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ORIGINAL RESEARCH

The impact of nonmotor symptoms on quality of life in patients with Parkinson's disease in Taiwan

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Purpose: The nonmotor symptoms (NMS) of Parkinson's disease (PD) are important factors for quality of life (QoL). Few studies on NMS have been conducted in Asian PD patients. Additionally, effects of anti-PD drugs on risk of NMS are still controversial. We therefore conducted this hospital-based cross-sectional study to examine the clinical factors, including concomitant anti-PD medication use, on the occurrence of NMS and QoL in Taiwanese PD patients.

Patients and methods: PD patients who received long-term follow-up in the movement disorders clinics were enrolled and received NMS questionnaire (NMSQuest) and the 39-item Parkinson's Disease Questionnaire (PDQ-39). Spearman's rank correlation coefficient was checked for the correlation between clinical factors and NMSQT/PDQSI. Multiple linear regressions were applied to assess the influence of clinical factors on NMSQT/PDQSI.

Results: A total of 210 PD patients (mean age 66.1±9.86 years, Hoehn and Yahr stage 2.2±0.9) were included in this study. Up to 98% of patients reported at least one symptom of NMS. The most prevalent symptom was urinary complaints (56%), followed by memory/apathy (30%) and depression/anxiety (28%). The correlation between NMSQT and PDQSI was strong (r_s=0.667), especially the item of depression/anxiety (r_s=0.607). The regression model for NMSQT indicated that disease duration and severity, but not pharmacological therapy, were major predictors of NMS.

Conclusion: Our data indicated a high prevalence rate of NMS in PD patients. Among symptoms of NMS, depression and anxiety had the greatest impact on QoL. Concomitant anti-PD medication use did not affect the occurrence of NMS and QoL.

Keywords: NMS, NMSQuest, NMS questionnaire, PD, PDQ-39, PDQSI

Introduction

The nonmotor symptoms (NMS) of Parkinson's disease (PD) are recognized as important disability-causing factors. NMS include autonomic dysfunction,[1] neuropsychological problems,[2] sleep disturbance,[3,4] and sensory symptoms.[5] These symptoms constitute a burden on the caregiver and the public health system. In the PRIAMO study,[6] up to 98.6% of PD patients had NMS. Recently, the correlation between NMS and PD patients' health-related quality of life (HRQoL) has been emphasized. Several studies indicate that NMS, rather than motor symptoms, are a major cause of poor HRQoL.[7–9] The NMS screening questionnaire (NMSQuest), a self-completed questionnaire comprising 30 items, is a rapid screening tool for the early detection of patients' NMS.[10,11] Previous studies have compared NMS in different countries and showed more prevalent gastrointestinal symptoms in Asian countries, probably due to ethnic and economic differences.[12,13] However, the NMSQuest is still not routinely used for Taiwanese PD patients. Demographic data regarding NMS in Taiwanese PD patients remain unknown.

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The pathophysiology of NMS is suspected to involve dopamine, noradrenaline, and serotonin. A previous review indicated that current dopaminergic anti-Parkinson medication has a limited effect on NMS.[14] Although dopamine agonists reportedly have some antidepression effects,[15,16] they also precipitate other NMS, such as orthostatic hypotension, hallucination, and impulse control diorder.[17–19] Thus, whether dopamine agonists improve patients' NMS and HRQoL remains a point of controversy.

The purpose of our study is to investigate the prevalence of NMS in PD patients in Taiwan and the impact of NMS on HRQoL since few studies on NMS have been conducted in Asian PD patients and the effects of anti-PD drugs, especially dopamine agonists, on risk of NMS are still controversial. We therefore conducted this hospital-based cross-sectional study to examine the clinical factors, including concomitant anti-PD medication use, on the occurrence of NMS and HRQoL in Taiwanese PD patients. We used the NMSQuest and 39-item Parkinson's Disease Questionnaire (PDQ-39) to explore the correlation among NMS, clinical factors, pharmacological therapy, and HRQoL.

