Movement Disorders
Vol. 24, No. 11, 2009, pp. 1641–1649

The Priamo Study: A Multicenter Assessment of Nonmotor Symptoms and Their Impact on Quality of Life in Parkinson's Disease

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Members of the "PRIAMO Study Group" are listed as an Appendix.

Potential conflict of interest: Angelo Antonini, Paolo Barone, Carlo Colosimo, Roberto Marconi, and Letterio Morgante have received consultancy fees from Boehringer-Ingelheim, Italy.

Received 19 January 2009; Revised 30 March 2009; Accepted 4 April 2009

Published online 9 June 2009 in Wiley InterScience (www.interscience.wiley.com).

DOI: 10.1002/mds.22643

Abstract: We performed a multicenter survey using a semi-structured interview in 1,072 consecutive patients with Parkinson's disease (PD) enrolled during 12 months in 55 Italian centers to assess the prevalence of nonmotor symptoms (NMSs), their association with cognitive impairment, and the impact on patients' quality of life (QoL). We found that 98.6% of patients with PD reported the presence of NMSs. The most common were as follows: fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urgency and nocturia (35%), drooling of saliva and difficulties in maintaining concentration (31%). The mean number of NMS per patient was 7.8 (range, 0–32). NMS in the psychiatric domain were the most frequent (67%). Frequency of NMS increased along with the disease duration and severity. Patients with cognitive impairment reported more frequently apathy, attention/memory deficit, and psychiatric symptoms. Apathy was the symptom associated with worse PDQ-39 score but also presence of fatigue, attention/memory, and psychiatric symptoms had a negative impact on QoL. These findings further support a key role for NMS in the clinical frame of PD and the need to address them specifically in clinical trials using dedicated scales. © 2009 Movement Disorder Society

Key words: nonmotor symptoms; Parkinson's disease; quality of life; cognition; psychiatric symptoms

INTRODUCTION

Nonmotor symptoms (NMSs) in Parkinson's disease (PD) have gained relevance in recent years for their impact on patients' quality of life and their contribution to institutionalization at advanced disease stage.[1,2] NMSs are present already at disease onset and some, like psychiatric and sleep disorders, may even precede motor symptoms.[3–5] The pathophysiology of NMS is still poorly understood, and a dysfunction of both dopaminergic and nondopaminergic systems contributes to their development.[6]

Scales have been proposed for NMS evaluation addressing individual aspects such as sleep, cognition, mood, behavior, and quality of life.[7] Recently, the first largely comprehensive, self-completed NMS questionnaire for PD (NMSQuest) has been developed and validated.[8,9] It considers 30 items distributed in nine different domains: gastrointestinal, urinary, memory, hallucinations, depression/anxiety, sexual function, cardiovascular, sleep disorder, and miscellany. However, the total number of examined patients is still small and additional data are needed to assess the relevance of NMS features for PD disability.

To expand current knowledge, we used a structured interview to study both NMS epidemiologic characteristics and evolution in a large cohort of consecutive patients with PD using a multicenter design (PRIAMO: Parkinson and nonmotor symptoms). We aimed at determining the prevalence of NMS, their relevance for cognitive impairment and most importantly their overall impact on quality of life (QoL).

PATIENTS AND METHODS

Study Design

Methodology applied in the PRIAMO study was extensively described elsewhere.[10] The Steering Committee for the project (Appendix) designed the study and defined instruments for data collection. Participating centers (Appendix) were selected on the basis of previous participation in clinical studies and proven ability to administer study tools. The study was approved by the Ethics Committees of participating centers and all patients provided written informed consent.

