsychiatric symptoms, sleep disorders, autonomic dysfunction, gastrointestinal symptoms and sensory symptoms [6]. Unfortunately, NMS are still underdiagnosed, and therefore undertreated [7]. A comprehensive assessment including both motor and non-motor symptoms is essential in clinical practice [8], but adequate instruments for the detection and assessment of the burden of NMS in patients with PD are still lacking in Italy.

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The Non-Motor Symptoms Scale for PD (NMSS) was developed and validated for a comprehensive assessment of non-motor symptoms [9]. The NMSS is a 30-item scale including the following 9 domains: cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous.

Although translations in several languages exist, the NMSS has not yet been translated into Italian.

The aim of this study was to perform a translation and adaptation of the NMSS into Italian following a precise translation protocol based on international standards, and to analyze the reliability and construct validity of the translated version and its usefulness as a measure for non-motor symptoms in Italian patients with PD.

2. Methods

2.1. Study participants

We enrolled consecutive outpatients with PD from two university centres-affiliated hospitals in Italy - in Rome and Milan-between September 2015 and December 2015. PD was defined according to Gelb's criteria [10]. The NMSS was based on structured questions that movement specialists already use in several countries, and the assessment is an example of good clinical practice. Thus, specific approval for use of the scale was not required. However, we have specified in the informed consent form and the informative sheet submitted to all patients included in this study that it is essential to investigate the possible presence of non-motor symptoms and that this study could provide additional insights into Parkinson's disease. Moreover, the study protocol was proposed in accordance with the standards of good clinical practice and the current revision of the Declaration of Helsinki. Personal data were treated in accordance with Italian privacy laws. The written informed consent to participate was obtained from all patients.

2.2. Adaptation of the NMSS

The NMSS was adapted into Italian from the original English version following a precise translation protocol based on international standards [11,12]. First, the NMSS was translated into Italian by two professional translators, and then a reconciled version was elaborated by an independent translator competent in movement disorders and highly proficient in both languages (NV), who identified and resolved any possible inadequate expressions or discrepancies between the two forward translations. Then, a professional translator, different from the translators who performed the original English-to-Italian translation and with no knowledge of the English original scale, translated the reconciled version back into English. This back-translation was compared to the original version by a panel of experts to verify the equivalence of the two English versions in terms of meaning and conceptual content. The two versions resulted equivalent, thus the last Italian version of the NMSS was considered final. The translated instrument was then pre-tested on 10 patients with PD to assess their understanding of the questions. No major issues were found during the pre-testing phase, thus the final joint translation was carried out, named NMSS-PD Italian version (esupp. file 1).

2.3. Patients assessment

Demographic data including age, gender and education, and information on the disease such as age at onset, length of disease and treatment were collected. The levodopa equivalent daily dose (LEDD) [13] was calculated.

All patients underwent a clinical examination. The Hoehn and Yahr scale (H&Y) [14] and the Unified Parkinson's Disease Rating Scale (UPDRS) part III [15] were used for the motor assessment and the staging of disease. Somatic comorbidities were quantified using the Modified Cumulative Illness Rating Scale (CIRS) [16].

The answers to the NMSS were obtained through interviews carried out by the neurologist in regular follow-up visits. The NMSS-PD scale includes 30 items grouped in the following 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 function (3 items); sexual function (2 items); and miscellaneous (4 items). The assessment period was “the past 1 month”. The scores for each item are based on a combination of severity (from 0 to 3) and frequency scores (from 1 to 4), to capture symptoms that are severe but relatively infrequent or that are less severe but persistent. The total NMSS score ranges from 0 to 360.

Non-motor symptoms were further investigated, in addition to the NMSS, by specialized clinical psychologists (CP or GA) in the centre of Rome using a set of tests including the Montreal Cognitive Assessment (MoCA) [17] to assess cognitive disorders, the Beck Depression Inventory (BDI) [18] for depression, the Neuropsychiatric Inventory (NPI) [19] for behavioral disturbances, the Epworth Sleepiness Scale (ESS) [20] for sleepiness, the Autonomic Scale for Outcomes in Parkinson's disease-Motor (SCOPA-Aut) [21] for autonomic issues, and the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part I [22] for a global non-motor assessment.

