Effects of Sleep Disorders on the Non-Motor Symptoms of Parkinson Disease

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Study Objectives: To evaluate the impact of sleep disorders on non-motor symptoms in patients with Parkinson disease (PD).

Design: This was a cross-sectional study. Patients with PD were evaluated for obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic limb movement syndrome (PLMS), and REM sleep behavior disorder (RBD). Cognition was assessed with the Montreal Cognitive Assessment and patients completed self-reported questionnaires assessing non-motor symptoms including depressive symptoms, fatigue, sleep complaints, daytime sleepiness, and quality of life.

Setting: Sleep laboratory.

Participants: 86 patients with PD (mean age = 67.4 ± 8.8 years; range: 47–89; 29 women).

Interventions: N/A.

Measurements and Results: Having sleep disorders was a predictor of overall non-motor symptoms in PD ($R^2 = 0.33$, $p < 0.001$) while controlling for age, PD severity, and dopaminergic therapy. These analyses revealed that RBD ($p = 0.006$) and RLS ($p = 0.014$) were significant predictors of increased non-motor symptoms, but OSA was not. More

specifically, having a sleep disorder significantly predicted sleep complaints ($\Delta R^2 = 0.13$, $p = 0.006$), depressive symptoms ($\Delta R^2 = 0.01$, $p = 0.03$), fatigue ($\Delta R^2 = 0.12$, $p = 0.007$), poor quality of life ($\Delta R^2 = 0.13$, $p = 0.002$), and cognitive decline ($\Delta R^2 = 0.09$, $p = 0.036$). Additionally, increasing number of sleep disorders (0, 1, or ≥ 2 sleep disorders) was a significant contributor to non-motor symptom impairment ($R^2 = 0.28$, $p < 0.001$).

Conclusion: In this study of PD patients, presence of comorbid sleep disorders predicted more non-motor symptoms including increased sleep complaints, more depressive symptoms, lower quality of life, poorer cognition, and more fatigue. RBD and RLS were factors of overall increased non-motor symptoms, but OSA was not.

Keywords: Parkinson disease, sleep disorders, non-motor symptoms, quality of life

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Parkinson disease (PD) is a progressive neurodegenerative disorder primarily characterized by motor symptoms and increasing motor-related disability, including bradykinesia, rigidity, and tremor.¹ Non-motor symptoms (NMS) such as sleep dysfunction, sleepiness, fatigue, pain, and depressive symptoms, are common in PD. In a large multicenter study, NMS were reported by 99% of 1072 PD patients.² The presentation of NMS in PD is highly variable, and the understanding of such heterogeneity in PD is limited and incomplete.^{3,4} Chaudhuri et al.⁴ suggested that NMS dominate the clinical picture in patients with PD and contribute to the severe disability these patients experience, impair quality of life, and even shorten life expectancy. Studies have suggested that NMS, more than motor symptoms, may impact caregiver distress, quality of life, institutionalization rates, and overall costs related to PD.^{4–6} A 15-year follow-up study of patients with PD reported that the NMS that did not respond to dopamine therapy (e.g., dementia, sleep disruption) were “more disabling than end-of-dose failure or dyskinesia” and were the major cause of morbidity and mortality.⁷

BRIEF SUMMARY

Current Knowledge/Study Rationale: Parkinson disease (PD) is a progressive neurodegenerative disorder primarily characterized not only by motor symptoms but also by non-motor symptoms (NMS) such as sleep dysfunction, sleepiness, fatigue, pain, and depressive symptoms. This study evaluated the impact of sleep disorders on non-motor symptoms in patients with (PD).

Study Impact: These findings indicate a significant relationship between sleep disorders and increased NMS impairment in patients with PD. More specifically, having sleep disorders predicted increased sleep complaints, lower quality of life, increased depressive symptoms, poorer cognition, and more fatigue. The finding of increased NMS in RBD adds further support to a growing body of literature that suggests that RBD is related to increased frequency and severity of non-motor impairment and subsequent poorer quality of life.

Sixty to 98% of patients with PD complain of sleep-related difficulties.^{4,8,9} In a community-based study of sleep disorders in PD, 32% complained of difficulty falling asleep, 39% reported frequent awakenings during the night, and 23% reported early morning awakenings.¹⁰ A longitudinal study of

Figure 1—Consort table

CPAP, continuous positive airway pressure; DBS, deep brain stimulation; PSG, polysomnography; REM, rapid eye movement.

nocturnal sleeping problems in PD reported that 83% of the patients with PD reported sleep complaints at one or more visits during the 8-year study, and such complaints were related to disease duration and depression.⁹ Another study reported that sleep complaints significantly predicted poor health-related quality of life in PD.¹¹

Sleep disorders such as obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic limb movements syndrome (PLMS), and REM sleep behavior disorder (RBD) are commonly reported in patients with PD in rates similar or higher than in the general older adult population.^{12–25} Sleep disorders result in complaints about disturbed sleep, excessive daytime sleepiness, cognitive decline, and depression, all of which are also recognized as NMS of PD.^{26–29} Additionally, sleep disorders have been shown to substantially impact health-related quality of life in patients with PD.³⁰

Few studies have assessed possible relationships between any given sleep disorder and different NMS in PD population. Those studies that did question this relationship primarily assessed RBD, which has been demonstrated to be associated with hallucinations,^{31–33} cognitive impairment,^{34,35} psychiatric comorbidity,³⁶ increased falls,^{36,37} poor emotional functioning, and lower quality of life.³⁸ Studies looking at OSA in PD had conflicting results, with only one study reporting that OSA was

the most important risk factor associated with EDS in PD,²¹ while another study reported no relationship with NMS (e.g., sleepiness, depression, and cognitive impairment).¹⁶ Finally, previous findings from our laboratory suggested a relationship between increased periodic leg movements during the night (not associated with arousals), sleep complaints, and poorer quality of life.³⁹ However, to our knowledge, there have been no studies that simultaneously assessed multiple sleep disorders in patients with PD and the effect of having these sleep disorders on overall NMS impairment. We hypothesized that sleep disorders would be significant contributors to the overall NMS experienced and reported by patients with PD and that PD patients with more sleep disorders would experience more NMS impairment.

