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RESEARCH ARTICLE

Pilot Study of the International Parkinson and Movement Disorder Society-sponsored Non-motor Rating Scale (MDS-NMS)

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ABSTRACT: Background: Non-motor symptoms (NMS) are integral to Parkinson's disease (PD) and have a detrimental effect on patients and their caregivers. Clinical quantification has been aided by the development of comprehensive assessments such as the Non-Motor Symptoms Questionnaire (NMSQuest) and Scale (NMSS). The NMSS has been widely used in clinical studies and trials; however, since its validation in 2007, our understanding of NMS has changed substantially. With the support of the International Parkinson and Movement Disorder Society (IPMDS), after a detailed peer review an initiative to develop an updated version of NMSS, the MDS-NMS was launched in 2015.

Objective: This paper encapsulates the data from the pre-validation phases carried out under the auspices of the IPMDS Non-Motor PD Study Group.

Methods: Item selection and wording (formatted as a rater-based tool) were based on the NMSS, literature review, and expert consensus. Neurologists, PD patients, and healthy controls were included in the cognitive pretesting and administration of the preliminary version of the MDS-NMS. Primary data on acceptability and reliability were obtained.

Results: The pilot study, carried out in English in the United Kingdom and the United States, demonstrated that the preliminary version of the MDS-NMS was comprehensive, understandable, and appropriate. Data quality was excellent; moderate floor effect was present in patients for most MDS-MNS domains, with some components showing weak internal consistency. The results led to additional instrument modifications.

Conclusion: Qualitative and quantitative research results have led to an updated NMSS, the definitive version of the MDS-NMS, which is currently being validated.

Introduction

Although James Parkinson described a range of non-motor symptoms (NMS) in his description of the "shaking palsy" 200 years ago, for many years, the impact of NMS on patients with Parkinson's disease (PD) was largely overlooked.[1,2] Since the development and validation of assessment instruments such as the NMS Questionnaire (NMSQ),[3] and the PD Non-Motor Symptoms Scale (NMSS),[4,5] assessing NMS has become more acceptable in clinical practice, and in some countries (e.g., the UK) it is considered a quality standard as a patient-reported experience measure (UK Parkinson's Audit, 2017).[6]

The impact of the burden of NMS on quality of life has been articulated in a large number of publications,[7–11] and spans prodromal to late stages of PD.[12–15] The impact of the NMS has also underpinned the concept of the syndromic nature

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of PD,[16] and non-motor endophenotypes have been postulated.[17]

The NMSS has been used as an outcome measure in several international clinical trials and has demonstrated sensitivity to change,[18–25] with published cut-off scores describing the different levels of NMS burden.[26,27] However, the NMSS is now dated, as it was developed in 2005 and published in 2007. Key limitations in the current version of NMSS include, for example, deficiencies in the structure of this scale (e.g., items for depression, anxiety, and apathy are in the same domain, as are sleep disorders and fatigue), lack of questions related to drug-induced issues such as non-motor fluctuations and impulse control disorders, and limited coverage of cognitive deficits.

After a detailed consultation, the International Parkinson and Movement Disorder Society (IPMDS) proposed the development of an updated scale to assess NMS, the IPMDS-Non-Motor Rating Scale (MDS-NMS), to take into account the following issues: (1) a critical appraisal of the experience of using NMSS in clinical trials and studies in over 1,000 patients since 2007, including a diversity of epidemiological studies and a first approach to data mining[28]; (2) feedback from clinical raters who have used the NMSS regarding individual questions in the NMSS; and (3) feedback from patient groups in relation to the use of NMSS in real life.

