Insomnia and Sleepiness in Parkinson Disease: Associations with Symptoms and Comorbidities

Seockhoon Chung, M.D., Ph.D.^{1,2}; Nicolaas I. Bohnen, M.D., Ph.D.^{3,4}; Roger L. Albin, M.D.⁴; Kirk A. Frey, M.D., Ph.D.^{3,4}; Martijn L. T. M. Müller, Ph.D.³; Ronald D. Chervin, M.D., M.S., F.A.A.S.M.¹

¹Sleep Disorders Center and Department of Neurology, University of Michigan, Ann Arbor, MI; ²Department of Psychiatry, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; ³Department of Radiology, Division of Nuclear Medicine, University of Michigan, Ann Arbor, MI; ⁴Department of Neurology, University of Michigan, Ann Arbor, MI

Study Objectives: Insomnia and daytime sleepiness are common complaints in Parkinson disease (PD), but the main causes remain unclear. We examined the potential impact of both motor and non-motor symptoms of PD on sleep problems.

Methods: Patients with PD (n = 128) were assessed using the Insomnia Severity Index, Epworth Sleepiness Scale, Unified Parkinson Disease Rating Scale, Beck Depression Inventory, Fatigue Severity Scale, Survey of Autonomic Symptoms, and the 39-item Parkinson Disease Questionnaire. A subset of subjects (n = 38, 30%) also completed nocturnal polysomnography and a multiple sleep latency test (MSLT).

Results: Multivariate stepwise logistic regression models revealed that subjective insomnia was independently associated with depressed mood (odds ratio [OR] = 1.79; 95% confidence interval [CI] [1.01-3.19]), autonomic symptoms (1.77 [1.08-2.90]), fatigue (1.19 [1.02-1.38]), and age (0.61 [0.39-0.96]). Subjective daytime sleepiness was associated with dosage of dopaminergic medication (1.74 [1.08-2.80]) and fatigue (1.14 [1.02-1.28]). On polysomnography, longer sleep latency correlated with autonomic symptoms ($\rho = 0.40$,

$p = 0.01$) and part I (non-motor symptoms) of the Unified PD Rating Scale ($\rho = 0.38$, $p = 0.02$). Decreased sleep efficiency correlated with autonomic symptoms ($\rho = -0.42$, $p < 0.0001$). However, no significant difference emerged on polysomnography and MSLTs between patients with or without insomnia or daytime sleepiness. Higher rates of apneic events did predict shorter sleep latencies on the MSLTs.

Conclusions: Non-motor symptoms appear to be associated with subjective insomnia, whereas fatigue and dopaminergic medication are associated with subjective daytime sleepiness. Objective sleep laboratory data provided little insight into complaints of insomnia and sleepiness, though obstructive sleep apnea predicted worsened sleepiness when measured objectively.

Keywords: Parkinson disease, insomnia, daytime sleepiness, depression, non-motor symptoms

Citation: Chung S; Bohnen NI; Albin RL; Frey KA; Müller MLTM; Chervin RD. Insomnia and sleepiness in Parkinson disease: associations with symptoms and comorbidities. *J Clin Sleep Med* 2013;9(11):1131-1137.

Sleep-related disturbances, including insomnia and excessive daytime sleepiness, are some of the most common complaints of patients with Parkinson disease (PD). As many as 60% to 76% of PD patients experience insomnia.^{1,2} Nocturnal hypokinesia, nocturnal and early morning dystonia, and impaired bed mobility are thought to be common causes.^{2,3} In practice, attention often focuses on motor symptoms of PD, and these are probably considered first as possible causes of sleep disturbance. Although non-motor symptoms, such as depressed mood, anxiety, pain, or frequent nocturia tend to receive less clinical consideration, such symptoms could have substantial impact on sleep.⁴ In particular, depression is the most common psychiatric problem in PD, with an estimated prevalence of 17% to 50%,^{5,6} depending on the rating scales or structured clinical diagnosis used to identify the problem. Several studies have examined the relationship between depressed mood and sleep disturbance in PD patients.⁷ The relative contributions, however, of motor and non-motor features to sleep disturbance remains unclear, despite the important impact that sleep disturbance can have on quality of life in patients with PD. Furthermore, the potential value of objective sleep laboratory data, in understanding sleep-related

BRIEF SUMMARY

Current Knowledge/Study Rationale: Sleep disturbance and daytime somnolence are common complaints in patients with Parkinson disease (PD), but the main causes remain unclear. This study was done to explore associations between sleep-related complaints and potential contributors, including both motor and non-motor PD symptoms.