Materials and methods

Patients

This cohort study was conducted in the neurology department of National Taiwan University Hospital (NTUH), a tertiary referred medical center in Taipei, Taiwan. From February 2014 to December 2014, PD patients who fulfilled the United Kingdom Parkinson's Disease Brain Bank Criteria[20] and received long-term follow-up in NTUH movement disorder clinics were recruited. Patients who were diagnosed with atypical parkinsonism or secondary parkinsonism were excluded. Since the National health insurance of Taiwan pays the cost of the anti-cholinesterase inhibitor, rivastigmine, for subjects with PD with dementia, we therefore excluded subjects with concomitant use of rivastigmine to exclude participants with PD with dementia.[21] All patients in this study provided written informed consent. The study was approved by the Ethical Research Committee of NTUH.

Measures

Patients who fulfilled the diagnostic criteria were asked to complete the Chinese version of the NMSQuest[22] and PDQ-39[23] while they were in the waiting room of the clinic. Previous studies have validated the Chinese versions of these two tests and the reliability of each domain of these two tests in the Chinese version are between 71% and 95%, which represents an acceptable psychometric property. If necessary, aid from patients' caregivers or a nurse was acceptable. Demographic data, including patients' age, sex, age at onset, duration, Hoehn and Yahr (H&Y) stage, disease type, and current medication, were collected from medical records. Patients' disease type was classified as tremor-at-onset type or bradykinesia/rigidity-at-onset type by review of their medical record, depending on their initial presentation at their first visit to our clinics.[24,25] Individuals with resting tremor predominant as initial presentation were classified as tremor-at-onset type; others were classified as bradykinesia/rigidity-at-onset type.

The NMSQuest is a validated self-completed yes–no-type questionnaire to assess patients' NMS. This 30-items questionnaire measure nine domains of NMS: digestive, urinary, sexual, cardiovascular, memory/apathy, hallucination/delusion, depression/anxiety, sleep, and miscellany.[10] Positive responses are summed up to yield a total score (NMSQT) that ranges from 0 to 30. Higher scores indicate worse NMS condition.[11] The prevalence of each item was calculated on the total 210 samples by computing the number of positive responses and transforming them into a percentage. Positive answers in each domain were summed to obtain the score for the domain. The standardized prevalence of each domain was calculated by the number of positive responses divided by the total number of responses in the domain and transforming this values into a percentage.

Patients' HRQoL was assessed by the PDQ-39,[7] which contains 39 items. Each item was rated by the patients using one of five categories, from 0 (never) to 4 (very frequent). PDQ-39 summary index (PDQSI) was calculated by dividing the sum of the total raw score by the maximum possible score (156 or 152 points, depending on the patient's marriage status) and multiplying by 100. In this study, we used PDQSI as a standardized index for representing PD patients' life quality.

Statistical analysis

Spearman's rank correlation coefficient was calculated to check the correlation between clinical factors, pharmacological therapy, NMSQT, and PDQSI. *P*-values of less than 0.05 were accepted as significant. The strength of the association for correlation coefficients was interpreted as follows: ≤0.19, negligible correlation; 0.20–0.39, weak correlation; 0.40–0.59, moderate correlation; 0.60–0.79, strong correlation; and ≥0.80, very strong correlation.[26] A stepwise multiple linear regression analysis was calculated to demonstrate which clinical factors contributed significantly to NMSQT. Age, sex, age at PD onset, duration of PD symptoms, H&Y stage, levodopa dosage, and dopamine agonist

dosage (transformed into levodopa-equivalent dosage)[27] were involved as independent variables. Owing to collinearity between patients' current age and their age at disease onset (r=0.92), age at PD onset was transformed into dummy variables (<50 years =0; ≥50 years =1). Stepwise multiple linear regression analysis was also applied to assess the contribution of clinical factors to the PDQSI. For the regression model of PDQSI, we involved the aforementioned factors and NMSQT as independent variables.

To compare our prevalence of each symptom with others', we chose two international studies (one included only Europe and USA, the other included Europe, USA, Israel, and Japan) and one study from People's Republic of China. χ^2 test was used for comparison (Table S1).[10,28,29] SPSS version 22.0 was used for the statistical analyses.

Results

We collected data from 210 patients (110 males, 100 females; mean age: 66.1±9.86 years; median: 67 years; mode: 63 years; age range: 33–86 years; mean age at onset: 60±10.53 years; median: 61 years; mode: 61 years; onset age range: 26–83; disease duration 6.11±4.13 years; and H&Y stage 2.2±0.9). Demographic data are shown in Table 1. Half of our subjects were in H&Y stage 2. Most of our patients were using levodopa (97.6%) and dopamine agonists (81%).