METHODS

Participants

Participants were recruited for this study at talks given at PD support group meetings, by flyers, advertisements, or were referred by neurologists at either the University of California, San Diego (UCSD) or in the San Diego County community. A consort table is provided (Figure 1). Of the 183 patients with

Table 1—Inclusion/exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. A clinical diagnosis of PD	1. Bronchospastic and symptomatic chronic obstructive pulmonary disease as indicated by regular use of bronchodilators, steroids, history of carbon dioxide retention, waking hypoxemia, or use of supplemental oxygen
2. MMSE $\geq$ 18	2. Current diagnosis of active seizure disorder; presence of any neurodegenerative disorder other than PD
3. Over the age of 50 years	3. Symptomatic coronary or cerebral vascular disease (history of myocardial infarction, angina, stroke, or transient ischemic attacks), history of life-threatening arrhythmias, cardiomyopathy, or current alcohol or drug abuse
4. Stable health	4. Receiving current treatment for obstructive sleep apnea
5. Fluent English speaking	5. Receiving deep brain stimulation treatment for PD
6. Participants willing and able to remain stable on the same medication regimen for 2 months prior to enrollment in the study	6. Current alcohol and/or drug abuse/dependence
	7. Any significant physiological (e.g., incontinence) or psychological impairments (i.e., bipolar depression) that would have limited their participation

PD that were contacted, 106 patients met inclusion/exclusion criteria (Table 1), agreed to participate, and consented for this study. The study was approved by UCSD Human Research Protection Program and San Diego Veterans Administration Healthcare System.

Procedures

All participants were screened by telephone. For those meeting inclusion criteria, a meeting was scheduled and the study was described in detail and signed informed consent was obtained. All enrolled participants were tested for cognitive performance by a research associate, were evaluated by a neurologist, and were assessed by a physician trained in sleep medicine for a detailed sleep history, assessment of possible sleep disorders, overall medical condition, and medication use. Additionally, all participants completed the self-administered questionnaire packet that included questionnaires assessing daytime sleepiness, sleep complaints, mood, quality of life, multiple symptoms of PD, and fatigue. All patients were admitted to the General Clinical Research Center (now Clinical and Translational Research Institute) Gillin Laboratory for Sleep and Chronobiology for an overnight video-enabled polysomnography (PSG).

PD Assessment

Participants were evaluated for PD by a neurologist using the Unified Parkinson's Disease Rating Scale (UPDRS)⁴⁰ to characterize the progression of PD. Additionally the Hoehn and Yahr Scale (H&Y)⁴¹ was utilized to assess PD severity. The H&Y grades patients from stage 0 (no signs of disease) to stage 5 (wheelchair bound or bedridden unless assisted).

Clinical Sleep Evaluation

All participants were evaluated by a physician trained in sleep medicine for RBD, RLS, medication use, and overall health. RBD was evaluated using the REM Behavior Disorder Sleep Questionnaire (RBDSQ).⁴² The RBDSQ was used to assess clinical history of dream enactment behavior. This screening tool for RBD is based on the clinical criteria of the International Classification of Sleep Disorders, second edition (ICSD-II).⁴³ The RBDSQ was previously validated with a cutoff score of 5, exhibiting 96% sensitivity and 56% specificity.⁴² RLS was evaluated using a structured questionnaire according to the 4 criteria

delineated in the International Restless Legs Syndrome Study Group criteria.⁴⁴ All 4 criteria had to be satisfied for diagnosis of RLS.

Medications

Medication use (i.e., type, dose, frequency, time of administration, reason for use, and duration of use) was assessed for all patients. As dopaminergic therapy regimen highly differs between patients with PD, and in order to allow comparisons among patients on different dopaminergic regimens, drug dosages were converted to levodopa dosage equivalents (LDE) according to the formula provided by Tomlinson et al.⁴⁵

Cognitive Evaluation

The Montreal Cognitive Assessment (MoCA)⁴⁶ was used to assess cognition. The MoCA is a brief screening tool designed to identify mild cognitive impairment. The MoCA was administered by trained study staff during consent. The MoCA has been demonstrated to have good reliability and validity in PD⁴⁷ and is more sensitive in detecting mild cognitive impairment than the Mini Mental State Exam.⁴⁸ A cutoff of 26 is suggestive of mild cognitive impairment.

NMS Questionnaires

Multiple Symptoms Evaluation

The Non-motor Symptoms Questionnaire (NMSQuest)⁴⁹ is a 30-item questionnaire that was completed by patients. The NMSQuest allows a brief yet comprehensive assessment of the non-motor features of PD, including neuropsychiatric, sleep, autonomic, gastrointestinal, sensory, and other disturbances. Number of symptoms endorsed is added up for a total score. This scale was shown to have good psychometric properties and to be valid as an instrument for detecting NMS in PD.⁵⁰

Mood Evaluation

Beck Depression Inventory- 2nd edition (BDI-II)⁵¹ was used to evaluate symptoms of depression and was completed by the patients. The BDI-II is well validated and is the most frequently used scale for depression.⁵²⁻⁵⁴ Visser et al. evaluated the reliability and validity of the BDI-II in PD.⁵⁵ A study that validated sub-threshold depression in PD concluded that a BDI-II score of 9-15 best differentiates sub-threshold depression in

this population.⁵⁵ The use of the BDI-II in PD was championed by expert panels for monitoring severity of symptoms and for evaluation of therapeutic interventions.⁵⁶