Data Collection and Methods

Diagnosis of PD was based on current clinical criteria.[11] These criteria were preferred to others because easily applicable in clinical routine setting and especially in a wide observational study, such as PRIAMO. Moreover, unlike others,[12] these criteria take into account genetic parkinsonisms. A neurologist experienced in movement disorders examined patients at each site and administered the semistructured interview. This consisted of 12 NMS domains (gastrointestinal symptoms, pain, urinary symptoms, cardiovascular symptoms, sleep disorders, fatigue, apathy, attention, skin disorders, psychiatric symptoms, respiratory symptoms, other symptoms), each one including 2 to 10 specific questions with dichotomous (yes/no) answers. We also included drooling of saliva, cough, and dyspnea in the questionnaire because they are often underreported in PD surveys even if not strictly NMSs. Patients were asked to report specific symptoms and domains as "present/absent" with reference to the month before the visit. The list of NMSs was defined by the steering committee of the PRIAMO study.

The Unified Parkinson's Disease Rating Scale part III (UPDRS-III) was used to evaluate motor disability.[13] Overall disease severity was graded according to the modified Hoehn and Yahr (HY) scale.[14] Cognitive abilities were investigated with the Mini-Mental State Examination (MMSE)[15] and the Frontal Assessment Battery (FAB).[16] Quality of life was assessed with the 39-item Parkinson's Disease Questionnaire (PDQ-

39).[17] All scales are available and validated for the Italian population.

Given the naturalistic nature of the study, investigators were asked to classify patients with PD according to their clinical status as a: (1) "*naïve*" patient, who had never taken dopaminergic agents; (2) "stable" patient, who was under dopaminergic treatment and had no motor complications; (3) "complicated" patient who had developed motor fluctuations and/or dyskinesia under dopaminergic treatment. Patients were all evaluated during the "on" state.

Statistical Analysis

The frequency distribution of specific NMS and domains was calculated as the ratio between the total number of patients complaining of a symptom/domain and the total number of patients with PD.

Only fully completed scales were used for statistical analysis, i.e., all items had to be answered. No recoding or interpolation of missing items was performed. MMSE data were handled differently: questionnaires with all items not completed were not considered evaluable for statistical analysis; the missing responses in the remaining questionnaires were considered equal to 0, according to McDowell and Newell.[18]

The total scores of PDQ-39 and UPDRS-III were calculated by summing single items. For both MMSE and FAB, age- and education-adjusted scores were calculated and cognitive impairment was defined as a MMSE score $\leq$ 23.8[19] and/or FAB score $\leq$ 13.48,[20] according to Italian normative data.

Comparisons were performed by *T* test for mean values, Wilcoxon rank sum test for median values, Chi-square test or Fisher exact test for frequency distribution. The significance threshold was set to 0.05. We applied Bonferroni's correction in case of multiple comparisons. When the statistical distribution of quantitative variables was not skewed, we reported the mean and standard deviation (SD). In all other cases we reported nonparametric statistics, i.e., median and interquartile range (IQR). Data were analyzed using the SAS software package for Windows, release 8.2.

RESULTS

Patient Population

Table 1 lists the demographics of the 1,072 patients with PD enrolled in this study. There were 647 (60.4%) males with a mean age of 66.8 (SD, 9.6) years, and 425 (39.6%) females with a mean age of 68.2 (SD, 9.1) years. The most frequently reported concomitant non-neurological disorders were: hypertension (41.5%), heart diseases (17.8%) and dyslipidemia (16.4%). Forty-nine subjects (4.6%) had a diagnosis of dementia according to DSM-IV diagnostic criteria: as far as anamnestic data is concerned, they were assessed with the help of an informant, usually the spouse or son/daughter.

TABLE 1. *Sample characteristics at baseline*

	Total N = 1,072
Men, N (%)	647 (60.4)
Age (yr), mean (SD)	67.4 (9.4)
Disease onset age (yr), mean (SD)	61.0 (10.6)
Disease duration (yr), median (IQR)	5.1 (2.8–9.1)
UPDRS-III score, mean (SD)	24.2 (13.1)
Hoehn & Yahr stage, median (IQR)	2 (1.5–2.5)

With respect to dopaminergic therapy, 10% of the patients were not treated (*naïve*), 70.2% had a stable response, whereas 19.8% reported motor fluctuations and/or dyskinesia. Dopaminergic treatment was as follows: levodopa (N = 189 patients, 17.6%), dopamine agonists (N = 199 patients, 18.6%), or both (N = 577 patients, 53.8%). Additional medications were as follows: catechol *O*-methyltransferase (COMT) inhibitors (N = 153, 14.3%), MAO-B inhibitors (N = 87, 8.1%), amantadine (N = 122, 11.4%), anticholinergics (N = 63, 5.9%), antidepressants (N = 169, 15.8%), and benzodiazepines (N = 160, 14.9%).