For most rating scales (BDI, NPI, ESS, SCOPA-AUT and MDS-UPDRS part I), higher scores reflect higher severity on the construct being measured, whereas for MoCA lower scores correspond to worse cognitive performances.

To evaluate the stability of the Italian version of the NMSS (test-retest reliability), a group of patients (n 15) repeated the NMSS two weeks after the first evaluation with a different researcher than the one who performed the previous evaluation (CP or GA).

2.4. Data analysis

Descriptive statistics were used for the characterization of the sample. The univariate ANOVA test for continuous variables and the Pearson's χ^2 test for categorical variables were used to compare separately the characteristics of males and females among the two groups of patients (Rome and Milan).

The following characteristics were explored for the Italian version of the NMSS.

2.4.1. Quality of data

The proportion of computable data was considered adequate if more than 95% of the NMSS data were fully computable [9].

2.4.2. Acceptability

The range of scores, the floor and ceiling effects (maximum acceptable value for both: 15%), and the skewness (limits: −1 and +1) were calculated.

2.4.3. Reliability

Precision for the NMSS domains was determined by means of the standard error of measurement (SEM), the smaller the standard error of measurement, the more reliable the test (a SEM value < ½ standard deviation was used as a criterion of acceptable precision).

Internal consistency was tested using the Cronbach's alpha coefficient (values $\geq$ 0.70 was considered appropriate). Test-retest reliability over a time interval of 14 days was assessed in a group of 15 patients through the Intra-class Correlation (ICC), for which

values higher than 0.70 were considered acceptable.

2.4.4. Construct validity

For convergent and divergent validity, we explored the relationship among the different domains of NMSS with other measures for the same construct (or other related constructs) and motor scores, respectively, by means of Pearson's correlation coefficient (r). A r value of at least 0.30 has been used as evidence for convergent validity and less than 0.30 indicated evidence for divergent validity.

Standard values for acceptability and reliability were established based on previous studies [9,23,24]. Statistical analyses were performed by means of the Statistical Package for the Social Sciences (SPSS 23).

3. Results

Seventy-one patients (43 patients in Rome and 28 in Milan) (mean age 69.8 ± 9.6 SD; 31% women; 48% non-tremor subtype of PD) were included in the study. Included patients had a mean age at the onset of symptoms of 63.3 ± 9.6 years (range: 40–82 years), and a mean length of the disease of 6.3 ± 4.6 years. The median H&Y stage was 2 (stage 1, 18.3%; stage 2, 52.1%; stage 3, 26.7%; stage 4, 1.4%) and the median LEDD was 506.6 ± 319.0.

Demographic variables and clinical features (length of the disease in years, subtype of disease, motor assessment, comorbidities, LEDD, NMSS total score) did not differ between patients from Rome and patients from Milan.

Score distribution of NMSS and other scales are shown in Table 1.

Complete data on the NMSS were available for 97.2% of the enrolled patients (the only missing information was sexual functioning for two patients).

The acceptability of the NMSS and the distribution of scores for each domain are shown in Table 2.

As for the NMSS domains, only one domain (urinary function) covered the full possible range of scores (Table 2). All domains showed a floor effect. The most prominent floor effects were observed in the following domains: perceptual problems/hallucinations (76%), sexual function (69.6%), cardiovascular function (59.2%). No ceiling effect was observed on the NMSS domains. Neither a floor nor a ceiling effect was observed in the NMSS total score (Table 2). The NMSS skewness was 0.95, indicating that the distribution is moderately right-skewed (its right tail is longer and most of the distribution is centered on the left) [25].

Table 1
Assessment of motor symptoms, non-motor symptoms, and comorbidities in patients with Parkinson's disease.

	N	Mean	SD	Min	Max
UPDRS III	46	16.2	8.0	6	40
MOCA	43	23.3	4.5	11	29
BDI	43	8.8	6.9	0	30
NPI	43	8.0	7.0	0	28
ESS	43	5.1	4.1	0	20
SCOPA aut	43	13.2	7.5	0	30
MDS-UPDRS I	43	9.7	5.3	0	22
NMSS	71	39.8	31.9	0	154
CIRS	71	0.5	0.2	0	1.2

SD, standard deviation; Min, minimum; Max, maximum.
UPDRS III, Unified Parkinson's Disease Rating Scale part III; MOCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; NPI, Neuropsychiatric Inventory; ESS, Epworth Sleepiness Scale, SCOPA-Aut, Autonomic Scale for Outcomes in Parkinson's disease-Motor; MDS-UPDRS part I, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part I; NMSS, Non Motor Symptoms Scale; CIRS, Modified Cumulative Illness Rating Scale.