Quality of Life Evaluation

Parkinson's Disease Questionnaire (PDQ-39)⁵⁷ was designed and validated specifically for evaluating quality of life in PD. The PDQ-39 has 39 items on mobility, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort. A higher score on this scale indicates poorer quality of life. In a review of different quality of life scales for patients with PD, Marinus et al. concluded that the PDQ-39 is the single most appropriate quality of life instrument for this population.⁵⁹

Daytime Sleepiness Evaluation

The Epworth Sleepiness Scale (ESS)⁵⁸ is a self-administered questionnaire assessing daytime sleepiness. The ESS has been shown to reliably distinguish good sleepers from those with excessive daytime sleepiness disorders including obstructive sleep apnea, narcolepsy, and idiopathic hypersomnolence. A cutoff score ≥ 10 suggests clinically significant daytime sleepiness.

Fatigue Evaluation

The Short Form of the Multidimensional Fatigue Symptom Inventory (MFSI-SF)⁵⁹ is a short questionnaire (30 questions) that provides a total fatigue score and 5 subscales: General, Physical, Emotional, Mental, and Vigor. A total score is computed based on subscales with higher scores indicating worse fatigue. Assessment of the MFSI-SF showed sound psychometric properties and a stable multidimensional factorial structure.

Sleep Complaints Evaluation

The Parkinson's Disease Sleep Scale (PDSS)^{60,61} is a self-administered questionnaire that is designed to assess sleep complaints and nocturnal difficulties that are more pertinent in PD. Items address overall quality of sleep, sleep onset and sleep maintenance insomnia, nocturnal restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, sleep refreshment, and daytime dozing. Scores for each of 15 items range from 0 (symptom severe and always present) to 10 (symptom free). The mean of the scales is computed, with lower scores suggesting more severe sleep disruption.

Overnight PSG and Diagnostic Criteria for Sleep Disorders

The first 4 patients were evaluated with the Embla (Planegg, Germany) while the remaining participants were evaluated with the video-enabled Compumedics Somt (Charlotte, NC). Electroencephalography (F4, C4, O1 or O2), electrooculography (left and right outer canthus), submental electromyography, respiratory effort (thoracic and abdominal piezoelectric bands), airflow (nasal pressure transducer), electrocardiogram, oximetry, and tibialis electromyography were recorded. In addition, technicians noted any visible arousals (e.g., restroom visits, taking medication), any environmental changes (e.g., noise), any vocalization during sleep (e.g., yelling/talking), and any movements (e.g., kicking/arms flailing), both on the PSG recording and in a journal.

All PSG records were staged according to accepted American Academy of Sleep Medicine criteria.⁶² Apnea-hypopnea index (AHI; the number of apneas + hypopneas/h of sleep), periodic leg movement index (PLMI; the number of leg kicks in a 5- to 90-sec period of ≥ 4 consecutive leg movements/h of sleep), and periodic leg movement arousal index (PLMARi; periodic leg movements associated with arousals/h of sleep) were computed.

To assess for RBD, submental electromyography was assessed for REM sleep without atonia using criteria nearly identical to the scoring method developed by Lapierre and Montplaisir⁶³ and validated by Consens et al.,⁶⁴ including computation of tonic and phasic components as defined by the American Academy of Sleep Medicine guidelines.⁶² An electromyography score (EMG score) was calculated as the average of the percent of tonic REM sleep epochs and the percent of phasic REM sleep mini-epochs. The EMG score is similar to the RBD measure previously proposed by Consens et al.,⁶⁴ which established a cutoff score of 10% with a sensitivity of 89% and specificity of 57%.

Sleep Disorders Criteria

OSA definition was based on an AHI (yes-OSA [AHI ≥ 10] and no-OSA [AHI < 10]), PLMS definition was based on the PLMARi (yes-PLMS [PLMARi ≥ 5] and no-PLMS [PLMARi < 5]), and RLS diagnosis was based on the RLS criteria (yes-RLS [endorsed all 4 RLS questions] and no-RLS [endorsed < 4 RLS questions]).

Finally, RBD diagnosis was based on the ICSD-II,⁴³ which requires subjective clinical history with objective documentation of either REM sleep without atonia or dream enactment behavior during an overnight PSG. Patients were classified into 3 RBD groups based on subjective (RBDSQ) and objective (EMG-score and/or clear evidence of REM sleep without atonia as recorded during overnight PSG) measures; Group 1, Yes-RBD group (RBDSQ ≥ 5 and EMG score $\geq 10\%$ or clear evidence of REM sleep without atonia as recorded during overnight PSG); Group 2, No-RBD group (RBDSQ < 5 and EMG score $< 10\%$); and Group 3, Probable-RBD group (either RBDSQ ≥ 5 or EMG-score $\geq 10\%$).

Analysis

Summary statistics (means, SDs, ranges, frequencies) were computed for all variables of interest. Of the 7 outcome measures, only the BDI-II and MoCA violated normality assumption and thus were appropriately transformed for subsequent analyses. Analyses were computed both with the transformed and untransformed data. Pearson correlations were used to assess the relationship between NMS measures.