Prevalence of NMS

All patients with PD reported at least one NMS except 15 (1.4%). Table 2 shows the frequency of NMS grouped by domain. Mean (SD) number of NMS per patient was 7.8 (4.9), ranging from 0 to 32. The most frequently reported symptoms were fatigue (58.1%), anxiety (55.8%), leg pain (37.9%), insomnia (36.9%), urgency and nocturia (35%), drooling of saliva and difficulties to maintain the concentration (31%). When patients were asked about NMS at PD onset, joint/muscular pain (298; 27.8%), anxiety (272; 25.4%), fatigue (252; 23.5%), and depression (240; 22.4%) were the most frequently recalled.

Given the wide range of NMS, they were grouped into 12 domains (NMSd). Mean (SD) of NMSd was 5.5 (2.5) ranging from 0 to 12, with 50% of patients with 4 to 7 NMSd. The most frequently (>30%) reported NMSd were as follows: psychiatric (716; 66.8%), sleep disorders (687; 64.1%), gastrointestinal (654; 61%), pain (653; 60.9%), fatigue (623; 58.1%),

TABLE 2. *Prevalence of NMS*

Domain (Number of symptoms per domain)	Symptoms	N = 1,072 (%)
Gastrointestinal (7)	Drooling of saliva	333 (31.1)
	Difficulty in swallowing	173 (16.1)
	Nausea/vomiting	104 (9.7)
	Constipation	295 (27.5)
	Lowered number of evacuations (<3 times/week)	264 (24.6)
	Incomplete bowel emptying	122 (11.4)
	Incontinence	8 (0.8)
Pain (5)	Undefined pain	223 (20.8)
	Leg Pain	406 (37.9)
	Abdominal pain	61 (5.7)
	Pain related to intake of drugs (e.g., levodopa)	11 (1.0)
	Shoulder pain	205 (19.1)
Urinary (3)	Urgency	375 (35.0)
	Frequency (voiding every 2 hrs)	279 (26.0)
	Nocturia	371 (34.6)
Cardiovascular (2)	Lightheadness/dizziness during the postural changes	152 (14.2)
	Fall because of syncope	11 (1.0)
Sleep (4)	Behavioral sleep disturbances (REM)	317 (29.6)
	Insomnia	395 (36.9)
	Excessive day time sleepiness	227 (21.2)
	Restless legs	163 (15.2)
Fatigue (1)	Fatigue limiting the patient's day activities	623 (58.1)
Apathy (3)	Loss of interest in surrounding matters	209 (19.5)
	Loss of interest in activities of daily living	225 (21.0)
	Awareness deficit	44 (4.1)
Attention/ memory (3)	Difficulties to maintain concentration	337 (31.4)
	Short-term memory problems	269 (25.1)
	Forget to do daily things	93 (8.7)
Skin (2)	Seborrhea	176 (16.4)
	Hyperhidrosis	135 (12.6)
Psychiatric symptoms (10)	Anhedonia	114 (10.6)
	Anxiety	598 (55.8)
	Panic attacks	45 (4.2)
	Aggressive behavior	38 (3.5)
	Suicidal ideas	16 (1.5)
	Nervousness	192 (17.9)
	Frightened without reason	58 (5.4)
	Sadness/depression	241 (22.5)
	Delirium	17 (1.6)
	Hallucinations	39 (3.6)
Respiratory (3)	Dyspnea	123 (11.5)
	Cough	82 (7.7)
	Stridor	15 (1.4)
Miscellaneous (5)	Olfactory dysfunction	288 (26.9)
	Dysgeusia	84 (7.8)
	Diplopia	74 (6.9)
	Weight change	103 (9.6)
	Sexual dysfunction	210 (19.6)

urinary (614; 57.3%), attention/memory (479; 44.7%) (Table 3).