This multicenter effort showed that the current NMSS requires both consolidation and expansion, as well as refinement and improvement in relation to scoring and ease of application. Also, there is a growing demand for NMSS to be used in the context of new clinical trials, both those with and without a primary focus on NMS. Examples of clinical trials using the NMSS are RECOVER,[19] PANDA,[22] and TOLEDO,[29] and worldwide registries such as GLORIA, related to intrajejunal l-dopa infusion therapy.[30]

The development and cognitive pretesting of MDS-NMS have been completed,[31] and an international (UK and USA) validation of the original English version through IPMDS sponsorship is underway. The overall goal is to develop a standard global PD NMS rating scale to be used in all clinical trials and epidemiological studies assessing clinical features of PD, regardless if the primary focus is on motor or non-motor symptoms.

The pilot study reported here aimed to explore the feasibility/acceptability, appropriateness, rank of the response options, identification of flaws (e.g., ambiguity, irrelevance, and redundancy), and review of the format of the new MDS-NMS.

Methods

Development of the Preliminary Version of the MDS-NMS

The preliminary version of the MDS-NMS was drafted and refined by PD clinical researchers with expertise in non-motor symptoms and scale development in a series of in-person meetings, video conferences, and by e-mail (from October 2013–January 2016). It was composed of 63 items in 15 domains: (A) Depression (5 items), (B) Anxiety (4 items), (C) Apathy (4 items), (D) Psychosis (5 items), (E) Impulse control and related disorders (4 items), (F) Other neuropsychiatric symptoms (NPS; 4 items), (G) Cognition (6 items), (H) Orthostasis (2 items), (I) Urinary (5 items), (J) Sexual (2 items), (K) Gastrointestinal (4 items), (L) Thermoregulatory (2 items), (M) Sleep and wakefulness (7 items), (N) Pain (4 items), and (O) Others (5 items). Items were selected from the NMSS and other scales relating to NMS, review of the literature, and expert consensus. Items were phrased as questions on the presence of the symptoms and designed for administration by healthcare professionals (i.e., rater-administered).

Each item was scored twice based on five options, for frequency (0 = never to 4 = majority of time) and severity (0 = not present to 4 = severe). Specific explanations for each of these anchors were provided. Item score was calculated by multiplying frequency x severity, total domain scores were calculated by the sum of their respective item scores, and a total instrument score generated by summing the domain scores represented total NMS burden. The MDS-NMS total score ranges, in theory, from zero to 1,008; however, reaching the maximum score is very unlikely, given the low possibility of simultaneously reaching the maximum frequency and severity scores on all instrument items. This is similar to findings using the NMSS.[26]

The MDS-NMS also includes an optional section to rate non-motor fluctuations (NMFs), including depression, anxiety, thinking or cognitive abilities, bladder symptoms, restlessness, pain, and fatigue. Each item was scored on a 5-point scale for typical degree of change from *on* to *off* periods (0 = no change to 4 = large), and for time spent in *off* state with non-motor symptoms (0 = no *off* time to 4 = majority of the time, ≥51% of waking day). The item score was calculated by multiplying the two components, and the sum of individual item scores generated the total NMFs score.

The time frame evaluated is the "past two weeks," as a longer time frame may be difficult for PD patients to remember accurately.

Design of the Pilot Study

An open, cross-sectional international study on a sample of users (neurologists) within the target population (PD patients) compared to healthy controls.

Participants

Three categories of subjects participated in the study: (1) operationalized neurologists with expertise in PD, attending ≥300 PD patients per year; (2) patients with a diagnosis of idiopathic PD, given by a neurologist, based on international criteria (Movement Disorder Society criteria),[32] and without significant cognitive impairment according to the judgment of the evaluating neurologist; (3) healthy, 50- to 80-year-old, community-dwelling controls without PD, dementia, or neurological or

psychiatric disorders. Control participants were included, as the scale may be used in patients in diagnostic evaluation.

Exclusion Criteria

Neurologists without experience in PD; patients with a parkinsonism other than idiopathic PD; the presence of significant cognitive impairment; psychiatric or medical conditions that would interfere with ability to complete study assessments; those on a current medication with a known effect on mental state (cognitive or emotional); controls with a comorbid disease or disorder at a moderate or severe level; and institutionalized patients. Also excluded were patients and controls unable to consent and those with an inability to read and write English or complete written questionnaires correctly.