Study Impact: Non-motor features of PD, such as mild depressive symptoms, fatigue, and autonomic symptoms, are associated with subjective insomnia, whereas fatigue and dopaminergic medication dose are associated with subjective daytime sleepiness. In evaluation of PD patients who complain of insomnia or sleepiness, clinicians should explore other non-motor symptoms, in particular, as possible causes or co-morbidities.

complaints in PD, remains unclear. The main objective of this study was to examine associations of both motor and non-motor PD symptoms with reported sleep problems. We hypothesized that non-motor and motor symptoms of PD patients would each show independent association with subjective insomnia or daytime sleepiness. In a subset of patients, we also assessed the extent to which polysomnography and the multiple sleep latency test (MSLT) may help to understand sleep complaints in PD.

METHODS

Subjects

A total of 128 subjects, including 96 men and 32 women, were recruited from the Movement Disorders Clinics at the University of Michigan and the Veteran Affairs Ann Arbor Health System. Inclusion criteria included PD according to the UK Parkinson Disease Society Brain Bank Research Center clinical diagnostic criteria.⁸ Subjects' PD severity ranged, from modified Hoehn and Yahr stages 1 to 4, and brain imaging showed a typical pattern of nigrostriatal dopaminergic denervation on [¹¹C]dihydrotetrabenazine (DTBZ)-positron emission tomography (PET).⁹ Subjects were not selected on the basis of any specific sleep complaints. Among the 128 subjects, 38 (30%) volunteered to undergo nocturnal polysomnography and MSLTs. Some data from subjects who underwent sleep studies have been described previously in a report about [¹¹C]-3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile (DASB) positron emission tomography (PET) imaging.¹⁰ We recorded information on demographics, motor symptoms, medications, and comorbidities. Of the 128 subjects, 67 (52%) took carbidopa/levodopa, 11 (8%) took a dopamine agonist, 42 (33%) took a combination of carbidopa/levodopa and a dopamine agonist, and 8 (6%) subjects did not take any medication. For ≥ 2 months prior to study entry, no subjects received neuroleptics, psychostimulants, antimuscarinics, or acetylcholinesterase inhibitors. Among the 38 subjects who underwent nocturnal polysomnography, none were taking trazodone, modafinil, St. John's Wort, or bupropion. None of subjects who underwent nocturnal polysomnography were taking antidepressants, which could have interfered with tracer binding during [¹¹C]DASB PET imaging required for the parent protocol.¹⁰ During the 2 weeks prior to sleep studies, no subjects received activating or sedating medications, including benzodiazepines and antihistamines. In contrast, 19 (21%) of the 90 subjects who did not have a nocturnal polysomnography were taking an antidepressant.

Clinical Assessment

All patients were clinically evaluated by a movement disorder neurologist. A family member or caregiver provided additional information. Each subject signed a written informed consent, approved by the University of Michigan Medical School Institutional Review Board (IRBMED). Clinical information collected included assessment of disease severity with the Movement Disorder Society-sponsored revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS).¹¹ This instrument has 4 sections: Part I - non-motor experiences of daily living, Part II - motor experiences of daily living, Part III - motor examination, and Part IV - motor complications of medication. We included only parts I-III as primary independent variables in statistical analyses. Subjective measures of sleep disturbance and daytime sleepiness were assessed with the well-validated Insomnia Severity Index (ISI)¹² and Epworth Sleepiness Scale (ESS).¹³ Secondary exploratory variables included the Montreal Cognitive Assessment,¹⁴ Beck Depression Inventory,¹⁵ trait portion of the State-Trait Anxiety Inventory,¹⁶ Fatigue Severity Scale,¹⁷ Survey of Autonomic Symptoms,¹⁸ and the 39-item

Parkinson Disease Questionnaire¹⁹ (as a quality of life rating scale for Parkinson disease patients).