Pain, fatigue, and psychiatric NMSd were significantly more prevalent in women, namely 67.5, 65.9, and 73.9%, respectively, versus 56.6, 53.0, and 62.1% in men (Chi-square test, $P < 0.0042$, with Bonferroni's correction). Skin disorders were significantly more prevalent in men than women (28.8% vs. 17.4%; Chi-square test, $P < 0.0001$). There were no differences between genders for the remaining NMSd.

Mean ± SD age was significantly higher in patients with gastrointestinal NMS than in those without (68.3 ± 9.3 vs. 66 ± 9.3; *T* test, $P < 0.0042$, with Bonferroni's correction). The same applies to the attention domain (68.5 ± 9.6 vs. 66.5 ± 9.1; *T* test, $P < 0.0042$, with Bonferroni's correction). Differently, patients with skin symptoms were significantly younger than patients without [mean age: 65.5 (SD, 9.8) vs. 68 (SD, 9.2); *T* test, $P < 0.0042$, with Bonferroni's correction]. There were no significant age differences as regards the other NMSd.

Disease duration (mean ± SD) was significantly longer (*T* test; $P < 0.0042$, with Bonferroni's correction) in patients with NMS than in patients without NMS related to the domains: skin disorders (7.4 ± 5.6 vs. 6.1 ± 4.8 years), urinary symptoms (7.1 ± 5.4 vs. 5.5 ± 4.2 years), fatigue (7.0 ± 5.3 vs. 5.7 ± 4.5 years), gastrointestinal (7.0 ± 5.3 vs. 5.6 ± 4.5 years), and sleep disturbances (7.0 ± 5 vs. 5.4 ± 4.6 years).

The frequency of NMS domains increased with disease severity. Respiratory symptoms were reported by 9.6 and 30.6% of patients with mild (HY stage = 1) and severe (HY stage = 4–5) disease, respectively. Similarly skin symptoms, fatigue, urinary symptoms, and apathy were reported respectively by 14.4, 37.7, 43.1, and 24.6% of patients at a mild severity disease stage and by 32.7, 81.6, 89.8, and 49% of patients at an advanced disease stage (Table 3).

As shown in Figure 1, gastrointestinal, pain, urinary, sleep, skin disorders, and "miscellaneous" NMSd were less frequent in the *naïve* subgroup of patients (not previously treated with dopaminergics) than in the stable and "complicated" treated subgroups (Chi-square test; $P < 0.0042$, with Bonferroni's correction). The prevalence of sleep disorders in *naïve* (41.1%) was almost half than in complicated patients (78.3%). The frequency of cardiovascular symptoms, fatigue, apathy, attention/memory, psychiatric, and respiratory symptoms did not differ among the three subgroups.

With the exception of cardiovascular and miscellaneous domains, UPDRS motor score was higher in patients with NMSs (*T* test; $P < 0.0001$). Specifically,

TABLE 3. *Prevalence of NMS domains and disease stage*

		Disease Stage (Hoehn and Yahr scale)			
	All	1	1.5–2	2.5–3	4–5
NMS domains	N = 1,072 (%)	N = 167 (%)	N = 515 (%)	N =325 (%)	N = 49 (%)
Gastrointestinal	654 (61.0)	76 (45.5)	280 (54.4)	250 (76.9)	36 (73.5)
Pain	653 (60.9)	85 (50.9)	302 (58.6)	218 (67.1)	39 (79.6)
Urinary	614 (57.3)	72 (43.1)	266 (51.7)	222 (68.3)	44 (89.8)
Cardiovascular	158 (14.7)	22 (13.2)	70 (13.6)	53 (16.3)	11 (22.5)
Sleep	687 (64.1)	80 (47.9)	312 (60.6)	245 (75.4)	40 (81.6)
Fatigue	623 (58.1)	63 (37.7)	291 (56.5)	224 (68.9)	40 (81.6)
Apathy	328 (30.6)	41 (24.6)	138 (26.8)	119 (36.6)	24 (49.0)
Attention/memory	479 (44.7)	63 (37.7)	208 (40.4)	168 (51.7)	32 (65.3)
Skin	260 (24.3)	24 (14.4)	102 (19.8)	112 (34.5)	16 (32.7)
Psychiatric	716 (66.8)	102 (61.1)	326 (63.3)	238 (73.2)	41 (83.7)
Respiratory	191 (17.8)	16 (9.6)	80 (15.5)	74 (22.8)	15 (30.6)
Miscellaneous	515 (48.0)	62 (37.1)	247 (48.0)	168 (51.7)	29 (59.2)