Sample Size

Usually, sample sizes proposed for pilot studies on the development of a scale or questionnaire range from 20 to 40 representatives; however,[33,34] due to the complexity of the preliminary version of the MDS-NMS, a sample >50 neurologists and patients was proposed for this study.

Other Assessments

In addition to sociodemographic data, feedback questionnaires about the MDS-NMS were prepared for neurologists (n = 50), patients (n = 15), and controls (n = 15). These questionnaires include questions about the word choice, understanding, relevance, appropriateness, comprehensiveness, length, comfortableness, issues with response options, and a section for additional comments or suggestions.

Procedures

Neurologists and patients participating in the study were informed of the objective of the study. Each neurologist completed the MDS-NMS for one patient and the Questionnaire for the Neurologist. In addition to being administered the MDS-NMS, each patient or control also completed the Questionnaire for the Patient or the Questionnaire for Controls about the instrument.

Data from the scale application and questionnaires were entered into a database for analyses. After analysis (see below), and based on the results of the pilot study used to create the final MDS-NMS for use in the formal validation study, the developers made decisions for changes.

Ethical Aspects

Each site contributing to the study received approval of their respective ethics committee/IRB for participation. In the UK, the study was approved for adoption to the UK Clinical Research Network (UKCRN No 18003). Patients and controls provided written informed consent.

Data Analysis

For depicting the characteristics of the sample, descriptive statistics (mean, standard deviation, percentage) were used. Total daily l-dopa equivalent dose (LEDD) was calculated according to Tomlinson et al., 2010.[35] Data did not follow a normal distribution (Shapiro-Francia test).

For the MDS-NMS: Data quality (standard values: missing data <10%; full computable scores, >90%), floor and ceiling effects (standard, ≤15%), and skewness (standard, from -1 to +1)[36,37] were determined in the PD patients and healthy controls.

Preliminary results of reliability (Cronbach's alpha, standard value >0.70; inter-item correlation, 0.20–0.75; item homogeneity coefficient, >0.15; and corrected item-total correlation, ≥0.30) were explored only in patients.[37–41]

The questionnaires for neurologists, patients, and controls were analyzed descriptively to assess their opinions and criticisms of the scale.

Results

Participant Characteristics

Fifty-two neurologists and 69 PD patients (69.6% male) were included in the study. Patients' mean (± SD) age was 67.2 ± 9.5 (range: 37–90) years and the average years of education were 14.9 ± 4.5 (range: 8–30). Most of the patients were married (72.5%) or single (15.9%) and retired (72.5%) or employed (18.8%). Mean age at PD onset was 59.9 ± 10.6 years (range: 32–84) and disease duration was 7.2 ± 5.2 years. LEDD was 665.0 ± 434.7 mg (range: 100–2080). Six patients (8.7%) had undergone deep brain stimulation surgery (4.7 years previously on average; range: 1–20).

Nineteen healthy controls (89.5% female) participated in the study. Their age was 53.4 ± 13.9 years (range: 24–68) and years of education were 17.0 ± 4.7 (range: 10–24) years. Most were married (68.4%) and employed (77.8%).

MDS-NMS Scores

MDS-NMS scores for PD patients and healthy controls are shown in Table 1. Scores were higher in all domains for PD patients. Among patients, the possible maximum total score for a domain was reached only for the sexual and thermoregulatory domains, and among controls only for the thermoregulatory domain

Out of 4,347, there were four missing data points (0.1%) in the patient group: one in item D3, Visual hallucinations; two in item J2, Difficulty with sex; and one in item O2, Impaired olfaction. Fully computable data were available for 97.1%–100% of cases for the domain scores, and 95.6% for the total score. Part P, Non-motor fluctuations, was completed for 49 patients (71.0%). There were no missing data in the control group.