The SEMs values for the NMSS domains were small, ranging from 0.23 (perceptual problems/hallucinations; ½ SD = 0,93) to 1.13 (mood/apathy; ½ SD = 4,65). SEM value for total score was 3.88 (value lower of ½ SD of total score).

Internal consistency was adequate, as the Cronbach's alpha coefficient resulted 0.72 for the total scale. The Cronbach's alpha coefficients for the 9 NMSS subscales were respectively 0.72, 0.64, 0.68, 0.73, 0.69, 0.69, 0.68, 0.73 and 0.71.

Test-retest reliability of the total NMSS score was assessed in a subset of patients with PD (n = 15), and a high correlation coefficient (ICC 0.83, $p < 0.0001$) was reported.

The NMSS total score did not result significantly correlated with the age of patients. A weak association was observed between NMSS total score and disease duration (r 0.23, $p < 0.05$). No significant correlation was observed between LEDD and NMSS total score (r 0.20, $p = 0.09$).

Highly significant correlations were observed between the total score of the NMSS-PD and all the other scales used to assess non-motor symptoms, but not with the scales used for motor symptoms, such as the UPDRS III (Table 3). No significant correlation was observed between the NMSS and comorbidities assessed with CIRS. The observed correlations between each of the domains included in the NMSS and the other considered scales are shown in Table 3.

A significant correlation was observed between all of the subscale domains included in the NMSS, with the exception of sexual domain, and the total score (Table 4), indicating a strong association with the related construct.

4. Discussion

The Italian version of the NMSS resulted a comprehensive instrument to assess NMS burden in Italian patients with PD, and showed adequate satisfactory clinimetrics in terms of data quality, precision, acceptability, internal consistency and reliability. This scale is easy and short to complete, and showed a significant correlation with other NMS assessments, such as BDI, MoCA, NPI, SCOPA-Aut, ESS, MDS-UPDRS part I. As for the BDI, NPI, SCOPA-Aut, and ESS, a significant correlation ($p < 0.05$) was also found with NMSS domains. Interestingly, no correlation was found between the NMSS and comorbidities assessed with the CIRS. This strengthens the idea that non-motor symptoms are an integrating part of PD rather than being part of different diseases.

To our knowledge, no other previous study assessed the metric properties of the Italian version of the NMSS. Previous independent validations of this scale are available for Chinese, Korean, Brazilian and Arabic languages. The validation and widespread availability of a simple and complete NMS assessment could allow the systematic collection of data on non-motor features of patients with PD across different countries. Comparing these epidemiological data may also help to outline different non-motor PD subtypes [26].

As in the original validation study, the Italian NMSS total score was free of both a floor and a ceiling effect. Similarly, none of the domains showed a ceiling effect, while a floor effect was found in all domains.

No significant association was observed between the total scores from the Italian NMSS and the UPDRS part III. This result differed from the findings from the original study [9].

This data support the view that the burden of non-motor symptoms is independent from the severity of motor signs, at least in the earliest stages of the disease: the patients enrolled in our study were in a less severe motor stage of PD compared to the patients enrolled in the original study (H&Y ≤ 2, 71.4% vs. 55.5%).

The mean total NMSS score in our study was 39.7 ± 31.9, which is lower than the mean score observed in the original Chaudhuri's validation [9] and Arabic version [24], and higher than the mean

Table 2
Acceptability of the Non-Motor Symptoms Scale (NMSS) in Parkinson's disease.

NMSS	Mean	SEM	SD	Min	Max	Floor effect, %	Ceiling effect, %
Cardiovascular	1.35	0.27	2.25	0	8	59.2	4.2
Sleep/Fatigue	7.65	0.94	7.73	0	36	22.5	1.4
Mood/Apathy	5.86	1.13	9.31	0	49	35.2	1.4
Perceptual problems	0.90	0.23	1.86	0	7	76.1	2.8
Attention/Memory	3.39	0.68	5.62	0	27	45.1	2.8
Gastrointestinal	6.04	0.78	6.41	0	23	31,0	1.4
Urinary	7.87	1.06	8.70	0	36	25.4	2.8
Sexual function	1.94	0.43	3.56	0	14	67.6	1.4
Miscellaneous	4.80	0.78	6.47	0	26	39.4	1.4
Total score	39.76	3.88	31.90	0	154	7.0	1.4

SEM, standard error of measurement; SD, standard deviation; Min, minimum; Max, maximum.