The result of NMSQuest and PDQ-39 are shown in Table 2. The mean NMSQT was 7.77±4.74, which was considered as moderate in severity according to a previous study.[11] The prevalence of NMS was 98.57%. Only three patients had no NMS. Among 30 NMS, nocturia was the most frequently reported NMS (prevalence =62.86%). Constipation was the second most prevalent problem among patients (prevalence =50.95%). The least frequent complaint was bowel incontinence, which happened in 2.86% of patients (Table S1). Of the nine NMS subdomains, the urinary domain had the highest prevalence (56.19%), followed by memory/apathy (30.48%) and depression/anxiety (27.86%), while hallucination/delusion had the lowest prevalence (9.76%). The mean PDQSI was 16.13±15.61.

Spearman's rank correlation coefficients indicated that the NMSQT and all subdomains correlated with the PDQSI (Table 3). NMSQT had stronger correlation with PDQSI than H&Y stage (r_s of NMSQT =0.667; r_s of H&Y stage =0.503). Among nine NMS subdomains, depression/anxiety correlated most strongly with PDQSI (r_s=0.607), while the urinary domain exhibited the weakest correlation (r_s=0.172). Age and disease types at onset did not significantly correlate with NMSQT and PDQSI, but there was significant difference between sexes in some NMS subdomains (Table S2). Females had higher scores in memory/apathy and depression/anxiety (prevalence of memory/apathy, female vs male: 57%

Table 1 Demographic, clinical, and medical characteristics for our subjects

		Range
Patients, n	210	
Male/female	110/100	
Mean age ± SD, years	66.1±9.86	33–86
Mean age at onset ± SD, years	60±10.53	26–83
Age ≥50/age <50, n	173/37	
Mean disease duration ± SD, years	6.11±4.13	0–23
H&Y stage, n (%)		
Stage 1	47 (22.4)	
Stage 2	98 (46.7)	
Stage 3	44 (21.0)	
Stage 4	20 (9.5)	
Stage 5	1 (0.5)	
Disease type at onset, n (%)		
Tremor	102 (48.6)	
Bradykinesia/rigidity	108 (51.4)	
Medication, n (%)		
Levodopa	205 (97.6)	
Dopamine agonist	170 (81)	
BZD	75 (35.7)	
MAOBI	36 (17.1)	
Antidepressant	7 (3.3)	
Antipsychotics	10 (4.8)	
Anticholinergics	59 (28.1)	
Amantadine	97 (46.2)	

Abbreviations: BZD, benzodiazepines; H&Y, Hoehn and Yahr; MAOBI, monoamine oxidase B inhibitor; SD, standard deviation.

Table 2 Descriptive statistics of the NMSQT and PDQ-39 rating scales in 210 Taiwanese patients with Parkinson's disease

	Prevalence, %	Mean score ± SD	Range
NMSQuest (number of items)			
NMSQuest total score (30)	98.57	7.77±4.74	0–24
NMSQT domains			
Digestive (7)	24.97	1.75±1.38	0–6
Urinary (2)	56.19	1.12±0.74	0–2
Sexual dysfunction (2)	23.81	0.48±0.73	0–2
Cardiovascular (2)	24.29	0.49±0.62	0–2
Memory/apathy (3)	30.48	0.91±1.06	0–3
Hallucination/delusion (2)	9.76	0.20±0.48	0–2
Depression/anxiety (2)	27.86	0.56±0.81	0–2
Sleep disorders (5)	30.00	1.50±1.34	0–5
Miscellany (5)	15.43	0.77±0.97	0–5
PDQ-39			
PDQ-39 total scores		25.11±24.30	0–125
PDQ-39 summary index		16.13±15.61	0–119

Abbreviations: NMSQT, nonmotor symptoms questionnaire total score; PDQ-39, 39-item Parkinson's Disease Questionnaire; SD, standard deviation; NMSQuest, nonmotor symptoms questionnaire.