Cochran-Armitage trend test <0.0045 (with Bonferroni's correction) for all NMS except cardiovascular symptoms ($P = 0.0774$).

it was 8 points higher for fatigue (mean UPDRS score 27.5 ± 13.6 vs. 19.6 ± 11.0), 6.5 points higher for apathy (28.7 ± 14.9 vs. 22.2 ± 11.8), and 6.4 points higher for attention/memory problems (27.7 ± 13.9 vs. 21.3 ± 11.8) and gastrointestinal symptoms (26.6 ± 13.8 vs. 20.3 ± 10.9).

NMS and Cognitive Impairment

Twenty-one patients (2%) did not complete the MMSE questionnaire and were excluded from analyses. Eleven percent (N = 119) of patients with PD had MMSE score lower than 23.8.

Patients with PD and cognitive impairment complained about more NMS than those without (Fig. 2). Cognitive impairment (MMSE ≤ 23.8) was associated with greater frequency of apathy, attention/memory, fatigue, psychiatric, and respiratory features (Fisher exact Test; $P < 0.0001$). A similar difference was found for gastrointestinal symptoms (Fisher exact Test; $P = 0.0026$) but not for other NMSd.

Twenty-nine percent of patients (N = 311) had missing items at the FAB and were thus excluded from

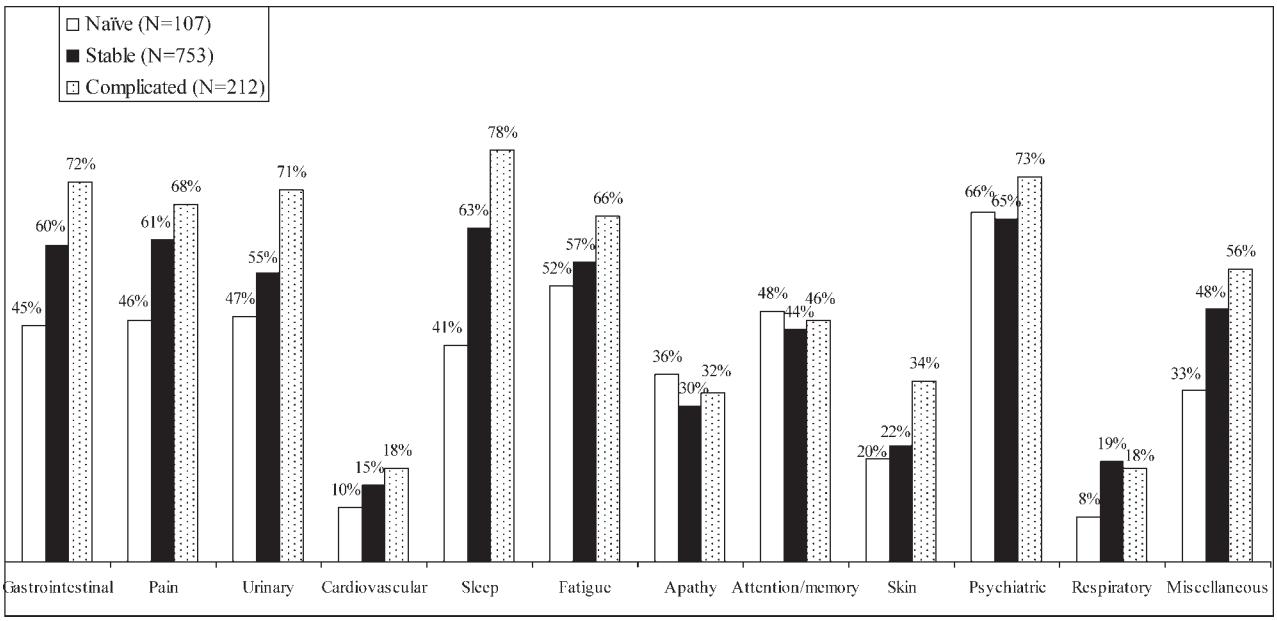

FIG. 1. Prevalence of NMS domains according to patients' clinical status. Fisher exact test <0.0042 (with Bonferroni's correction) for the following NMSd: gastrointestinal, urinary symptoms, pain, sleep disorders, skin. Patients' clinical status is indicated in the "Data Collection and Methods" section.

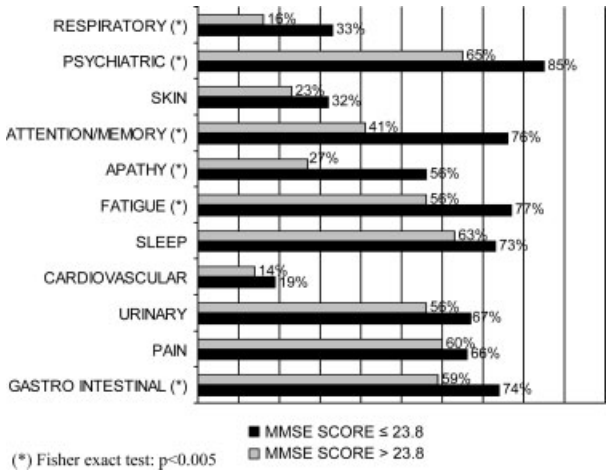

FIG. 2. Frequency of NMS according to MMSE score. Fisher exact test <0.0045 (with Bonferroni's correction) for all NMS except skin ($P = 0.04015$), sleep disorders ($P = 0.03298$), cardiovascular ($P = 0.2148$), urinary symptoms ($P = 0.02364$), and pain ($P = 0.27367$).