TABLE 1 *Movement Disorder Society-Non-Motor Symptoms scale scores*

	% F.C.	Mean	SD	Median	IQR	Observed Min	Observed Max	Theoret. Max
PD patients								
A. Depression	100	8.17	13.98	3.00	0-8	0	72	80
B. Anxiety	100	6.94	11.01	3.00	0-8	0	45	64
C. Apathy	100	7.32	13.02	3.00	0-8	0	60	64
D. Psychosis	98.5	1.85	5.05	0.00	0-0	0	25	80
E. ICD & related disorders	100	1.19	3.26	0.00	0-0	0	18	64
F. Other NPS	100	1.81	3.67	0.00	0-2	0	21	64
G. Cognition	100	10.80	15.04	4.00	1-14.5	0	64	96
H. Orthostasis	100	2.80	5.01	0.00	0-3.5	0	21	32
I. Urinary	100	10.28	15.56	4.00	0-13	0	72	80
J. Sexual	97.1	4.06	7.97	0.00	0-4	0	32	32
K. Gastrointestinal	100	4.51	7.08	2.00	0-6	0	50	64
L. Thermoregulatory	100	3.68	6.19	0.00	0-5.5	0	32	32
M. Sleep & wakefulness	100	13.33	15.66	9.00	3.5-17.5	0	88	112
N. Pain	100	8.91	11.90	4.00	0-15	0	56	64
O. Others	98.5	9.40	10.78	7.00	1-14.8	0	67	80
MDS-NMS Total score	95.64	91.55	100.50	54.00	28.5-125.5	10	491	1008
P. NM fluctuations	71.01	7.71	17.74	0.00	0-9	0	112	112
Controls								
A. Depression	100	2.37	6.00	0.00	0-1	0	22	80
B. Anxiety	100	1.95	4.12	0.00	0-2	0	18	64
C. Apathy	100	1.11	3.35	0.00	0-0	0	12	64
D. Psychosis	100	0.21	0.63	0.00	0-0	0	2	80
E. ICD & related disorders	100	0.68	2.21	0.00	0-0	0	9	64
F. Other	100	2.11	3.49	0.00	0-2	0	12	64
G. Cognition	100	4.89	9.69	2.00	0-4	0	35	96
H. Orthostasis	100	0.26	0.73	0.00	0-0	0	3	32
I. Urinary	100	2.74	9.12	0.00	0-1	0	40	80
J. Sexual	100	0.63	1.86	0.00	0-0	0	8	32
K. Gastrointestinal	100	1.11	1.94	0.00	0-2	0	7	64
L. Thermoregulatory	100	2.89	7.74	0.00	0-1	0	32	32
M. Sleep & wakefulness	100	3.26	5.61	2.00	0-4	0	24	112
N. Pain	100	2.63	5.77	0.00	0-4	0	24	64
O. Others	100	1.63	5.74	0.00	0-0	0	25	80
MDS-NMS Total score	100	28.47	39.44	12.00	6-28	0	151	1008

Abbreviations: PD, Parkinson's disease; SD, standard deviation; MDS-NMS, Movement Disorder Society-Non-Motor Symptoms scale; NM fluctuations, non-motor fluctuations; % F.C., percentage of fully computable scores; IQR, interquartile range; Theoret., thoretical.

Acceptability

In PD patients, the MDS-NMS showed moderate floor effects, but no ceiling effect for the domains as the maximum total score of the domain was reached by only three patients (4.5%) in Sexual and one (1.5%) in Thermoregulatory. The MDS-NMS total score showed no floor or ceiling effects (Table 2). In controls, floor effects ranged from 31.6% ([M] Sleep and wakefulness) to 89.5% (domains [C] Apathy, [D] Psychosis, and [E] Impulse control and related disorders), and ceiling effect was absent for all domains (Table 2). Differences in floor effects between patients and controls were statistically significant for domains (A) Depression, (B) Anxiety, (C) Apathy, (H) Orthostasis, (I) Urinary, (K) Gastrointestinal, (N) Pain, and (O) Others (*P* from 0.04 to <0.001; Table 2). A moderate skewness was present in all scores of both groups (Table 2).