Sleep Evaluation

Polysomnograms included 6 electroencephalography (EEG) channels, 2 electrooculography (EOG) channels, chin and bilateral anterior tibialis surface electromyography (EMG), 2 electrocardiography (EKG) leads, nasal and oral airflow (thermocouples), nasal pressure monitoring, thoracic and abdominal excursion (uncalibrated inductance plethysmography), snoring, and finger oximetry, all in accordance with American Academy of Sleep Medicine 2007 recommendations.²⁰ Scoring also was performed according to standard guidelines²⁰ by a single, experienced registered technologist masked to results of patients' clinical assessments and measurements. A board-certified sleep specialist (R.D.C.), masked to patients' clinical data, reviewed scoring and interpreted each sleep study. The apnea-hypopnea index ([AHI] events per hour of sleep), was used to identify absence of significant obstructive sleep apnea (< 5 , no OSA), mild OSA (5 to < 15), moderate OSA (15 to < 30), and severe OSA (≥ 30). Subjects underwent polysomnography after taking their normal schedule of dopamine replacement medications. On the day following polysomnography, MSLTs were performed using only the EEG, chin EMG, EKG, and EOG channels. The test consisted of 5 nap opportunities of 20 min every 2 hours throughout the day, and followed standard guidelines.²¹

Statistical Analysis

Statistical analyses were performed with SPSS Ver. 19.0 for Windows (IBM software). Data are summarized as means $\pm$ SD. The level of significance was defined as $p < 0.05$ in 2-tailed tests for all analyses. We analyzed our data in 2 ways. First, we performed logistic regression analysis with subjective insomnia (ISI) or daytime sleepiness (ESS) as the dependent variables and parts I-III of MDS-UPDRS as the primary independent variables to test our hypothesis that non-motor and motor symptoms of PD patients show independent association with subjective insomnia and daytime sleepiness. Second, we followed a 2-step analysis approach to examine the influence of secondary measures. We performed a data reduction step by exploring which variables correlated with the subjective sleep measures using the nonparametric Spearman correlation coefficient *rho*. Significant variables were then entered into stepwise logistic regression models with subjective insomnia (ISI) or sleepiness (ESS) as the dependent variables.

RESULTS

The mean age of the 128 participants was 65.7 ± 7.6 years old (range: 50-84); 96 (75%) were men; and the mean duration of illness was 5.9 ± 4.3 years (range: 0.5-20). The mean Hoehn and Yahr stage was 2.4 ± 0.5 (range: 1-4). Mean score on the Montreal Cognitive Assessment was 25.9 ± 2.5 , and 70 (61%) of the subjects showed normal cognitive function as defined by a score ≥ 26 .¹⁴ The mean levodopa equivalent dosage of medications taken for PD was 689.2 ± 521.7 mg/day. Male and female patients showed no significant difference in age, duration of illness, Hoehn and Yahr stages, cognitive function, subjective insomnia severity, subjective daytime sleepiness, depressed

Figure 1—Frequency distribution of insomnia severity index (A) and Epworth sleepiness scale (B) scores in patients with Parkinson disease **Table 1**—Results of multivariate logistic regression analysis (n = 128)

Outcome variables	Overall model F	Explanatory variables*	B	S.E.	Odds ratio	95% CI
Insomnia Severity Index ≥ 8	F = 21.46 P < 0.01	MDS-UPDRS part I#	0.95	0.26	2.58	1.54-4.33
		MDS-UPDRS part II	0.10	0.26	1.10	0.66-1.85
		MDS-UPDRS part III	-0.20	0.23	0.82	0.52-1.29
Epworth Sleepiness Scale ≥ 10	F = 4.93 P = 0.18	MDS-UPDRS part I#	0.21	0.22	1.24	0.80-1.90
		MDS-UPDRS part II	0.10	0.24	1.10	0.68-1.77
		MDS-UPDRS part III	0.20	0.21	1.22	0.81-1.86