analyses. When considering a cut-off of 13.48 on FAB, 28.5% (N = 217) of patients with PD had a FAB score lower than the cut off. Patients with PD and abnormal score reported higher frequency of attention/memory problems ($P < 0.0001$), fatigue ($P = 0.0001$), psychiatric symptoms and apathy ($P = 0.0006$ and $P = 0.0008$ respectively). Other domains did not differ.

NMS and QoL

Twenty-three percent of patients (N = 246) had missing items in the PDQ-39 questionnaire and were thus excluded from the analyses. Considering the relatively high proportion of missing data, we analyzed the clinical characteristics of this subgroup vs. the overall study population. There were no differences in disease duration, HY score, NMS number and domains, but UPDRS motor score ($P = 0.0243$) was higher and MMSE ($P = 0.0034$) and the FAB ($P = 0.0005$) lower.

Among PDQ-39 dimensions, patients had the best QoL in social support (median = 0; IQR: 12.5) while higher values of PDQ-39 scores (meaning lower QoL) were recorded in emotional wellbeing (median = 31.3) and bodily discomfort (median = 33.3) dimensions scores; for both of them IQR = 16.7–50.0.

Presence of apathy was associated with the worst QoL score (median PDQ-39 SI score = 36.0; IQR: 23.3–47.0) followed by cardiovascular symptoms, fatigue, attention/memory, and respiratory symptoms (Fig. 3). The greatest difference in PDQ-39 score (present vs. absent NMSd) was recorded in patients presenting apathy followed by fatigue, attention/memory, and psychiatric symptoms (differences ranged from 15.9 points for apathy to 11.8 for psychiatric symptoms; $P < 0.0001$).