Table 3 Correlations of scores of NMSQuest, Hoehn and Yahr stage, and PDQSI

	r_s	*P*-value
Hoehn and Yahr stage	0.503	<0.001
NMSQT	0.667	<0.001
Digestive	0.336	<0.001
Urinary	0.172	0.013
Sexual dysfunction	0.253	0.006
Cardiovascular	0.403	<0.001
Memory/apathy	0.411	<0.001
Hallucination/delusion	0.371	<0.001
Depression/anxiety	0.607	<0.001
Sleep disorders	0.461	<0.001
Miscellany	0.376	<0.001

Abbreviations: NMSQT, nonmotor symptoms questionnaire total score; NMSQuest, nonmotor symptoms questionnaire; r_s, Spearman's rank correlation coefficient; PDQSI, 39-item Parkinson's Disease Questionnaire summary index.

vs 47%, average score: 1.1 vs 0.75; prevalence of depression/anxiety, female vs male: 42% vs 29%, average score: 0.69 vs 0.44). Males had higher a score in sexual symptoms (prevalence of sexual dysfunction, female vs male: 26% vs 41%, average score: 0.34 vs 0.6). The PDQSI, NMSQT, and almost all NMS subdomains were correlated positively with disease duration, H&Y stage, and levodopa dosage. However, dopamine agonist dosage did not correlate significantly with the PDQSI, NMSQT, or almost all subdomains.

The regression model for the NMSQT indicated that duration of disease and H&Y stage were independent variables (Table 4). The regression model for the PDQSI revealed that independent variables included NMSQT, H&Y stage, age at onset, and sex (Table 4).

Discussion

This was the first study, to our knowledge, to use NMSQuest to evaluate NMS in Taiwanese PD patients. In our study of 210 PD patients, we observed a high prevalence rate of NMS (98.57%). Among nine subdomains, the most prevalent domains were urinary complaints, followed by memory/apathy and depression/anxiety. NMSQT and all subdomains were correlated with the PDQSI. Among those subdomains, depression/anxiety had the strongest correlation coefficient with the HRQoL of PD patients. The regression model indicated that disease duration and severity were major predictors of NMS. Concomitant use of anti-PD medication, including dopamine agonist, was not correlated with the occurrence of NMS or HRQoL of patients with PD.

The general prevalence of NMS in our study was close to that of previous studies in other countries (Table S3).[10,13,28–38] This indicates that NMS are very frequent and universal concerns in PD patients.[6] For each item in NMSQuest, we compared our study with the studies of Chaudhuri et al,[10] Martinez-Martin et al,[28] and Gan et al.[29] The results showed that there were no significant differences in most NMS rates between studies (Table S1). The three most common symptoms in our study were nocturia (62.85%), constipation (50.95%), and urgency (49.52%), and the least common symptom was bowel incontinence (2.86%). This result was the same as Chaudhuri[10] and Martinez-Martin's studies[28] in Europe and USA. In contrast, studies in the People's Republic of China[29–32] revealed that the most common symptom was easily forgetting (prevalence: 56.1%–68.56%) (Table S3). This suggests that factors other than race, such as age, disease duration, treatment strategy, education, and economical status, may be more influential on NMS. Further study for comparison among groups is needed. Previous studies have suggested that Asian PD patients may have higher rates of constipation or gastrointestinal problems.[12,13] However, our study and one recent large-scale study from the People's Republic of China[30] showed that constipation rates were not higher than Western groups (Table S3). Ethnic effect on NMS is still controversial.

Although urinary symptoms were the most common in patients, the correlation between urinary symptoms and

Table 4 Multiple linear regression analysis for NMSQT and PDQSI

	Standardized beta	Standard error	95% CI	*P*-value
Regression model of the NMSQT (Adjusted R^2=0.574)				
H&Y	0.241	0.390	0.49–2.03	0.001
Duration (years)	0.208	0.086	0.07–0.41	0.006
Regression model of the PDQSI (Adjusted R^2=0.613)				
H&Y	0.402	0.793	5.35–8.48	<0.001
NMSQT	0.509	0.153	1.38–1.98	<0.001
Age at onset	–0.113	1.776	–8.13 to –1.126	0.01
Sex	–0.175	1.349	–8.11 to –2.78	<0.001

Abbreviations: CI, confidence interval; H&Y, Hoehn and Yahr stage; NMSQT, nonmotor symptoms questionnaire total score; PDQSI, 39-item Parkinson's Disease Questionnaire summary index.

