Non-Motor Symptoms in Treated and Untreated Chinese Patients with Early Parkinson's Disease

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Non-motor symptoms (NMS) are important preclinical features of Parkinson's disease (PD) and have become the leading cause of poor quality of life with disease progression. There are little data on how antiparkinsonian medications influence the NMS in PD at early stage. In this study, we explored the distribution of NMS in treated and untreated PD and investigated the association between NMS and antiparkinsonian medications in Chinese patients with early PD. Subjects were enrolled from a Chinese PD patient cohort based on 2 clinical trials. Face-to-face interviews and evaluations were performed for clinical information. NMS were compared in patients with or without antiparkinsonian treatment, and between subgroups of dopaminergic medications. Eight hundred and sixteen PD patients were enrolled in this study, of whom 428 were newly diagnosed PD. Only 5 in 646 patients who completed all these NMS measurements (0.6%) were free of NMS. PD patients with antiparkinsonian medications had a significantly higher frequency of poor sleep (p = 0.001), depression (p = 0.0001) and constipation (p = 0.0001) after adjusted gender, onset age, duration, and Hoehn & Yahr stage. Moreover, patients treated by levodopa plus dopamine agonist had a higher percentage of bad sleepers (adjusted p = 0.040), and correlation analysis revealed that Levodopa Equivalent Dose (LED) was associated with constipation (coefficient 0.146, p = 0.005). These findings suggest that although NMS exist in the prodromal stage of PD, antiparkinsonian treatment is associated with increased frequency of some NMS, which may challenge the management for PD.

Introduction

Parkinson's disease (PD) is characterized by motor symptoms including resting tremor, rigidity, bradykinesia and postural instability. However, less is known about non-motor symptoms (NMS), which are very common and often go under-recognized and unreported by both patients and clinicians. NMS are comprised of a large range of symptoms including neuropsychiatric, autonomic, sleep, sensory, gastrointestinal, and other symptoms (Chaudhuri and Schapira 2009). They are increasingly prevalent over the course of the illness and have become important determinants of patients' quality of life with disease progression in PD (Duncan et al. 2013). NMS could occur at any stage of PD, even preceding the onset of motor symptoms, which is correlated with the Braak stages of Lewy pathology in PD (Braak et al. 2003; Wolters and Braak 2006).

Although antiparkinsonian medication is important for improving the motor performance of PD, its effect on NMS remains a matter of debate. Recently, a study with positron emission tomography highlighted the dopaminergic dysfunction in the hypothalamus that might contribute to the development of several NMS in PD, such as sleep disturbances and autonomic dysfunction, which provided the *in vivo* evidence of potential benefits from dopaminergic treatment for NMS management (Politis et al. 2008). Several NMS might be responsive to dopaminergic treatments, such as depression and constipation, whereas other NMS might be exacerbated with antiparkinsonian drugs, such as hallucinations and excessive daytime sleepiness (Chaudhuri and Schapira 2009). However, all the data were from clinical trials with a specific drug, and little is known about dopaminergic treatments on NMS in epidemiological studies. Here, we present a cross-sectional study to describe the dis-

tributions of NMS in Chinese PD patients with or without antiparkinsonian treatment and to investigate the effects of medications on NMS.

Materials and Methods

Subjects

Subjects were recruited from two trial-based multicenter PD cohorts, established by the Chinese Parkinson Study Group (CPSG) from 2005-2008. CPSG consists of 42 clinical centers and is coordinated by Xuanwu Hospital of Capital Medical University in Beijing, China. All the clinical centers belong to tertiary hospitals and have at least one movement disorders specialist. Individuals with PD were recruited from their movement disorders clinic. PD patients were diagnosed using the UK Brain Bank criteria (Litvan et al. 2003). Primary medical records were reviewed by specialists to confirm the diagnosis. Atypical and secondary parkinsonism were excluded. Patients with cognitive impairment (Mini-Mental Status Examination, MMSE $\leq$ 24) were also excluded due to the inability to complete the scales. Cases with onset age $\geq$ 30 years, Hoehn & Yahr (H & Y) stage $\leq$ 3.0, and with completed baseline information were enrolled in our study.