S.E., standard error; CI, confidence interval; MDS-UPDRS, Movement Disorder Society version of the Unified Parkinson Disease Rating Scale. #Items that ask directly about sleep problems (1.7) and daytime sleepiness (1.8) were excluded. *Explanatory variables were normalized ((x-mean)/SD), so that the associated odds ratio reflects the effect of 1 SD increase in the explanatory variable.

mood, anxiety, fatigue, and Parkinson disease-related quality of life, though scores on the Survey of Autonomic Symptoms did differ (male 4.2 ± 4.1 , female 6.1 ± 4.6 , $p = 0.03$). The distributions of ISI and ESS scores are presented in **Figure 1**.

Associations of Insomnia and Subjective Sleepiness with Motor and Non-Motor PD Symptoms

Multivariate logistic regression models showed that part I of MDS-UPDRS (non-motor symptoms) rather than parts II (motor symptoms) or III (motor examination findings) mainly contributed to subjective insomnia assessed using the ISI (**Table 1**). However, none of the MDS-UPDRS parts were significantly associated with subjective daytime sleepiness assessed using the ESS.

Associations of Insomnia and Subjective Sleepiness with Specific PD Features and Comorbidities

For the 128 subjects, insomnia severity as reflected by ISI score correlated significantly with age, levodopa equivalent dose, Beck Depression Inventory, Trait Anxiety Score, Fatigue Severity Scale, Survey of Autonomic Symptoms, 39-item Parkinson Disease Questionnaire, and parts I and II subcategories of the MDS-UPDRS (**Table 2**). Daytime sleepiness as assessed by the ESS was significantly correlated with Hoehn and Yahr stage, duration of illness, levodopa equivalent dose, Beck Depression Inventory,

trait score of State Trait Anxiety Inventory, Fatigue Severity Scale, Survey of Autonomic Symptoms, 39-item Parkinson Disease Questionnaire, and each of the 3 assessed components of the MDS-UPDRS. Subjects who were taking dopamine agonists alone ($n = 11$) and those who took levodopa alone ($n = 67$) showed no significant differences in ESS scores. The ISI and ESS scores were moderately correlated with each other.

A multivariable stepwise logistic regression model showed that Beck Depression Inventory, Survey of Autonomic Symptoms, Fatigue Severity Scale, and age each contributed statistically in an independent manner to insomnia (**Table 3**). The levodopa equivalent dose and Fatigue Severity Scale showed the closest independent associations with sleepiness.

Insomnia, Subjective Sleepiness, and Sleep Laboratory Findings

The 38 participants who volunteered to have polysomnography and MSLTs had a mean age of 64.3 ± 6.2 years; mean disease duration was 4.9 ± 3.6 years. Mean Hoehn and Yahr stage was 2.3 ± 0.4 , and 31 (81.6%) of these patients were male. There were no significant differences in these clinical characteristics or the rating scale scores (ISI, ESS, Montreal Cognitive Assessment, Beck Depression Inventory, State Trait Anxiety Inventory, Fatigue Severity Scale, Survey of Autonomic Symptoms, 39-item Parkinson Disease Questionnaire, and part I–III of

Table 2—Correlation of subjective sleep questionnaire (n = 128) and objective polysomnographic findings (n = 38) with age and measures of Parkinson disease or related symptom severity