Internal Consistency

Cronbach's alpha index was ≥0.70 for 10/15 domains and the section Non-motor fluctuations (Table 3). For the other domains, Impulse control and related disorders (0.45); Other NPS (0.58); Gastrointestinal (0.66); Thermoregulatory (0.57); and Others (0.63) obtained α values <0.70. The item, Homogeneity coefficient for domains ranged from 0.17 (ICD & related disorders) to 0.73 (Apathy), shown in Table 3.

The individual items with the lowest intra-domain inter-item correlation were: dopamine dysregulation syndrome, pseudobulbar affect, urinary incontinence, drooling of saliva, constipation, restlessness of limbs, snoring or apnea, and double vision items (data not shown). The item-total correlation was lower than the standard 0.30 for seven items: Other hallucinations (e.g., auditory), hobbyism, dopamine dysregulation syndrome, pseudobulbar affect, hypomania or mania, drooling of saliva, and a decreased sense of smell.

Qualitative Responses Regarding the Instrument

Table 4 shows the distribution of the responses to the questions regarding the scale provided by the neurologists and 15 patients. Responses were positive regarding the characteristics of the scale in >80% of survey respondents, with the highest proportion of negative opinions for the neurologists (23.1%) related to the long

TABLE 2 *Acceptability parameters of the preliminary Movement Disorder Society-Non-Motor Symptoms scale*

	Parkinson's disease patients			Healthy controls		
	Floor effect (%)	Ceiling effect (%)	Skewness	Floor effect (%)	Ceiling effect (%)	Skewness
A. Depression	29.0**	0	2.67	68.4	0	2.85
B. Anxiety	27.5*	0	2.36	52.6	0	3.63
C. Apathy	39.1***	0	2.64	89.5	0	2.92
D. Psychosis	76.5	0	3.21	89.5	0	2.80
E. ICD & related disorders	79.7	0	3.43	89.5	0	3.48
F. Other NPS	53.6	0	3.49	52.6	0	1.93
G. Cognition	18.8	0	1.89	36.8	0	2.63
H. Orthostasis	55.1*	0	2.16	84.2	0	3.31
I. Urinary	33.3**	0	1.95	68.4	0	4.22
J. Sexual	61.2*	4.5	2.45	63.2	0	3.84
K. Gastrointestinal	31.9*	0	4.21	63.2	0	2.03
L. Thermoregulatory	55.1	1.5	2.24	73.7	0	3.38
M. Sleep & wakefulness	7.3**	0	2.57	31.6	0	3.14
N. Pain	34.8*	0	1.82	63.2	0	3.19
O. Others	22.1***	0	2.53	78.9	0	4.18
MDS-NMS total	0**	0	2.43	10.5	0	2.17
P. Non-motor fluctuations	51.0***	2.0	4.64	--	--	--

Abbreviations: MDS-NMS, Movement Disorder Society-Non-Motor Symptoms scale.
Statistically significant difference between patients and controls for floor effect:
*p < 0.05; **p < 0.01; ***p < 0.001.
The rest of differences was not significant.

length of the scale. Particular comments of participants are summarized in the Table 4.

After careful consideration of the comments on the scale and the results of acceptability and internal consistency, the scale was modified as follows: (1) instructions for navigating across the scale scoring options were added; (2) item scoring assignment was more clearly specified; (3) 14 items were reworded; (4) several items were deleted, one from the domain Apathy, two from the domain Urinary, and one from the domain Sleep and wakefulness; (5) two domains (Other NPS and Thermoregulatory) were deleted; and (6) one item was moved from Thermoregulatory to Others domain, and one item was added to the subscale of Non-motor fluctuations. In summary, the revised, final version of the MDS-NMS was consolidated to a total of 52 items across 13 domains, plus the subscale for Non-motor fluctuations with eight items.