Data collection

Demographic information and clinical characteristics were collected by face-to-face interviews. Motor symptoms of PD were evaluated with the Unified Parkinson Disease Rating Scale (UPDRS). NMS of PD were evaluated using specific questionnaires. Depression was measured by the full-length, 20-item version of the Center for Epidemiological Studies Depression Scales (CES-D). The Pittsburg Sleep Quality Index (PSQI) was used to evaluate the quality of sleep. Subscales of memory, orientation, and identification in the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) were used to measure cognition status. Constipation was assessed according to item 21 on the Non-Motor Symptoms Scale (NMSS), by which constipation was defined as one bowel movement every other day or less. Fatigue was determined by a yes-or-no question.

Medication

Detailed information of antiparkinsonian medications in their lives was collected. Patients who had/were having antiparkinsonian medications were defined as 'treated' ones. Prescription details of Levodopa, Levodopa-Carbidopa controlled-release (Sinemet), Piribedil, Entacapone, Trihexyphenidyl (Artane), Selegiline and Amantadine were recorded.

Ethics

This study was approved by the Ethics Committee of XuanWu Hospital of Capital Medical University. The use of human subjects was carried out with adequate understanding and written consent of the subjects or their legal guardians.

Statistical Analysis

SPSS11.5 was used for database and analyses. Data for each NMS was only analyzed in the available cases. Subscales of UPDRS III were used to measure motor symptoms. Depression was defined by a CES-D score $\geq$ 16. A PSQI score $\leq$ 5 was considered to be good sleep quality. Cognition status was measured by the ADAS-Cog total score and also by the subscales of memory, orientation, and identification. Differences of NMS distributions were compared between

untreated and treated patients, and also between different medication subgroups. Levodopa Equivalent Dose (LED) was calculated as follows: (regular levodopa dose $\times$ 1) + (levodopa controlled-release dose $\times$ 0.75) + (Piribedil dose $\times$ 1) + ((regular levodopa dose $\times$ 1+levodopa controlled-release dose $\times$ 0.75) $\times$ 0.33) if taking entacapone (Tomlinson et al. 2010). The chi-square test was performed to analyze the differences in discrete data, and analysis of variance (ANOVA) test was used for continuous data. Logistic regression model and linear model were used to control the effects of gender, onset age, disease duration, and H & Y stage. Pearson correlation coefficient and regression models were used to analyze the associations for LED and NMS. $P < 0.05$ was considered to be statistically significant.

Results

Demographic and clinical characteristics

A total of 816 subjects were enrolled in our study, of which 428 cases were non-treated PD, and 388 were treated with antiparkinsonian medications. All the PD patients who had received antiparkinsonian therapy had dopaminergic drugs. Patients under treatment were much older than those untreated (mean age 64.29 $\pm$ 9.57 vs. 60.62 $\pm$ 10.77 years, *p* = 0.0001), while there was no difference in gender distribution in two groups (*p* = 0.222). The basic clinical features of PD are compared in Table 1. Treated patients had a longer disease duration (41.80 $\pm$ 22.92 vs. 22.97 $\pm$ 21.00 months) and more severe disease stages (H & Y stage 1.98 $\pm$ 0.66 vs. 1.61 $\pm$ 0.57) and motor symptoms (UPDRS-III score 23.47 $\pm$ 11.47 vs. 16.78 $\pm$ 9.59) than untreated ones. The average LED was 439.09 $\pm$ 213.10 mg/day in treated patients, and 20.9% (81/388), 14.7% (57/388), 34.0% (132/388) of the treated patients were also taking Trihexyphenidyl, Selegiline and Amantadine, respectively.

NMS distribution in treated and untreated PD

PSQI, CES-D, constipation, fatigue, and ADAS-Cog measurements were available in 668, 814, 682, 659 and 813 cases, respectively. A total of 646 patients completed all these NMS measurements, and had a longer disease duration than those who did not complete all the measurements (33.66 $\pm$ 24.82 vs. 25.31 $\pm$ 18.37 months, *p* = 0.0001) but had similar age at evaluation, age at onset, H & Y stage, and gender distribution. In those who had all the NMS data, only five patients (0.6%) reported no NMS, while 117 patients (18.1%) had all the five symptoms. Among all the cases, 48 (7.4%), 111 (17.2%), 174 (26.9%), and 191 (29.6%) cases had one, two, three and four NMS, respectively.

The distribution of NMS is listed in Table 2. Sleep quality assessed by PSQI suggested that 68.6% of the patients were bad sleepers. The percentage was even higher in patients treated with antiparkinsonian medications (75.5%) as compared to those untreated (59.2%) (*p* = 0.0001). Totally 42.6% PD patients were suffering from depression. 54.4% treated patients presented depression, which were significantly more frequent than observed in

Table 1. Demographic and clinical characteristics of the enrolled PD patients.