	Sleep questionnaires (n = 128)		Polysomnography (n = 38)		MSLT (n = 38)
	ISI	ESS	Sleep latency	Sleep efficiency	Mean sleep latency (min)
	(rho)	(rho)	(rho)	(rho)	(rho)
Age	-0.25**	-0.05	-0.14	-0.06	-0.15
Hoehn & Yahr stage	0.04	0.28**	-0.13	-0.04	0.07
Duration of illness	0.16	0.23**	-0.02	-0.07	-0.17
Levodopa equivalent dose of PD medications	0.20*	0.32**	-0.15	0.08	-0.16
Insomnia Severity Index	—	0.37**	-0.05	0.01	-0.01
Epworth Sleepiness Scale	0.37**	—	-0.18	0.05	-0.23
Montreal Cognitive Assessment	0.06	-0.03	0.13	-0.31	-0.01
Beck Depression Inventory	0.49**	0.31**	-0.17	0.28	-0.19
State-Trait Anxiety Inventory (trait score)	0.28**	0.19*	0.28	-0.06	0.05
Fatigue Severity Scale	0.45**	0.37**	0.14	-0.12	-0.08
Survey of Autonomic Symptoms	0.39**	0.22*	0.40*	-0.42**	0.06
Parkinson Disease Questionnaire-39	0.41**	0.39**	0.11	0.16	-0.07
MDS-UPDRS Part I [#]	0.40**	0.29**	0.38*	-0.22	-0.08
MDS-UPDRS Part II	0.22*	0.29**	-0.1	-0.3	-0.02
MDS-UPDRS Part III	0.1	0.26**	-0.09	-0.19	0.13

ISI, insomnia severity index; ESS, Epworth sleepiness scale; MSLT, multiple sleep latency test; PD, Parkinson disease; MDS-UPDRS, Movement Disorder Society version of the Unified Parkinson Disease Rating Scale. * $p < 0.05$; ** $p < 0.01$ for Spearman correlation coefficient. [#]Items that ask directly about sleep problems (1.7) and daytime sleepiness (1.8) were excluded.

Table 3—Results of multivariate stepwise logistic regression of insomnia symptoms or sleepiness on specific Parkinson disease features and comorbidities (n = 128)

Outcome variables	Overall model F	Explanatory variables*	B	S.E.	Odds ratio	95% CI
Insomnia Severity Index ≥ 8	F = 45.66 P < 0.01	Beck Depression Inventory	0.58	0.29	1.79	1.01-3.19
		Survey of Autonomic Symptoms	0.57	0.25	1.77	1.08-2.90
		Fatigue Severity Scale	0.18	0.08	1.19	1.02-1.38
		Age	-0.49	0.23	0.61	0.39-0.96
Epworth Sleepiness Scale ≥ 10	F = 17.09 P < 0.01	Levodopa equivalent dosage of medication	0.55	0.24	1.74	1.08-2.80
		Fatigue Severity Scale	0.13	0.06	1.14	1.02-1.28

S.E., Standard error; CI, confidence interval. *Explanatory variables were normalized ((x-mean)/SD), so that the associated odds ratio reflects the effect of 1 SD increase in the explanatory variable.

MDS-UPDRS) between patients who underwent sleep studies and those who did not. **Table 4** shows the results of nocturnal polysomnography for the 38 subjects. Subjects with insomnia and without it showed no significant difference in several polysomnographic variables (**Table 4**). Similarly, subjects with and without subjective daytime sleepiness showed no significant difference on polysomnography. Objective measure of daytime sleepiness (mean sleep latency ≤ 8 min on MSLT) was significantly associated with only short nocturnal sleep latency among polysomnographic variables.

Among the 38 subjects who had polysomnography, sleep latency correlated with autonomic symptoms as assessed by the Survey of Autonomic Symptoms and part I of the MDS-UPDRS (**Table 2**). Sleep efficiency correlated with Survey of Autonomic Symptoms. Sleep efficiency was not correlated with PLM index or PLM arousal index. In addition, the mean sleep latency on the MSLT was not significantly correlated with demographic variables of subjects and various rating scales scores.

The AHI was not significantly correlated with rating scale scores or demographic variables except for body mass index (BMI, $\rho = 0.50$, $p = 0.002$). Obstructive sleep apnea (AHI ≥ 5 events per hour of sleep) was found in 28 (74%) of the subjects. The AHI suggested no OSA in 10 subjects, mild OSA in 5, moderate OSA in 12, and severe OSA in 11. No significant difference emerged in total sleep time, sleep latency, and sleep efficiency among these 4 groups. However, the AHI correlated with objective daytime sleepiness, as reflected by shorter mean sleep latency on the MSLT ($\rho = -0.47$, $p = 0.003$). Urinary problems (on the MDS-UPDRS part-I) and OSA (AHI, RDI, or mean O_2 saturation) showed no significant correlation.