Given that 7 NMS variables were under consideration (i.e., MoCA, NMSQuest, BDI-II, MFSI-SF, PDQ-39, PDSS, and ESS), and in order to avoid multiple comparisons, principal component analysis (PCA) was used to derive component/factor scores that best described the NMS of PD by distinguishing sets of variables with stronger relationships among multiple observed variables (e.g., mood, sleepiness, functional impairment, and quality of life).⁶⁵

A hierarchical linear regression correlation was used to assess the relationship between the NMS score (i.e., first principal

Table 2—Clinical and sleep characteristics by sleep disorder

	Total Sample	OSA		p	RBD				RLS		
		Yes-OSA	No-OSA		Yes-RBD	Probable-RBD	No-RBD	p	Yes-RLS	No-RLS	p
N [%]	86 [100]	47 [54.7]	39 [45.3]		36 [41.9]	24 [27.9]	26 [30.2]		19 [22.1]	67 [77.9]	
Gender: Male/Female	57/29	34/13	23/16	0.19	25/11	14/10	18/8	0.63	13/6	44/23	0.82
Age: mean (SD)	67.4 (8.8)	68.1 (9.4)	66.6 (9.0)	0.44	67.3 (7.3)	66.6 (9.7)	68.4 (10.0)	0.77	67.6 (10.3)	67.4 (8.4)	0.94
PD Duration: mean years (SD)	6.3 (5.3)	6.0 (5.5)	6.5 (5.2)	0.67	6.9 (6.4)	5.7 (4.9)	5.8 (4.0)	0.62	6.4 (6.2)	6.2 (5.1)	0.91
Hoehn & Yahr: n [%]											
Stage I	24 [27.9]	14 [29.8]	10 [25.6]		10 [27.8]	7 [29.2]	7 [26.9]		4 [21.1]	20 [29.9]	
Stage II	44 [51.1]	23 [48.9]	21 [53.8]		19 [52.8]	12 [50.0]	13 [50.0]		9 [47.4]	35 [52.2]	
Stage III	12 [14.0]	5 [10.6]	7 [17.9]	0.64	5 [13.9]	3 [12.5]	4 [15.4]	0.99	4 [21.1]	8 [11.9]	0.51
Missing	6 [7.0]	5 [10.6]	1 [2.6]		2 [5.6]	2 [8.3]	2 [7.7]		2 [10.5]	4 [6.0]	
UPDRS: mean (SD)											
Part 1	14.1 (6.3)	13.6 (6.5)	14.6 (6.0)	0.45	15.9 (6.6)	15.1 (6.4)	10.5 (3.9)	0.003	16.6 (5.0)	13.4 (6.4)	0.06
Part 2	18.5 (7.5)	18.8 (8.1)	18.2 (6.9)	0.73	19.4 (7.5)	18.8 (8.5)	16.9 (6.7)	0.46	21.2 (7.0)	17.8 (7.5)	0.09
Part 3	3.5 (2.3)	3.0 (1.9)	4.1 (2.5)	0.02	3.5 (2.4)	3.8 (2.3)	3.3 (2.2)	0.7	4.5 (1.7)	3.2 (2.4)	0.05
Total	36.1 (13.2)	35.3 (14.1)	36.9 (12.3)	0.58	38.7 (13.3)	37.8 (14.4)	30.7 (10.5)	0.06	42.3 (9.7)	34.4 (13.6)	0.02
Medications:											
LDE: mean (SD)	853.0 (592.1)	852.8 (534.9)	853.3 (661.8)	0.99	828.9 (618.9)	897.6 (595.1)	845.2 (572.1)	0.91	935.8 (551.8)	829.6 (605.0)	0.49
Benzodiazepine: n [%]	9 [10.5]	6 [12.8]	3 [7.7]	0.44	6 [16.7]	3 [12.5]	0	0.1	3 [15.8]	6 [9.0]	0.69
Antidepressants: n [%]	24 [27.9]	12 [12.5]	12 [30.8]	0.59	9 [25.0]	11 [45.8]	4 [15.4]	0.05	6 [31.6]	18 [26.9]	0.39
BMI: mean (SD)	26.8 (4.2)	27.2 (4.2)	26.3 (4.2)	0.29	26.4 (3.9)	26.9 (4.5)	27.3 (4.4)	0.68	27.6 (4.7)	26.6 (4.0)	0.35
AHI: mean (SD)	14.1 (13.8)	22.7 (13.5)	3.7 (2.1)	< 0.001	10.3 (10.9)	20.6 (18.4)	13.4 (10.7)	0.02	11.3 (10.0)	14.9 (14.7)	0.33
PLMI: mean (SD)	21.0 (25.4)	24.3 (29.2)	17.0 (19.6)	0.17	25.2 (27.1)	22.6 (27.1)	13.7 (20.2)	0.2	17.5 (18.7)	22.0 (27.1)	0.51
EMG score: mean % (SD)	12.8 (12.2)	10.4 (9.7)	15.7 (14.3)	0.06	19.6 (11.1)	11.4 (14.3)	4.3 (2.1)	< 0.001	12.8 (10.0)	12.8 (12.9)	0.99
RBDSQ: mean (SD)	5.9 (3.5)	5.6 (3.6)	6.3 (3.4)	0.4	8.1 (2.7)	6.5 (3.3)	2.4 (1.1)	< 0.001	6.4 (4.0)	5.8 (3.4)	0.52

OSA, obstructive sleep apnea; RBD, REM sleep behavior disorder; RLS, restless legs syndrome; UPDRS, unified Parkinson's disease rating scale; LDE, levodopa dosage equivalence; BMI, body-mass index; AHI, apnea hypopnea index; PLMI, periodic limb movement index; RBDSQ, REM behavior disorder symptoms questionnaire.

component of each principal component analysis) and the presence of sleep disorders while controlling for age, PD severity, and dopaminergic therapy (LDE). Using regression analysis allowed the assessment of the unique effects of each explanatory variable (unique sleep disorders) while statistically controlling (partialing) the effects of the other explanatory variables in a single model, thus minimizing the likelihood of a type I error.⁶⁶ Age, PD severity (H&Y), and dopaminergic therapy (LDE) were included in block 1 and the sleep disorders were included in block 2 to assess if the inclusion of sleep disorders into the model resulted in significant increases of variance explained in the NMS score (ΔR^2 and ΔF statistic). Additionally, a separate model assessed the impact of having 0, 1, or ≥ 2 sleep disorders on NMS score while controlling for age, disease severity, and dopaminergic therapy (LDE). All analyses were executed using SPSS (version 17.0, SPSS, Chicago, IL).