Variables		Total	Untreated PD	Treated PD	P value
Gender	Male	508 (62.3)	258 (60.3)	250 (64.4)	0.222
	Female	308 (37.7)	170 (39.7)	138 (35.6)	
Age (years)		62.36 ± 10.37	60.62 ± 10.77	64.29 ± 9.57	0.0001
Onset age (years)		59.78 ± 10.19	58.75 ± 10.55	60.92 ± 9.67	0.002
Duration (months)		31.92 ± 23.86	22.97 ± 21.00	41.80 ± 22.92	0.0001
H & Y		1.78 ± 0.64	1.61 ± 0.57	1.98 ± 0.66	0.0001
UPDRS total score		30.05 ± 15.15	25.11 ± 12.98	35.51 ± 15.51	0.0001
UPDRSIII subscore		19.96 ± 11.04	16.78 ± 9.59	23.47 ± 11.47	0.0001
LED ($N = 376/388$, mg/day)			NA	439.09 ± 213.10	
Trihexyphenidyl ($N = 81/388$, mg/day)			NA	4.10 ± 2.03	
Selegiline ($N = 57/388$, mg/day)			NA	5.96 ± 2.53	
Amantadine ($N = 132/388$, mg/day)			NA	210.23 ± 51.59	

PD, Parkinson's disease; H & Y, Hoehn & Yahr stage; UPDRS, Unified Parkinson Disease Rating Scale; LED, Levodopa Equivalent Dose; NA, not applicable.

Continuous variables were presented as mean ± s.d.; discrete variables were presented as numbers (%).

Table 2. Associations between NMS and antiparkinsonian treatment.

Variables		Total	Untreated PD	Treated PD	P value	Adjusted P value*
Sleep quality	Good sleeper	210 (31.4)	116 (40.8)	94 (24.5)	0.0001	0.001
	Bad sleeper	458 (68.6)	168 (59.2)	290 (75.5)		
Depression	CES-D score < 16	467 (57.4)	291 (68.0)	176 (45.6)	0.0001	0.0001
	CES-D score ≥ 16	347 (42.6)	137 (32.0)	210 (54.4)		
Constipation	No	335 (49.1)	194 (65.8)	141 (36.4)	0.0001	0.0001
	Yes	347 (50.9)	101 (34.2)	246 (63.6)		
Fatigue	No	208 (31.6)	100 (34.1)	108 (29.5)	0.205	0.871
	Yes	451 (68.4)	193 (65.9)	258 (70.5)		
ADAS-Cog	($N = 813$)	5.54 ± 3.30	5.43 ± 3.64	5.66 ± 2.88	0.320	0.195
Memory		3.52 ± 1.66	3.35 ± 1.71	3.72 ± 1.59	0.002	0.148
Orientation		0.14 ± 0.59	0.16 ± 0.60	0.11 ± 0.57	0.205	0.001
Identification		1.60 ± 1.85	1.63 ± 2.10	1.56 ± 1.52	0.548	0.047

PD, Parkinson's disease; NMS, non-motor symptoms; CES-D, Center for Epidemiological Studies Depression Scales; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive.

Continuous variables were presented as mean ± s.d.; discrete variables were presented as numbers (%).

*Adjusted by gender, onset age, disease duration, and Hoehn & Yahr stage.

non-treated patients (32.0%, $p = 0.0001$). The overall frequency of constipation was 50.9% in PD patients, among whom 63.6% were treated. Fatigue was reported in 68.4% patients, which was distributed in the treated and non-treated groups with a similar frequency (70.5% vs. 65.9%, $p = 0.205$). The average subscore was 0.14 for orientation and 1.60 for identification. The average subscore for memory was 3.52, which was significantly higher in the treated group than in the untreated group ($p = 0.002$). In the logistic regression analysis adjusted for gender, onset age, duration and H & Y stage, antiparkinsonian treatment was associated with bad sleep quality ($p = 0.001$), depression ($p = 0.0001$), constipation ($p = 0.0001$), orientation ($p = 0.001$) and identification ($p = 0.047$), while memory, which

appeared to be associated with medication, was not significantly different in the two groups after the regression models were performed (memory score 3.35 ± 1.71 vs. 3.72 ± 1.59, $p = 0.148$).