HRQoL was lowest (r_s=0.176). This may be due to the fact that urinary symptoms rarely induce motor disturbance and psychosocial problems, which are mainly evaluated in PDQ-39. Measurement bias should be carefully considered when evaluating the impact of urinary symptoms on patients' life quality. Neuropsychological symptoms exerted the greatest influence over our patients' quality of life; among those, depression/apathy correlated most strongly with PDQSI (r_s=0.607). This finding is consistent with previous studies indicating that depression has the greatest impact on PD patients.[8,12,26,28,39] In our study, 30% of patients self-reported having depressed mood, which was compatible with the newest meta-analysis on the prevalence of depression among individuals with a PD diagnosis (36.6%).[40] Depression is two- to threefold more prevalent among PD patients compared to healthy people, and can precede the diagnosis of PD by 4–6 years.[41] This evidence suggests an underlying neurodegenerative process for depression in PD patients. Braak et al's pathology study demonstrated that the degeneration of PD is not limited to the substantia nigra; it also affects the locus coeruleus and raphe nucleus before the beginning of PD motor symptoms.[42] This finding indicates that noradrenaline and serotonin were also involved in the pathology of depression in PD. Positron emission tomography has provided evidence of decreasing dopamine and noradrenaline transporter levels in the locus coeruleus and several regions of limbic system.[43] ^{18}F-fluorodeoxyglucose positron emission tomography has shown decreasing availability of the serotonergic 1A receptor in the limbic and orbitofrontal regions.[44] Several studies that employed resting-state functional magnetic resonance imaging have revealed reduced functional connectivity in the prefrontal–limbic network in PD patients with depression.[45–47]

Pramipexole was found to improve depression in 12 weeks in 323 depressive PD patients.[15] In that study, the Beck Depression Inventory score decreased by 5.9 points in the pramipexole group, compared with 4.0 points in the placebo group. In another study that involved only 44 patients, the Hamilton Anxiety Scale and the Montgomery–Asberg Depression Rating Scale also dropped in PD patients using ropinirole.[48] However, in the present study, we did not find a significant correlation between calculated dopamine agonist dosage and NMSQT (including all subdomains) (Table S2). In addition, we compared NMSQT, score of depression/anxiety subdomain, and PDQSI between the patients with and without using dopamine agonists. None of those showed significant difference (Mann–Whitney test; NMSQT: *P*=0.766; depression/anxiety: *P*=0.111; PDQSI: *P*=0.406). The negative results indicate that dopamine agonists did not eliminate depression and might not improve patients' life quality. However, only a yes/no question can be answered for each symptom in NMSQuest. Dopamine agonists cannot completely eliminate depressive symptoms but they may partially relieve the depression symptoms. The Non-Motor Symptoms Scale,[49] another assessment tool which is able to evaluate the severity of each symptom, should be applied for further evaluation of dopamine agonists' antidepression effects.

Our regression model demonstrates that only disease severity and duration are independent variables for NMSQT. In contrast to Martinez-Martin et al's study,[28] our regression model does not reveal age of onset as an independent predictor. In our correlation study, patients with young-onset PD (YOPD) surprisingly had higher NMSQT and PDQSI (ie, worse HRQoL), possibly because our YOPD group featured longer disease duration (YOPD vs late-onset PD [LOPD]: 7.9 years vs 5.8 years). The other regression model for PDQSI indicates that NMSQT, H&Y stage, age at onset, and sex are independent values, in which NMSQ plays the most important role. This result is quite similar to previous studies' findings that NMS are the major predictor for patients' quality of life, suggesting that NMS cause more disability than motor symptoms.[7–9] In our regression model for PDQSI, sex and age at onset were also independent values, although they have minor roles. Looking at our data (Figure 1), YOPD and female patients had similar NMSQT (YOPD vs LOPD: 9.41 vs 7.48, *P*=0.238; female vs male: 7.95 vs 7.61, *P*=0.784). However, they had slightly higher PDQSI (YOPD vs LOPD: 22.3 vs 15.02, *P*=0.008; female vs male: 18.77 vs 13.74, *P*=0.202). This may indicate that, although they had similar number of NMS, they still subjectively felt that they had a poor life quality. In Dubayova et al's study,[50] females also had slightly higher PDQ-39 scores although there was no significant difference. In female patients, age and neuroticism were more significantly correlated with PDQ-39 score than they were in males. In Nutt et al's study,[51] multiple linear regression showed age and sex were independent variables contributing to PDQSI.