DISCUSSION

We found that nearly all patients with PD reported at least one NMS, with fatigue and anxiety being the most frequent. Most previous studies on the prevalence of NMS in PD focused on selected symptoms in small populations. The prevalence of fatigue in PD ranged from 33 to 58%[21,22] consistent with our results. Fatigue

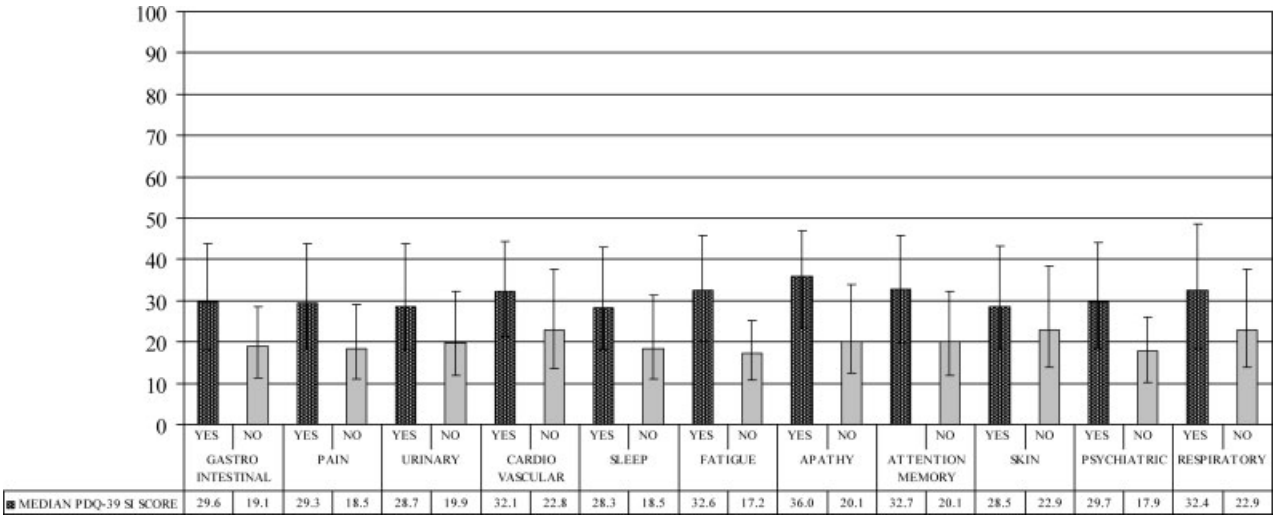

FIG. 3. NMS domains and QoL. Median and IQR for PDQ-39 Summary Index score. Wilcoxon rank-sum test <0.0045 (with bonferroni's correction) for all NMS.

in PD may be heterogeneous in nature, including physical aspects such as muscle fatigue, but also mental and emotional aspects (sometimes called "central fatigue").[23] Anxiety was reported in 40%,[24] pain in 46%,[25] and apathy in 51% of patients with PD.[26] Some of the discrepancies in the frequency of each NMS might reflect methodological issues, including recruitment criteria and tools used to detect NMS. For example, the frequency of depression ranged from 10 to 45%[26–29] depending on whether an inclusive or exclusive approach was used.[24]

To our knowledge, only one study investigated the whole spectrum of NMSs in a large population (545 patients with PD) and this was carried out in six countries by means of a dedicated questionnaire.[9] While overall their conclusions are consistent with ours regarding to the relevance of NMSs in PD, there are also differences in the frequency of individual symptoms. These might relate to methodological issues. Firstly, in that study the primary objective was to verify the feasibility of the NMS questionnaire and to study the effect of demographic and anamnestic data on the presence of NMS. Secondly, the recorded NMSs differed in the two studies as did the domains classification: in our study NMSs were grouped as defined by the PRIAMO steering committee. Finally, discrepancies between the two studies may relate to cultural and geographic differences, as our study was conducted only in Italy. We found that the psychiatric symptoms were the most frequently reported (66.8% of the sample), followed by sleep (64.1%), gastrointestinal and pain (61.0%), fatigue (58.1%), urinary (57.3%), and attention/memory (44.7%). In the study by Martinez-Martin et al.,[9] urinary symptoms were the most frequent (59%) followed by depression/anxiety (48%) and attention/memory (42%).