NMS in PD patients on dopaminergic treatments

To confirm the association between treatment and NMS, we further compared the occurrence of NMS between specific dopaminergic medication groups. Eight patients did not take medications at time of evaluation, and four more patients did not take the medications included in LED equation; thus, these patients were excluded in the analysis of LED and NMS. For the remained 376 treated patients, 305 (81.1%) patients were on levodopa therapy, 3

Table 3. Differences of disease characteristics and NMS between the PD patients taken levodopa and levodopa plus dopamine agonist.

Variables		Levodopa (n = 305)	Levodopa+Dopamine Agonist (n = 68)	P value	Adjusted P value*
Gender	Male	191 (62.6)	50 (73.5)	0.089	
	Female	114 (37.4)	18 (26.5)		
Age (years)		64.65 ± 9.37	62.31 ± 10.58	0.070	
Onset age (years)		61.35 ± 9.53	58.69 ± 10.31	0.041	
Duration (months)		41.48 ± 23.58	43.16 ± 19.91	0.585	
H & Y		1.98 ± 0.67	1.96 ± 0.59	0.833	
UPDRS total score		35.68 ± 15.62	34.43 ± 14.87	0.548	
UPDRSIII subscore		23.50 ± 11.73	23.20 ± 10.29	0.845	
LED (mg/day)		429.08 ± 220.82	499.69 ± 151.57	0.013	
Trihexyphenidyl		70 (23.0)	9 (13.2)	0.076	
Selegiline		48 (15.7)	8 (11.8)	0.407	
Amantadine		108 (35.4)	19 (27.9)	0.240	
Sleep quality	Good sleeper	80 (26.5)	12 (17.6)	0.127	0.040
	Bad sleeper	222 (73.5)	56 (82.4)		
Depression	CES-D score < 16	129 (42.6)	37 (54.4)	0.076	0.120
	CES-D score ≥ 16	174 (57.4)	31 (45.6)		
Constipation	No	112 (36.8)	23 (33.8)	0.482	0.409
	Yes	192 (63.2)	45 (66.2)		
Fatigue	No	76 (26.4)	26 (40.6)	0.023	0.060
	Yes	212 (73.6)	38 (59.4)		
ADAS-Cog score	(N = 373)	5.60 ± 2.89	6.01 ± 3.00	0.295	0.142
Memory		3.71 ± 1.61	3.80 ± 1.49	0.688	0.447
Orientation		0.08 ± 0.37	0.25 ± 1.10	0.031	0.066
Identification		1.55 ± 1.53	1.63 ± 1.56	0.698	0.407

H & Y, Hoehn & Yahr stage; UPDRS, Unified Parkinson Disease Rating Scale; LED, Levodopa Equivalent Dose; CES-D, Center for Epidemiological Studies Depression Scales; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive.

Continuous variables were presented as mean ± s.d.; discrete variables were presented as numbers (%).

*Adjusted by gender, onset age, disease duration, and Hoehn & Yahr stage.

(0.8%) patients on dopamine agonist therapy, 68 (18.1%) patients on levodopa plus dopamine agonist therapy. Therefore, we compared NMS distribution in levodopa and levodopa plus agonists treated groups (Table 3). Patients taking levodopa plus agonists had a younger onset age (58.69 ± 10.31 vs. 61.35 ± 9.53 years, $p = 0.041$), and higher LED (499.69 ± 151.57 vs. 429.08 ± 220.82 mg/day, $p = 0.013$). While other disease characteristics did not differ significantly between the two groups. Percentages of patients using Trihexyphenidyl, Selegiline and Amantadine were not statistically different between the two groups, though the percentages in levodopa group were slightly higher (23.0% vs. 13.2% for Trihexyphenidyl; 15.7% vs. 11.85% for Selegiline; 35.4% vs. 27.9% for Amantadine). Patients with levodopa plus agonists treatments were more likely bad sleepers (82.4% vs. 73.5%, $p = 0.127$), less likely to have fatigue (59.4% vs. 73.6%, $p = 0.023$) and have lower score for orientation (0.25 ± 1.10 vs. 0.08 ± 0.37, $p = 0.031$). But constipation was not different between the groups (66.2% vs. 63.2%, $p = 0.482$). However, when adjusted by potential confounding factors, only sleep qual-

ity remained statistically significant (adjusted $p = 0.040$).

We further analyzed the association between LED and NMS in treated patients (Table 4). It appeared that LED was associated only with constipation (coefficient 0.146, $p = 0.005$), while sleep quality, depression and fatigue were significantly associated with each other ($p < 0.01$). In addition, constipation was also associated with cognition especially for memory ($p < 0.01$). Furthermore, when we used regression models adjusting potential confounding factors and also LED for the associations among NMS, the associations among sleep, depression and fatigue remained significant ($p < 0.02$) (Table 5).