RESULTS

A total of 86 patients with PD (mean age = 67.4 ± 8.8 years; range: 47-89, 29f) were included in this study (Figure 1). The majority of the sample was Caucasian (91%), married (73%), and retired (66.3%). The patients had been diagnosed with PD for an average of 6.3 years. The majority of the patients were at H&Y stage I or II (79%), and no patients had stage IV or V. The specific dopaminergic therapy (i.e., levodopa, carbidopa, dopamine agonist) widely differed between patients, and only 6 participants were not receiving any dopaminergic therapy. Additionally, 28% of the patients reported taking an antidepressant.

Of the total sample, 55% ($n = 47$) were diagnosed with OSA, 42% ($n = 36$) with RBD, and 22% ($n = 19$) with RLS. PLMI for the sample was considerably high ($PLMI = 21.0$) however, these events were rarely associated with arousals and only 2 patients (2%) were diagnosed with PLMS (had a $PLMAR \geq 5$). Due to this small number, PLMS was omitted from further analyses. Finally, 10 (11.6%) of the patients had no sleep disorders, 52 (60.5%) had only 1 sleep disorder, and 24 (27.9%) patients had ≥ 2 sleep disorders.

Complete clinical and sleep characteristics for the entire sample and by sleep disorder is provided in Table 2. Descriptive measures are provided in Table 3 and correlations between the measures in Table 4.

Principal Component Analysis

Principal component analysis on the 7 NMS outcome measures resulted in a single component extracted (NMS score) that explained 53.5% of the variance (Eigenvalue = 3.75). Each of the remaining components had an Eigenvalue < 1.0 and explained $\leq 14\%$ of the variability in the set of NMS variables. Examining the extracted weights for each variable revealed that most of the variable loaded heavily ($> |0.8|$) on this component with only subjective sleepiness ($ESS = 0.48$) and cognition ($MoCA = -0.27$) not heavily loading on this component.

Omnibus Testing of Sleep Disorders Relationship to NMS of PD

A hierarchical regression model with the NMS score as the dependent variable and LDE, age, and PD severity as

Table 3—Mean (SD) of NMS questionnaires by sleep disorder (p-values from the regression models)

NMS Measure	Total Sample	OSA			RBD				RLS		
		Yes-OSA	No-OSA	p	Yes-RBD	Probable-RBD	No-RBD	p	Yes-RLS	No-RLS	p
BDI-II	9.3 (6.4)	9.6 (6.5)	9.0 (6.2)	0.31	10.6 (6.6)	10.6 (6.4)	6.5 (5.2)	0.01	10.8 (5.5)	9.0 (6.5)	0.34
ESS	10.5 (4.6)	10.8 (4.5)	10.2 (4.8)	0.34	10.8 (4.2)	10.6 (4.9)	10.1 (4.9)	0.93	11.5 (5.1)	10.3 (4.5)	0.29
MFSI-SF	11.3 (13.3)	11.7 (13.5)	10.7 (13.1)	0.61	12.1 (13.3)	16.0 (16.3)	6.0 (7.7)	0.01	17.3 (14.3)	9.6 (12.5)	0.02
MoCA	24.6 (3.4)	24.0 (3.5)	25.3 (3.2)	0.01	25.2 (3.3)	23.5 (3.6)	24.7 (3.3)	0.31	23.5 (5.2)	24.9 (2.7)	0.51
NMSQuest	11.5 (5.2)	11.4 (5.6)	11.6 (4.6)	0.95	13.1 (5.0)	11.5 (5.4)	9.2 (4.4)	0.11	13.0 (4.6)	11.1 (5.3)	0.56
PDQ-39	34.7 (20.4)	36.0 (22.0)	33.2 (18.5)	0.08	34.9 (20.3)	40.2 (21.7)	29.4 (18.6)	0.03	48.7 (17.8)	30.8 (19.4)	< 0.01
PDSS	101.1 (20.8)	103.2 (19.7)	98.7 (22.1)	0.42	99.2 (20.1)	93.7 (21.1)	110.7 (18.6)	< 0.01	92.8 (21.7)	103.5 (20.1)	0.08

OSA, obstructive sleep apnea; RBD, REM sleep behavior disorder; RLS, restless legs syndrome; BDI-II, Beck depression inventory 2nd ed.; ESS, Epworth sleepiness scale; MFSI-SF, multidimensional fatigue symptom inventory - short form; MoCA, Montreal cognitive assessment; NMSQuest, non-motor symptoms questionnaire; PDQ-39, Parkinson's disease questionnaire; PDSS, Parkinson's disease sleep scale.