In our study, there was a mean of 7.8 NMS (range: 0–32) per patient and a mean of 5.5 NMSd (range: 0–12) per patient. In a study with 50 patients with PD with motor fluctuations, Witjas et al.[30] found that all of them had at least one NMS. In another study on depression, anxiety, fatigue, and sleep disturbances in 101 patients with PD, two or more NMS were reported in 59% of patients and the prevalence of NMS was associated with more severe PD.[31]

Concerning the relationship of NMS with cognitive impairment, we are aware that MMSE and FAB may be insufficient to draw conclusions on cognitive function in PD. Indeed, there was a discrepancy between the number of patients reported as demented based on DSM-IV (4.6%) and those with a MMSE score of <23.8 (11%). A pathological MMSE score may simply reflect a mild initial cognitive decline, in patients not fulfilling yet the criteria for full-blown dementia. In fact, further analyzing the 119 subjects with a MMSE score below the 23.8 cut-off value, we found that 50% were above 21. However, we observed that patients with low MMSE and FAB scores reported apathy, attention/memory deficit, and psychiatric symptoms more frequently than patients with a higher score. As a novel observation, the same patients reported also more frequently fatigue, gastrointestinal, and urinary symptoms, suggesting a wider than expected association between cognitive impairment and other NMSs.

Among the 48 NMSs explored in our study, apathy, attention/memory, and psychiatric symptoms did not correlate with disease duration and dopaminergic treatment suggesting that they may be present even early in the disease course. In particular, psychiatric NMS, mainly anxiety and depression, were reported by 61.1% of patients at HY stage 1, representing the most common NMS in early disease, consistently with the evidence of a high prevalence of depression in the initial or even prodromal phase of the disease.[3,32] These results may have impact on clinical practice, suggesting that NMS may be the target for medical interventions even in early stages of disease.

The domain that includes urinary symptoms was the most frequently reported (89.8%) at Hoehn and Yahr stage 4–5. Although we studied a relatively small number of advanced stage patients, it is possible that the high frequency of urinary symptoms may in part reflect the onset of a urinary disorder with increasing age.

Our study is the largest to explore the impact of a wide spectrum of NMS on QoL, and expands previous findings of a relationship between the NMS questionnaire score and QoL in 545 patients with PD.[33] In addition, we described specific NMS having the highest impact on QoL, such as apathy, psychiatric symptoms (including depression), fatigue, and attention-memory problems. This is consistent with data from a recent study showing that depression and anxiety are major predictors of poor QoL in PD.[34] Interestingly, patients who did not complete the PDQ-39 had lower MMSE and FAB scores compared to completers. This might relate to the difficulty in administering the questionnaire to patients with cognitive dysfunction.

We acknowledge that our study has two major limitations: (1) lack of normal controls to assess differences with PD, (2) recruitment of patients mainly in early stages of disease, as revealed by the low mean score of the UPDRS-part III scale (mean = 24.2), the low median stage of the Hoehn and Yahr scale (2), and the relative short mean disease duration (5.1 years). However,

this was counterbalanced by the large sample size and inclusion of patients from different outpatient clinics.

In conclusion, we found a high prevalence of NMS and a relationship with disease duration and severity, and cognitive dysfunction. The association of poor QoL with all screened NMS further supports their important role in the clinical manifestation of PD and the need to improve diagnostic accuracy possibly through the use of dedicated scales in clinical practice.

Acknowledgments: This study was supported by an educational grant issued by Boehringer-Ingelheim, Italy. In addition to this AA has received funding as advisor and speaker in sponsored symposiums from Boehringer-Ingelheim, Solvay, Novartis, UCB and GSK. PB has received compensation for consulting services and received research support from Boehringer Ingelheim; for consulting services from Novartis, Schwarz Pharma/UCB and Lundbeck. CC received honoraria from BI, Glaxo, Novartis, Allergan and Ipsen. RM and LM received consultancy fees from BI. We are grateful to Medidata for data collection and analysis and to Sara Rizzoli for helping writing the manuscript.

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