Discussion

Our study strengthens the notion that NMS are frequent and affect most of the PD patients. Only 0.6% subjects were free of NMS, and 18.1% patients had all five NMS we investigated. More than half of the patients experienced bad sleep quality, fatigue, or constipation, and over 40% of the patients suffered from depression. Even in untreated patients, the prevalence of NMS was high. This

Table 4. Pearson correlation coefficient analysis for LED and NMS (only in treated patients).

		LED	Sleep	Depression	Constipation	Fatigue	ADAS-Cog
LED	r	1	0.089	0.033	0.146**	−0.009	0.061
	P value	–	0.086	0.519	0.005	0.870	0.239
	N	376	373	374	375	355	373
Sleep	r	0.089	1	0.232**	0.025	0.185**	−0.086
	P value	0.086	–	0.0001	0.627	0.0001	0.093
	N	373	384	383	384	363	382
Depression	r	0.033	0.232**	1	0.062	0.229**	0.076
	P value	0.519	0.0001	–	0.227	0.0001	0.136
	N	374	383	386	386	365	384
Constipation	r	0.146**	0.025	0.062	1	0.021	0.140**
	P value	0.005	0.627	0.227	–	0.696	0.006
	N	375	384	386	387	366	385
Fatigue	r	−0.009	0.185**	0.229**	0.021	1	−0.003
	P value	0.870	0.0001	0.0001	0.696	–	0.959
	N	355	363	365	366	366	366
ADAS-Cog	r	0.061	−0.086	0.076	0.140**	−0.003	1
	P value	0.239	0.093	0.136	0.006	0.959	–
	N	373	382	384	385	366	385
Memory	r	0.059	−0.079	0.073	0.160**	0.014	0.796**
	P value	0.257	0.121	0.155	0.002	0.794	0.0001
	N	373	382	384	385	366	385
Orientation	r	0.058	−0.030	0.025	0.060	0.041	0.355**
	P value	0.261	0.562	0.627	0.242	0.438	0.0001
	N	373	382	384	385	366	385
Identification	r	0.017	−0.058	0.086	0.099	−0.040	0.798**
	P value	0.740	0.258	0.093	0.052	0.450	0.0001
	N	373	382	384	385	366	385

LED, Levodopa Equivalent Dose; NMS, non-motor symptoms; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive.
r for Pearson correlation coefficient; N for Number of patients who completed corresponding NMS measurement.
**$p < 0.01$.

Table 5. Regression models for associations among NMS (only in treated patients).

		Sleep	Depression	Constipation	Fatigue	ADAS-Cog
Sleep	Wald	–	11.664**	0.414	6.676*	5.985*
	P value	–	0.001	0.520	0.010	0.014
Depression	Wald	10.941**	–	0.062	6.374*	3.411
	P value	0.001	–	0.803	0.012	0.065
Constipation	Wald	0.410	0.098	–	0.020	2.293
	P value	0.522	0.754	–	0.888	0.130
Fatigue	Wald	6.511*	6.692*	0.047	–	0.275
	P value	0.011	0.010	0.828	–	0.600
ADAS-Cog	Beta	−0.126*	0.102	0.080	−0.026	–
	P value	0.019	0.064	0.135	0.635	–

NMS, non-motor symptoms; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive.
Adjusted by gender, onset age, disease duration, Hoehn & Yahr stage, LED.
Wald and *P* value by multiple logistic regression analysis; Beta and *P* value by linear regression analysis.
*$p < 0.05$; **$p < 0.01$.

is consistent with the PRIAMO study (Barone et al. 2009). They evaluated 12 NMS domains in 1,072 PD patients, and found 98.6% patients reported at least one NMS, and the average number of NMS experienced by participants was 7.8. The prevalence of NMS in de novo patients in their study was even higher compared to that in our untreated subjects. Different measurements might be a reason, since they used simple yes/no questions, and we also used complicated scales. The high occurrence of NMS challenges the clinical management. Whether antiparkinsonian treatments are associated with NMS will directly influence the decision of pharmacologic therapies for PD.