There are several limitations in the current study. Although our sample number is relatively small, it is comparable to other studies (Table S3). In addition, another limitation of our study is that few YOPD patients were involved (n=32), which may partly explain why age at onset did not play an important role in our study. Although YOPD predicts higher NMSQT in Martinez-Martin et al's study,[28] another study indicated that patients with LOPD have more gastrointestinal and urinary symptoms, dementia, and psychosis, which influence patients'

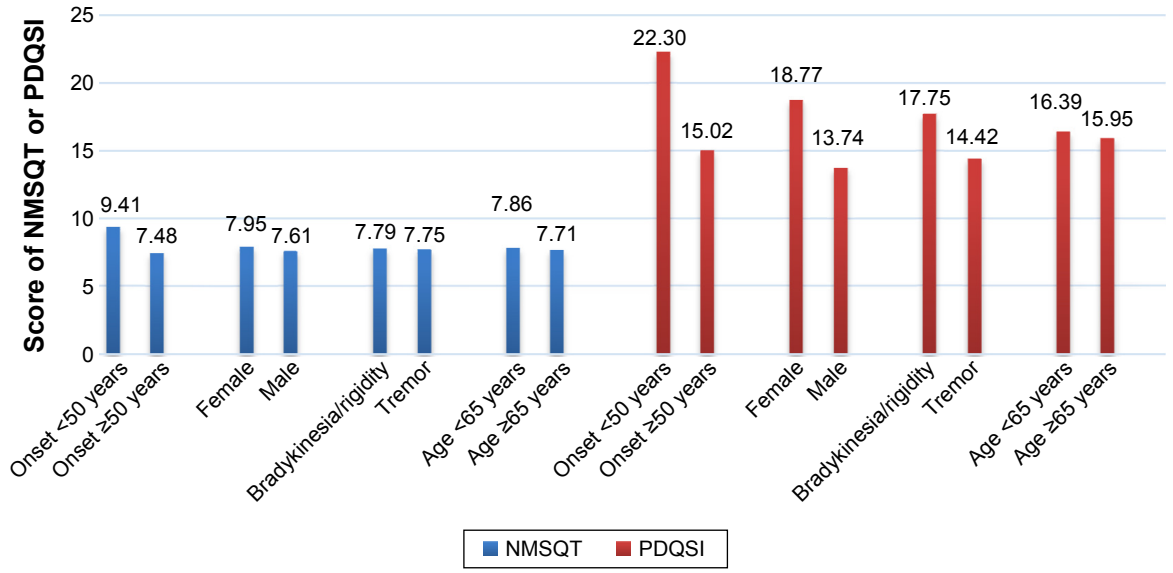

Figure 1 Comparison of NMSQT and PDQSI between different groups of onset age, sex, disease at onset, and current age.
Abbreviations: NMSQT, nonmotor symptoms questionnaire total score; PDQSI, 39-item Parkinson's Disease Questionnaire summary index.

quality of life more.[52] To better understand the differences in NMS between YOPD and LOPD patients, more YOPD patients should be included in future studies.

Conclusion

Our findings indicate that NMS are common in PD patients and determine the life quality of PD patients. NMS severity is positively correlated with disease severity and duration. Among NMS subdomains, depression and other neuropsychological symptoms most influence patients' quality of life. However, concomitant anti-PD medication use did not affect the occurrence of NMS and quality of life. Further study for treatment of NMS is mandatory to improve the life quality of patients.

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Disclosure

The authors report no financial disclosures or any conflicts of interest in this work.