Table 4—Correlational matrix

NMS Measure	PDSS	PDQ-39	NMSQuest	MoCA	MFSI-SF	ESS
BDI-II	-0.56***	0.6***	0.68***	-0.13	0.7***	0.27*
ESS	-0.28*	0.33**	0.29**	-0.1	0.4***	—
MFSI-SF	-0.59***	0.64***	0.67***	-0.24*	—	
MoCA	0.27*	-0.14	-0.1	—		
NMSQuest	-0.61***	0.68***	—			
PDQ-39	0.69***	—				

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; BDI-II, Beck depression inventory 2nd ed.; ESS, Epworth sleepiness scale; MFSI-SF, multidimensional fatigue symptom inventory - short form; MoCA, Montreal cognitive assessment; NMSQuest, non-motor symptoms questionnaire; PDQ-39, Parkinson's disease questionnaire; PDSS, Parkinson's disease sleep scale.

independent variables was significant ($R^2 = 0.20$, $F = 6.93$, $p < 0.001$). In this model only age ($\beta = -0.24$, $p = 0.016$) and LDE ($\beta = 0.37$, $p = 0.004$) were significant predictors of the NMS score, while PD severity was not ($\beta = 0.16$, $p = 0.13$). Including sleep disorders (i.e., OSA, RLS, RBD) into this model significantly improved the model ($\Delta R^2 = 0.13$, $\Delta F = 5.01$, $p = 0.003$). The full model with the NMS score as the dependent variable and age, PD severity, LDE, OSA, RBD, and RLS, as independent variables was significant ($R^2 = 0.33$, $F = 5.97$, $p < 0.001$) with age ($\beta = -0.23$, $p = 0.014$), LDE ($\beta = 0.28$, $p = 0.004$), RBD ($\beta = 0.26$, $p = 0.006$), and RLS ($\beta = 0.24$, $p = 0.014$) as significant predictors of the NMS score. PD severity ($\beta = 0.15$, $p = 0.12$) and OSA ($\beta = 0.06$, $p = 0.52$) were not significant predictors of the NMS score. In summary, sleep disorders (specifically, RBD and RLS) were significant contributors and predictors of NMS score above and beyond that which is explained by age, LDE, and PD severity. Sleep disorders alone accounted for 13% of the variance in the NMS score. Overall this model was significant and explained 33% of the variance in the NMS score.

Patients with RBD ($t = 2.51$, $p = 0.014$) and with RLS ($t = -2.57$, $p = 0.012$) had a significantly higher NMS score than those without RBD or RLS; there were no significant differences in patients with or without OSA.

Assessment of the impact of having multiple sleep disorders (0, 1, or ≥ 2 sleep disorders) on the NMS score and including this variable in the model while controlling for age, PD severity, and LDE, revealed that the model significantly improved ($\Delta R^2 = 0.07$, $\Delta F = 8.33$, $p = 0.005$). The full model with the NMS score as the dependent variable and age, PD

severity, dopaminergic therapy, and number of sleep disorders per patient as independent variables was significant ($R^2 = 0.28$, $F = 7.75$, $p < 0.001$) with age ($\beta = -0.25$, $p = 0.01$), LDE ($\beta = 0.3$, $p = 0.002$), and number of sleep disorders ($\beta = 0.27$, $p = 0.005$) being significant predictors of the NMS score.

There were no differences in NMS score between those with no sleep disorders and those with only 1 sleep disorder. However, compared to those with ≥ 2 sleep disorders, those with no sleep disorders ($t = 2.1$, $p = 0.04$) and those with only one sleep disorder ($t = 2.32$, $p = 0.023$) had significantly lower NMS scores.

Individual NMS Domain Assessment

As summarized in Table 5, after controlling for age, PD severity, and dopaminergic therapy, sleep disorders were significant predictors of sleep complaints evaluation (i.e., PDSS) ($\Delta R^2 = 0.13$, $\Delta F = 4.54$, $p = 0.006$), mood evaluation ($\Delta R^2 = 0.01$, $\Delta F = 3.17$, $p = 0.03$), quality of life evaluation ($\Delta R^2 = 0.13$, $\Delta F = 5.63$, $p = 0.002$), fatigue evaluation ($\Delta R^2 = 0.12$, $\Delta F = 4.29$, $p = 0.007$), and cognition evaluation ($\Delta R^2 = 0.09$, $\Delta F = 3.0$, $p = 0.036$).

Sleep Complaints

After controlling for age, PD severity, and LDE, only RBD ($\beta = -0.3$, $p = 0.003$) was a significant predictor of the subjective sleep evaluation, while OSA ($\beta = 0.08$, $p = 0.42$) and RLS ($\beta = -0.17$, $p = 0.078$) were not. Sleep disorders alone accounted for 14% of the variance in this measure. Overall this model was significant ($F = 4.85$, $p < 0.001$) and explained 27% of the variance in the subjective sleep evaluation.

Table 5—NMS domain regression analyses modeling results (values are standardized Beta coefficients)

	Age	PD Severity (H&Y)	Dopaminergic Therapy (LDE)	Restricted R ²	OSA	RBD	RLS	Sleep Disorders ΔR^2	Full Model R ²
Multiple Symptoms (NMSQuest)	-0.17	0.18	0.25*	0.16**	0.008	0.16	0.11	0.04	0.20**
Mood (BDI-II)	-0.29**	0.09	0.19	0.15	0.11	0.28**	0.1	0.1*	0.25**
Quality of Life (PDQ-39)	-0.23*	0.27**	0.32***	0.30***	0.16	0.2*	0.26**	0.13**	0.43***
Daytime Sleepiness (ESS)	-0.35**	0.06	0.01	0.11*	0.18	-0.002	0.03	0.03	0.14
Fatigue (MFSI-SF)	-0.17	-0.03	0.31**	0.15**	0.05	0.26**	0.23*	0.12**	0.27***
Sleep Complaints (PDSS)	0.21*	-0.16	-0.18	0.14**	0.08	-0.3**	-0.17	0.13**	0.27***
Cognition (MoCA)	-0.31**	-0.02	-0.25*	0.16**	-0.28**	-0.11	-0.07	0.09*	0.25***

Restricted models (i.e., restricted R²) included age, PD severity, and dopaminergic treatment. ΔR^2 represents unique variance accounted by sleep disorders (i.e., OSA, RBD, and RLS) when including them into the restricted model. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; PD, Parkinson disease; H&Y, Hoehn & Yahr; LDE, levodopa dosage equivalence; OSA, obstructive sleep apnea; RBD, REM sleep behavior disorder; RLS, restless legs syndrome; BDI-II, Beck depression inventory 2nd ed.; ESS, Epworth sleepiness scale; MFSI-SF, multidimensional fatigue symptom Inventory - short form; MoCA, Montreal cognitive assessment; NMSQuest, non-motor symptoms questionnaire; PDQ-39, Parkinson's disease questionnaire; PDSS, Parkinson's disease sleep scale.