Another interesting finding of this study is the apparent association between antiparkinsonian medications and the occurrence of NMS. In general, patients with antiparkinsonian treatments were more likely to be bad sleepers, depressed, and with constipation and cognition impairment compared with non-treated patients. When subgroups of dopaminergic medications were considered, patients taking levodopa plus agonists had worse sleep quality but less fatigue compared to levodopa alone treated. Moreover, constipation was significantly associated with LED but did not differ between patients with and without agonists. These findings partially confirmed previous studies. Barone et al. (2009) found that gastrointestinal, pain, urinary, sleep, skin disorder, and 'miscellaneous' (including olfactory dysfunction, dysgeusia, diplopia, weight change and sexual dysfunction) NMS were more frequent in treated subgroups.

There is still debate on whether dopaminergic medication can contribute to the development or deterioration of NMS such as poor nocturnal sleep, depression, constipation or cognitive impairment alone. Previous animal studies had proposed that higher dose of dopaminergic medication might inhibit sleep through action at post-synaptic D1 and possibly D2 receptors (Monti et al. 1989; Laloux et al. 2008). However, several open-label studies suggested that dopaminergic drugs could improve sleep dysfunction in PD (Eggert et al. 2008; Honig et al. 2009), and the RECOVER trial found that Rotigotine could improve nocturnal sleep disturbances and possibly dopaminergic nonmotor daytime symptoms (such as fatigue and mood) as well (Trenkwalder et al. 2011). To be noted, these agonists were not available in China when the study was carried out. Recent studies in animal models of PD suggested that L-dopa might interfere with norepinephrine (NE) and serotonin (5-HT) function in affect-related brain structures and induce symptoms of depression (Navailles et al. 2010a, b). A double blind randomized placebo-controlled trial also found that acute challenge with pramipexole had a negative effect on mood and fatigue (Drijgers et al. 2012). However, Chaudhuri and Schapira (2009) summarized several clinical trials on the effects of dopaminergic therapy on depression in PD, most of which suggested benefits from dopaminergic medications.

A possible constipating effect of dopaminergic treatment in PD is still debated, with controversial evidence. However, the potentiation of a pre-existing delay in colonic transit by dopamine has been presumed (Sakakibara et al. 2008). Besides, findings of studies on cognitive effect of levodopa and dopamine agonists are heterogeneous, and no clear conclusion can be drawn in relation to the effects of dopaminergic therapy on different cognitive domains. Previous study reported that dopaminergic medication could improve or impair cognitive performance depending on the nature of the task and the basal level of dopamine function in underlying cortico-striatal circuitry (Cools et al. 2001). Although the causality of NMS and dopaminergic therapy is not clear, since most of NMS in PD are likely multi-factorial in etiology, our findings suggest that dopaminergic medication needs to be considered in the management of NMS in the early stage of PD.

The pathology of PD suggested that Lewy bodies exist not only in the midbrain but also in the olfactory tract, anterior olfactory nucleus, and medulla oblongata, even up to the cortex (Braak et al. 2003). Various affected regions would result in different NMS, and it might be possible that several NMS coexist at the same time. Our study suggested when potential covariant were controlled, sleep quality, depression, and fatigue were significantly associated with each other. This phenomenon has been reported in previous studies. In patients with a major depression disorder, fatigue and sleep disturbances were common and had a high prevalence (Baldwin and Papakostas 2006). Our study indicated the coexistence of these three NMS, but coadministration of agonists with L-dopa improves fatigues while worsens sleep quality. In clinical practice, clinicians should pay attention to the other two NMS when one of them is presented and avoid medications, which might induce or aggravate symptoms.

Due to the limitation of the inclusion criteria at the baseline in the clinical trials, we excluded patients with MMSE ≤ 24; therefore, our results only applied to the early PD patients without obvious symptoms of dementia. 20.8% patients involved in this study did not complete all the evaluation forms, which might have caused a selection bias. We compared the demographic and clinical characteristics between patients who completed and did not complete all the evaluation scales. These characteristics were not different in the two groups, besides duration. Another limitation of our study was that the untreated patients had less disease burden compared to the treated patients, which might bias the results. Therefore, we used regression model to control potential influencing factors, which might have minimized the bias. Moreover, when we investigated the association between medication and NMS only in treated patients, there was still evidence that dopaminergic treatment was associated with NMS, no matter in subgroups or in LED. However, this is a cross-sectional study, which only provided evidence of the associations for clinical consideration. Prospective clinical observations would be needed to investigate the causality between NMS and dopaminergic

therapies.

In conclusion, NMS are highly prevalent in our Chinese PD population, either related to antiparkinsonian treatment or coexisting with each other. Well recognition of NMS and their related factors would help in disease diagnosis and management.

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Conflict of Interest

The authors declare no conflict of interest.

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