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Supplementary materials

Table S1 Comparison of the prevalence of each nonmotor symptom with other studies

	Current study (%)	Martinez-Martin et al[1] (%)	*P*-value (χ^2 test)	Chaudhuri et al[2] (%)	*P*-value (χ^2 test)	Gan et al[3] (%)	*P*-value (χ^2 test)
Dribbling	27.14	41.52	0.026*	35	0.14	17.70	0.128
Taste/smelling	16.19	28.95	0.028*	26	0.054	22.20	0.279
Swallowing	29.52	28.38	0.755	23.6	0.433	23.40	0.28
Vomiting	12.38	14.31	0.674	8.1	0.397	8.20	0.358
Constipation	50.95	52.48	0.887	46.7	0.831	64.60	0.036*
Bowel incontinence	2.86	8.21	0.121	4.9	0.435	0.60	0.312
Bowel emptying incomplete	35.71	29.90	0.367	27.6	0.308	15.20	0.001*
Urgency	49.52	55.81	0.395	61	0.022*	31.00	0.006*
Nocturia	62.86	61.90	0.884	66.7	0.116	61.40	0.84
Pains	22.86	28.76	0.333	27.6	0.225	27.20	0.487
Weight	16.67	18.29	0.852	22	0.25	22.20	0.353
Memory	38.10	44.85	0.315	43.9	0.169	65.80	<0.001*
Loss of interest	26.19	34.67	0.167	29.3	0.425	48.70	<0.001*
Hallucinations	13.33	22.52	0.066	19.5	0.143	11.40	0.663
Concentrating	27.14	45.71	0.005*	37.4	0.03*	38.00	0.097
Sadness/blues	30.00	50.10	0.004*	44.7	0.018*	36.70	0.228
Anxiety	25.71	45.33	0.005*	39.9	0.011*	30.40	0.471
Sex drive	24.29	34.17	0.119	29.3	0.073	16.50	0.296
Sex difficulty	23.33	32.43	0.154	24.4	0.166	12.00	0.064
Dizzy	34.76	37.14	0.768	39.8	0.308	16.50	0.004*
Falling	13.81	28.00	0.015*	30.9	0.002*	25.90	0.031*
Daytime sleepiness	12.86	31.11	0.002*	28.4	0.005*	38.60	<0.001*
Insomnia	37.14	45.71	0.196	40.6	0.414	39.20	0.728
Vivid dreams	39.52	33.90	0.38	30.9	0.31	43.70	0.486
RBD	35.24	35.69	0.883	32.5	0.927	27.80	0.332
Restless legs	25.24	41.71	0.011*	37.4	0.024*	20.30	0.419
Swelling	14.29	31.30	0.004*	30.9	0.001*	8.20	0.183
Sweating	10.48	29.90	<0.001*	25.2	0.002*	28.50	0.001*
Diplopia	12.86	20.00	0.182	21.9	0.065	5.70	0.096
Delusions	6.19	11.07	0.205	12.3	0.11	12.00	0.132

Notes: *Indicates statistical significance. Adapted with permission from 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. *Movement Disorders*. 2007;22(11):1623–1629. Published by John Wiley and Sons. Copyright © 2007 Movement Disorder Society.[1] And adapted with permission from 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. *Movement Disorders*. 2006;21(7):916–923. Published by John Wiley and Sons. Copyright © 2006 Movement Disorder Society.[2] And adapted from *Journal of Clinical Neuroscience*. 2014;21(5). Gan J, Zhou M, Chen W, Liu Z. Non-motor symptoms in Chinese Parkinson's disease patients. 751–754. With permission from Elsevier. Copyright © 2013 Elsevier Ltd. All rights reserved.[3]
Abbreviation: RBD, rapid eye movement sleep behavior disorder.