Mood

After controlling for age, PD severity, and LDE, only RBD ($\beta = 0.28$, $p = 0.01$) was a significant predictor of mood symptoms, while OSA ($\beta = 0.11$, $p = 0.31$) and RLS ($\beta = 0.1$, $p = 0.34$) were not. Sleep disorders alone accounted for 10% of the variance in this measure. Overall this model was significant ($F = 3.96$, $p = 0.002$) and explained 25% of the variance in the mood evaluation.

Quality of Life

After controlling for age, PD severity, and dopaminergic therapy, RLS ($\beta = 0.26$, $p = 0.005$), and RBD ($\beta = 0.2$, $p = 0.028$) were significant predictors of the quality of life while OSA ($\beta = 0.16$, $p = 0.079$) was not. Sleep disorders alone accounted for 13% of the variance in this measure. Overall this model was significant ($F = 9.02$, $p < 0.001$) and explained 43% of the variance in the quality of life evaluation.

Fatigue

Of the sleep disorders, RBD ($\beta = 0.26$, $p = 0.01$) and RLS ($\beta = 0.23$, $p = 0.023$) were significant predictors of fatigue, while OSA ($\beta = 0.05$, $p = 0.61$) was not. Sleep disorders alone accounted for 12% of the variance in this measure. Overall this model was significant ($F = 4.88$, $p < 0.001$) and explained 27% of the variance in the fatigue evaluation.

Cognition

Only OSA ($\beta = -0.28$, $p = 0.01$) was a significant predictor of cognition, while RBD ($\beta = -0.11$, $p = 0.31$) and RLS ($\beta = -0.07$, $p = 0.51$) were not. Sleep disorders alone accounted for 9% of the variance in this measure. Overall this model was significant ($F = 4.06$, $p = 0.001$) and explained 25% of the variance in the cognition evaluation.

Multiple Sleep Disorders

When assessing the impact of having multiple sleep disorders (0, 1, or ≥ 2 sleep disorders) on the individual NMS domains while controlling for age, PD severity, and dopaminergic therapy revealed that number of sleep disorders significantly improved the models of multiple symptoms

Figure 2—Number of sleep disorders impact on NMS measures

After controlling for age, PD severity, and dopaminergic therapy (LDE), increased number of sleep disorders significantly predicted worse scores on the multiple symptoms evaluation (NMSQuest, $p = 0.017$), quality of life (PDQ-39, $p = 0.006$), fatigue (MFSI-SF, $p = 0.03$), and mood (BDI-II, $p = 0.024$). Post hoc analyses revealed significant differences between those with 0, 1, or ≥ 2 sleep disorders only on the multiple symptoms evaluation and quality of life evaluation.

evaluation ($\Delta R^2 = 0.06$, $\Delta F = 6.01$, $p = 0.017$), quality of life evaluation ($\Delta R^2 = 0.07$, $\Delta F = 7.95$, $p = 0.006$), fatigue evaluation ($\Delta R^2 = 0.05$, $\Delta F = 4.92$, $p = 0.03$), and mood evaluation ($\Delta R^2 = 0.06$, $\Delta F = 5.31$, $p = 0.024$). In summary, increased number of sleep disorders significantly predicted more NMS symptoms, poorer quality of life, increased fatigue, and more severe mood symptoms (Figure 2).

DISCUSSION

This study assessed the relationship between sleep disorders and NMS in PD. Using dimension reduction techniques to derive a single factor score representing overall NMS for each individual, the analyses revealed that sleep disorders

were independent and significant contributors to the non-motor impairment experienced in PD. Specifically, the data revealed that having a sleep disorder predicted more NMS impairment (i.e., higher scores on the NMS score) with a moderate effect size ($R^2 = 0.33$) after controlling for age, PD severity, and dopaminergic therapy (LDE). This relationship between sleep disorders and overall NMS score held true when omitting the sleep related measures (i.e., ESS, MFSI-SF, and PDSS) from the derived factor, which indicated that sleep symptoms per se did not bias the finding that having sleep disorders increase overall NMS endorsement by patients with PD (data not shown). The multivariate results revealed that sleep disorders were significant predictors of increased sleep complaints, depressive symptoms, lower quality of life, increased fatigue, and poorer cognition.

Furthermore, these results revealed a relationship between the number of sleep disorders per patient and reports of NMS. More specifically, patients with at least two sleep disorders reported significantly more overall NMS than those having no sleep disorders or only one sleep disorder. Additionally, increased number of sleep disorders predicted higher scores on the individual measures of multiple symptoms, quality of life, fatigue, and mood.

Our results showed that RBD was associated with increased NMS in PD. Such findings align with previous research which has shown that patients with PD with RBD have unique clinical characteristics and experience increased NMS (e.g., more visual hallucinations, falls, more cognitive impairment).^{31-38,67,68} It is important to point out that many of these studies report conflicting findings which are likely due to the different methodology employed and different RBD definitions used.²⁵ Diagnosis of RBD is challenging and includes subjective and objective assessments which are costly and time consuming.⁶⁹ Additionally, in many of these studies NMS domains were assessed with a single question, and most studies assessed a single NMS domain post hoc. In this study, RBD was evaluated with both subjective and objective data according to the ICSD-II.⁴³ Additionally, increased NMS was tested across multiple domains and this study utilized established measures to assess a given domain and did not utilize single questions for indication of a specific NMS. The results of this study showed that having RBD was associated with overall increased NMS, specifically increased symptoms of depression, fatigue, sleep complaints, and quality of life.