Discussion

NMS in PD can have a major and detrimental effect on quality of life of PD patients as well as their caregivers. NMS occur from the prodromal stage of PD right through to the palliative phase and appear to have a distinctive trajectory of progression which may not parallel motor progression.[42] Much of this is related to a multi-neurotransmitter and varied brain involvement in the pathophysiological processes that may be operative in PD. Therefore, a clearer understanding of the range, nature, and impact of NMS is crucial for improving the management of PD. As an example, contrary to previous perception, cognition is now thought to be affected even in the prodromal stage of PD, and dementia at diagnosis is therefore no longer an excluding factor for the diagnosis of PD.[13,14,43]

TABLE 3 *Data of internal consistency of the preliminary MDS-NMS in Parkinson's disease patients*

	Cronbach's alpha	Inter-item correlation	Item homogenity index	Item-total correlation
A. Depression	0.91	0.41–0.57	0.67	0.73–0.84
B. Anxiety	0.85	0.37–0.68	0.59	0.53–0.82
C. Apathy	0.91	0.41–0.70	0.73	0.76–0.83
D. Psychosis	0.59	0.19–0.62	0.38	0.07–0.69
E. ICD & related disorders	0.42	-0.04–0.56	0.17	0.04–0.48
F. Other NPS	0.61	-0.06–0.59	0.25	0.19–0.76
G. Cognition	0.85	0.19–0.62	0.48	0.51–0.87
H. Orthostasis*	0.79	0.70	0.65	-
I. Urinary	0.84	0.05–0.64	0.51	0.42–0.83
J. Sexual*	0.72	0.43	0.56	-
K. Gastrointestinal	0.63	0.03–0.22	0.33	0.23–0.60
L. Thermoregulatory*	0.54	0.32	0.40	-
M. Sleep & wakefulness	0.75	-0.03–0.41	0.31	0.33–0.55
N. Pain	0.77	0.13–0.56	0.45	0.40–0.66
O. Others	0.49	-0.01–0.41	0.26	0.04–0.43
P. Non-motor fluctuations	0.93	0.10–0.80	0.64	0.68–0.85

Abbreviations: MDS-NMS Movement Disorder Society Non-Motor Symptoms scale.
*Each of these domains has only two items.

TABLE 4 *Synthesis of the responses of neurologists and patients about the MDS-NMS*

	Neurologists (n = 52)			Patients (n = 15)		
		N	%		N	%
1. Do you find the scale relevant?	No	1	1.9	No	1	6.7
	Yes	51	98.1	Yes	13	86.6
	NR	0	0.0	NR	1	6.7
2. Does this scale help you to better understand your patient's / your current health state?	No	6	11.5	No	2	13.3
	Yes	46	88.5	Yes	13	86.7
	NR	0	0.0	NR	0	0.0
3. Do you think this scale is comprehensive?	No	5	9.6	No	2	13.3
	Yes	46	88.5	Yes	13	86.7
	NR	1	1.9	NR	0	0.0
4. Do you think this scale is too long?	No	40	76.9	No	13	86.7
	Yes	12	23.1	Yes	2	13.3
	NR	0	0.0	NR	0	0.0
5. Do you find the questions easy to understand?	No	3	5.8	No	1	6.7
	Yes	48	92.3	Yes	14	93.3
	NR	1	1.9	NR	0	0.0
6. Did you find any question(s) embarrassing?	No	49	94.2	No	14	93.3
	Yes	3	5.8	Yes	1	6.7
	NR	0	0.0	NR	0	0.0
7. Did you find any particular question(s) difficult to answer?	No	42	80.8	No	14	93.3
	Yes	10	19.2	Yes	1	6.7
	NR	0	0.0	NR	0	0.0

Abbreviations: MDS-NMS, Movement Disorder Society Non-Motor Symptoms scale; NR, No response.