Table 3
Correlations between each of the domains included in the Non-Motor Symptoms Scale (NMSS) and the other considered scales, analyzed with the Pearson's correlation coefficient.

NMSS	UPDRS III	MOCA	BDI	NPI	ESS	SCOPA-Aut	MDS-UPDRS I	CIRS
Cardiovascular	0.19	−0.21	0.29	0.21	0.41**	0.25	0.46**	−0.05
Sleep/Fatigue	0.13	−0.11	0.57**	0.55**	0.37*	0.35*	0.75**	−0.19
Mood/Apathy	−0.01	−0.01	0.58**	0.66**	0.20	0.21	0.40**	−0.20
Perceptual problems	0.07	−0.03	0.28	0.40**	0.06	0.05	0.22	−0.12
Attention/Memory	0.06	−0.21	0.50**	0.27	0.20	0.05	0.40*	0.06
Gastrointestinal	0.28	−0.15	0.32*	0.28	0.33*	0.56**	0.45**	0.01
Urinary	0.33*	−0.37*	0.04	0.34	0.27	0.72**	0.63**	−0.19
Sexual function	0.13	−0.14	−0.07	0.05	0.02	0.50**	0.09	−0.20
Miscellaneous	0.09	0.02	0.22	0.29	0.23	0.17	0.41**	−0.26
Total score	0.28	−0.27	0.56**	0.65**	0.45**	0.66**	0.85**	−0.23

*p < 0,05 **p < 0,001.
UPDRS III, Unified Parkinson's Disease Rating Scale part III; MOCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; NPI, Neuropsychiatric Inventory; ESS, Epworth Sleepiness Scale, SCOPA-Aut, Autonomic Scale for Outcomes in Parkinson's disease-Motor; MDS-UPDRS part I, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale part I; NMSS, Non Motor Symptoms Scale; CIRS, Modified Cumulative Illness Rating Scale.

Table 4
The domains–total Non-Motor Symptoms Scale (NMSS) score correlation.

NMSS	r
Cardiovascular	0.35**
Sleep/Fatigue	0.80**
Mood/Apathy	0.71**
Perceptual problems	0.32**
Attention/Memory	0.57**
Gastrointestinal	0.62**
Urinary	0.70**
Sexual function	0.26
Miscellaneous	0.54**

*p < 0,05 **p < 0,001.

scores reported in the validations of the Korean and Chinese versions of the NMSS. These differences may reflect differences in age, ethnicity, duration of disease and motor stages in the recruited populations. Furthermore, in our study, we did not find a significant correlation between the NMSS total score and the LEDD. This finding is similar to what is reported by the validations of the Arabic and Chinese versions [23,24], and suggests that the side-effects of the dopaminergic treatment may not be the main causes of NMS.

The present study may have the following limitations: 1) lack of comparable measures for all assessed NMS; 2) small sample-size, in particular of the patients enrolled to study test-retest reliability; 3) relatively low number of patients with PD reaching both the extremes of the severity classification; patients in the advanced stages of the disease may have been underrepresented.

Therefore, a large scale study including more patients with PD may help to provide a more complete profile of NMS in Italian patients with PD.

In conclusion, our study showed that the Italian version of the NMSS is a helpful instrument for the assessment of the burden of non-motor symptoms in Italian patients with PD.

NMSS is a very quick and easy scale to administer and it should be integrated into all PD outpatients clinics in Italy.

Conflicts of interest

The authors declare no conflicts of interest.

Authors' roles

Research project: Conception: IC, DBME, NV; Organization: IC, DBME, NV; Execution: IC, DBME, CPP, GA, AR, MV, GM, PC.

Statistical Analysis: Design NV, IC, SP; Execution: IC, SP; Review and Critique: NV, ADP, EL.

Manuscript: Writing of the first draft: IC. Review and Critique: MEDB, SP, NV, ADP, EL, AP, CM.

Financial disclosures of all authors

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Disclosure statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2016.10.020.

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