RLS has been shown to significantly affect health related quality of life in other populations, but little is known about how RLS affects quality of life or other NMS in PD.⁷⁰ To our knowledge, this is the first study to show that RLS was a significant predictor of increased NMS in PD and that RLS was associated with increased fatigue and poorer quality of life.

Perhaps the most surprising result of our study was the lack of association between OSA and the NMS score, indicating that OSA was not a significant contributor to the overall NMS impairment in our sample. These findings align with a recent study that also did not find a relationship between OSA and NMS such as sleepiness, depression, and cognitive impairment, leading the authors to question the clinical relevance of OSA in PD.¹⁶ While OSA was not a significant predictor of overall NMS impairment in our sample, it was a significant predictor of

cognitive impairment after controlling for age, disease severity, and dopaminergic therapy. Such findings are not surprising as associations between OSA and some cognitive impairment are well established in multiple studies including sleep disorders clinic patients, older adults, patients with Alzheimer disease, and nursing home patients.⁷¹⁻⁷⁹ We also found that OSA treatment improves nighttime sleep in PD.⁸⁰ OSA treatment is therefore clinically indicated, as it may also reduce NMS impairment and improve quality of life.

In our study, only two patients met criteria for PLMS. Periodic leg kicks are thought to be more frequent in diseases with impaired dopaminergic transmission, like PD⁸¹ and multi-system atrophy.¹⁸ A previous study in our laboratory concurred with these reports and showed high prevalence in periodic kicks during the night in PD and an association with lower quality of life.³⁹ However, these studies assessed periodic leg kicks which were independent of arousals. In general, a diagnosis of PLMS is made when leg kicks result in arousals.

Sleep disruption in PD is likely due to a multitude of factors including the neurodegenerative process of the disease itself. PD is marked by dopamine dysfunction and degeneration of the dopaminergic neurons. Dopamine circuitry is also thought to be implicated in several major sleep disorders common in PD such as insomnia and RLS.⁸² There are reports suggesting that patients with PD exhibit dopamine dysfunction in the hypothalamus, a key area in the regulation of sleep-wake that may contribute to symptoms of insomnia, circadian rhythm disruption, and daytime sleepiness.⁸³ In addition, brain stem deterioration is reported in PD and is also implicated in the REM sleep processes such as muscle atonia during REM.⁴ Other factors may also be responsible for disturbed sleep in PD, including the medications used to treat the PD, motor symptoms, pain, nocturia, and other sleep disorders common in this age group.⁸⁴⁻⁸⁷ Nonetheless, our results suggest that even when controlling for disease (dopaminergic treatment and PD severity) and age, sleep disorders had a negative impact on NMS in PD.

These findings that sleep disorders are unique predictors of increased NMS and subsequently poorer quality of life is important for considering disease management approaches. Additional studies are now required to determine whether the treatment of sleep disorders in PD may offer significant benefit in terms of overall NMS and quality of life. A recent pilot study that provided behavioral treatment for sleep in a small sample of patients with PD suggested that improving nighttime sleep in these patients improved quality of life both for the patients and their caregivers.⁸⁸ While treating sleep disorders will likely not affect PD progression, it has the potential for improving NMS and may potentially reduce overall disability and thereby improve the lives of PD patients and their caregivers.

The major strengths of this study include the systematic and objective assessment of sleep disorders in this sample of patients with PD. The availability of overnight PSG data allowed for reliably diagnosing OSA, RBD, and PLMS in PD. Additionally, this study utilized multiple previously validated measures of NMS and the employed advanced statistics to assess different NMS in a cohesive manner and avoiding multiple comparisons.

Nonetheless, this study also had several limitations. Video recordings during PSG were available for less than half of the sample for diagnosing RBD. However, detailed clinical notes

were maintained by the technician and these notes were available for all patients. Additionally, the scorer of EMG activity was not blind to technician's notes as notes were made on the PSG records. In our study, only one-night PSG recording was conducted and while this more closely resembles clinical findings, single-night recordings may miss RBD occurrences due to high night-to-night variability.⁸⁹ However, while we may have underestimated RBD in our sample, our RBD occurrence rate was similar to other studies using similar methodology.^{36,90} In our sample, 28% were using antidepressants, which may result in increased muscle tone during REM sleep. However, EMG score was not significantly different between those taking vs. not taking antidepressants in the entire sample or in any of the RBD groups. Our study was also limited to a subjective assessment of self-reported symptoms (excluding cognition which was evaluated with a single objective measure) and future studies should include objective measures and/or clinical interviews to further support such findings. Also, due to inclusion/exclusion criteria, our sample may not be generalizable to the overall PD population or to patients with more severe PD. Although our models revealed that sleep disorders significantly predicted higher NMS scores and contributed to the variance explained above and beyond age, PD severity, and dopaminergic therapy, this study modeled associations among variables and thus no inferences of causality can be made. Future research will have to assess rather treating sleep disorders in this population will result in decreased non-motor symptomatology to better understand this observed association.

In summary, this study showed that in patients with PD, the presence of comorbid sleep disorders predicts more NMS symptoms in general. More specifically, having sleep disorders predicted increased sleep complaints, lower quality of life, increased depressive symptoms, poorer cognition, and more fatigue. Of the sleep disorders assessed in this study, RBD and RLS were indicators of overall increased NMS but OSA was not. The findings of increased NMS in RBD adds further support to a growing body of literature that suggests that RBD is related to increased frequency and severity of non-motor impairment and subsequent poorer quality of life. This is the first study to systematically assess the effect of RLS on NMS in PD and further research is needed to corroborate these findings.

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