Value-based healthcare is now a vital aspect of healthcare delivery worldwide, and measurement of symptoms and their burden are likely to become of day-to-day relevance in the management of PD. For example, the International Consortium for Health Outcomes Measurement (ICHOM) has now published recommendations of quality standards for PD, with NMS being an integral part of the outcome process.[44]

The NMSS has been used widely since its creation in 2005, highlighting the value of a comprehensive PD NMS rating scale. However, in light of the evolution of the field over the last 10+ years, updates and revisions were needed. The MDS-NMS was designed to overcome this need and address non-motor fluctuations in PD, which are frequently overlooked, yet very important, clinical syndrome. Furthermore, the scale also incorporates recognition and identification of impulse control disorders and related behavioral problems, now recognized to be a major clinical challenge in the management of PD worldwide.[45]

Data from the pilot study of MDS NMS are presented in this paper, and data quality was deemed excellent, with less than 1/1,000 missing data points in the patient group. Over 95% of the domains and scale scores were directly computable without any imputation. In the control group, there were no missing data at all.

The relatively high floor effect and skewness values observed in both groups are explained by the proportion of subjects who did not experience the respective symptoms. As the preliminary MDS-NMS was a broad, comprehensive scale, including 63 symptoms in 15 domains, it was expected that a considerable proportion of patients would be free of many of those symptoms. NMS as a whole can be present in otherwise healthy populations, but with lower prevalence of these manifestations than in PD.[3] Consistent with this reasoning, the floor effect was higher in the control group (except for the domain Other NPS).

Importantly, the floor effect was negligible for the total score, as was the ceiling effect for domains and total score in both groups. These results suggest appropriate acceptability of this preliminary MDS-NMS version.

Internal consistency of the scale was, as a whole, adequate. Most of the domains showed α coefficients higher than or close to the standard 0.70. Most of the items showed appropriate inter-relationship with the others in their domain and with the respective corrected total score, but some others showed deficient performance regarding these properties and were deleted (e.g., Pseudobulbar affect). Nonetheless, after review of their wording, if necessary, given their importance from a clinical perspective, some of these items (e.g., Drooling of saliva) were kept. The ICD & related disorders had low internal consistency, which is not surprising given the various symptoms or disorders included in this domain are distinct and often not co-morbid.

Cognitive pretesting comments and criticisms of the scale were gathered from user stakeholders (Table 4). Some critical comments related to item content and wording led to revisions. Comments that conflicted with each other and predictable (e.g., embarrassment related to questions about sex) or expressing opinions, solely based on personal experience (e.g., item considered not relevant because the subject has not that symptom), were not considered when modifying the MDS-NMS.

A limitation of this study was the predominance of women in the healthy controls, a fact that influence the differences observed between the groups. Nonetheless, the main objectives of this pilot study should be minimally affected by such discrepancy.

In conclusion, this pilot study of the preliminary version of the MDS-NMS showed that the scale was comprehensive, understandable, and appropriate according to the vast majority of participants. Complementary statistical analysis showed that

feasibility and acceptability of the preliminary MDS-NMS scale were satisfactory, with floor effect in most of the domains due to the proportion of patients not experiencing those symptoms, but not in the total score. Most of the internal consistency parameters were adequate, but some items showed clear flaws in this attribute, a fact that promoted their deletion. Both the information furnished by the participants and the primary analytic data led to modifications that resulted in the definitive version of the MDS-NMS to be validated in the next phase of the project.

Author 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 the First Draft, B. Review and Critique.

K.R.C.: 1A, 1B, 1C, 2C, 3B
P.M.M.: 1A, 1B, 2A, 2B, 3A
A.S.: 1A, 1B, 1C, 2C, 3B
D.W.: 1A, 1B, 1C, 2C, 3B
A.R.: 1B, 1C, 2C, 3B
C.R.B.: 2A, 2B, 3B

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Disclosures

Ethical Compliance Statement: Institutional review board or ethics committee that approved the study: (1) National Research Ethics Service (NRES) Committee East Midlands, Northampton, UK; (2) Institutional Review Board at the Perelman School of Medicine, University of Pennsylvania. All patients and controls participating in the study received information about the objective of the study and provided written informed consent. 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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