Table S2 Correlations of clinical factors with NMSQT, subdomains, and PDQSI

	NMSQT	Digestive	U	M/A	H/D	Dep/An	Sexual#	CV	Sleep	Mis	Auto	NP	PDQSI
Sex (r_s)	–0.019	0.054	0.072	–0.144	–0.033	–0.15	0.172	–0.071	0.057	–0.106	0.078	–0.155	–0.088
(*P*-value)	0.785	0.428	0.301	0.037*	0.633	0.03*	0.013*	0.303	0.411	0.126	0.263	0.025*	0.202
Age	–0.041	0.026	0.122	–0.05	0.084	0.006	–0.099	–0.071	–0.082	–0.042	–0.007	0.016	0.039
	0.552	0.712	0.078	0.493	0.224	0.926	0.151	0.308	0.237	0.544	0.918	0.887	0.077
Disease type	–0.012	0.033	0.008	–0.085	–0.125	–0.017	0.056	0.013	0.028	–0.004	0.002	–0.095	0.108
at onset	0.858	0.631	0.903	0.221	0.07	0.805	0.418	0.848	0.69	0.957	0.975	0.17	0.12
Age at onset	–0.163	–0.075	0.096	–0.121	0.012	–0.116	–0.132	–0.174	–0.137	–0.13	–0.085	–0.099	–0.111
	0.018*	0.278	0.165	0.081	0.866	0.093	0.056	0.012*	0.047*	0.06	0.222	0.152	0.108
Duration	0.322	0.251	0.053	0.241	0.202	0.257	0.164	0.288	0.144	0.2	0.225	0.288	0.353
	<0.001*	<0.001*	0.449	0.002*	0.003*	<0.001*	0.017*	<0.001*	0.038*	0.004*	0.001*	<0.001*	<0.001*
H&Y stage	0.324	0.265	0.191	0.17	0.258	0.253	0.071	0.207	0.143	0.2	0.186	0.295	0.503
	<0.001*	<0.001*	0.005*	0.013*	<0.001*	<0.001*	0.305	0.003	0.039*	0.004*	0.007*	<0.001*	<0.001*
LD	0.296	0.217	0.125	0.146	0.221	0.173	0.086	0.204	0.193	0.167	0.17	0.236	0.408
	<0.001*	0.002*	0.070	0.034*	0.001*	0.012*	0.212	0.003*	0.005*	0.015*	0.014*	0.001*	<0.001*
DA dose	0.082	0.099	–0.027	–0.046	0.024	–0.086	0.105	0.058	0.085	0.15	0.038	–0.62	0.078
	0.234	0.152	0.702	0.507	0.726	0.215	0.128	0.404	0.22	0.03*	0.581	0.371	0.263

Notes: Auto contains urinary, sexual, and CV subdomains. NP contains M/A, H/D, and Dep/An subdomains. *Indicates significance. #Sexual dysfunction.
Abbreviations: Auto, autonomic dysfunction; CV, cardiovascular problems; DA dose, dopamine agonist equivalence dose; Dep/An, depression/anxiety; H&Y, Hoehn and Yahr stage; H/D, hallucination/delusion; LD, levodopa dose; M/A, memory/apathy; Mis, miscellany; NMSQT, nonmotor symptoms questionnaire total score; NP, neuropsychological problems; PDQSI, 39-item Parkinson's Disease Questionnaire summary index; r_s, Spearman's rank correlation coefficient; U, urinary.

Table S3 NMS prevalence and rate of constipation and memory symptoms in other studies

Study	Location	Subject number	Age (mean ± standard deviation), years	Prevalence (%)	Constipation rate (%)	Memory rate (%)	Number of NMS per patient
Current study	Taiwan	210	66.1±9.86	98.6	50.95	38.1	7.77
Martinez-Martin et al[1]	International	525 (Japan =10, USA =42, UK =209, Italy =132, Germany =81, Israel =51)	67.66±10.5	98.4	52.48	44.85	10.25
Chaudhuri et al[2]	International	123 (UK, USA, Italy, and Germany)	68.1±10.3	97.6	46.7	43.9	9.48
Gan et al[3]	Shanghai, People's Republic of China	155	71.73±8.82	98.7	64.56	65.8	8.29
Wu et al[4]	Sichuan, People's Republic of China	301	58.4±10.9	Not given	29.6	58.1	8.0
Zhang et al[5]	Nanjing, People's Republic of China	493	65.06±10.76	98.88	57.2	68.56	10.45
Li et al[6]	Beijing, People's Republic of China	1,225	61.48±10.47	97.6	55.3	56.1	8.72
Cheon et al[7]	Korea	74	64.9±8.6	98.6	65.8	60.8	5.2
Tsuboi et al[8]	Japan	53	66.1±11.2	Not given	78.4	64.7	Not given
Rukmini Mridula et al[9]	India	53	56.64±8.22	100	71	25	8.4
Cosentino et al[10]	Peru	300	64.01±10.25	99.7	55.7	60.7	12.41
Khedr et al[11]	Egypt	112	61±12.7	96.4	51.79	30.36	9.52
Bostantjopoulou et al[12]	Greece	164	59.5±9.3	97	45.7	31.1	6.76
Crosiers et al[13]	Belgian	215	67.1±10.4	Not given	38.6	37.9	9.02

Abbreviation: NMS, nonmotor symptoms.

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