DISCUSSION

This study of 128 patients with PD demonstrates that non-motor symptoms, including fatigue, depressed mood, and autonomic problems, rather than motor symptoms, are most closely

Table 4—Results of nocturnal polysomnography among subjects with and without significant insomnia or daytime sleepiness (n = 38)

	Mean $\pm$ SD (n = 38)	Range	ISI $\geq$ 8 (n = 22)	ISI < 8* (n = 16)	ESS $\geq$ 10 (n = 16)	ESS < 10* (n = 22)
Total sleep time (min)	359.3 $\pm$ 80.9	72.0-478.0	352.2 $\pm$ 79.2	347.7 $\pm$ 85.6	372.8 $\pm$ 58.4	334.0 $\pm$ 91.8
Sleep latency (min)	17.9 $\pm$ 17.8	1.5-80.0	16.8 $\pm$ 16.8	19.4 $\pm$ 19.8	15.5 $\pm$ 20.1	19.6 $\pm$ 16.2
Wake after sleep onset (min)	103.8 $\pm$ 48.4	30.0-405.5	114.8 $\pm$ 78.3	107.4 $\pm$ 54.1	101.5 $\pm$ 49.3	119.1 $\pm$ 79.8
Sleep efficiency (%)	75.0 $\pm$ 10.7	15.0-93.4	72.8 $\pm$ 16.1	74.2 $\pm$ 12.0	76.0 $\pm$ 11.1	71.5 $\pm$ 16.4
Sleep stages						
N1 (%)	22.1 $\pm$ 19.7	1.8-81.6	21.4 $\pm$ 17.8	24.8 $\pm$ 23.0	25.2 $\pm$ 21.3	21.1 $\pm$ 19.2
N2 (%)	55.6 $\pm$ 15.9	17.2-87.8	54.6 $\pm$ 14.7	55.3 $\pm$ 18.7	55.8 $\pm$ 17.7	54.3 $\pm$ 15.5
N3 (%)	6.7 $\pm$ 9.2	0.0-44.8	7.7 $\pm$ 7.8	6.2 $\pm$ 11.5	5.3 $\pm$ 5.6	8.4 $\pm$ 11.3
REM (%)	15.6 $\pm$ 7.9	0.0-29.4	16.3 $\pm$ 7.9	13.7 $\pm$ 8.6	13.8 $\pm$ 8.6	16.2 $\pm$ 7.9
Apnea-hypopnea index (/h)	21.7 $\pm$ 20.6	0.4-88.5	20.1 $\pm$ 16.0	24.3 $\pm$ 25.5	22.4 $\pm$ 18.2	21.5 $\pm$ 22.1
Mean O ₂ saturation (%)	93.9 $\pm$ 1.7	90.0-97.0	93.7 $\pm$ 1.9	94.0 $\pm$ 1.5	93.9 $\pm$ 2.0	93.7 $\pm$ 1.6
Periodic limb movements index (events/h)	20.9 $\pm$ 31.5	0.0-98.5	22.4 $\pm$ 32.2	17.6 $\pm$ 30.7	9.6 $\pm$ 22.2	28.3 $\pm$ 34.9
Periodic limb movements related arousal index (events/h)	1.69 $\pm$ 3.4	0.0-16.3	2.1 $\pm$ 4.1	1.1 $\pm$ 2.0	0.7 $\pm$ 1.6	2.4 $\pm$ 4.1
Mean sleep latency in MSLTs (min)	8.4 $\pm$ 5.1	1.5-18.6	8.3 $\pm$ 5.4	8.6 $\pm$ 4.9	7.1 $\pm$ 5.0	9.4 $\pm$ 5.1

MSLTs, multiple sleep latency tests; ISI, insomnia severity index; ESS, Epworth sleepiness scale; SD standard deviation. *No differences between low and high ISI and ESS groups reached significance (T-test p-value all > 0.05).

and independently associated with reported insomnia. Younger age was also correlated with insomnia. Levodopa equivalent dose and fatigue severity showed the strongest independent associations with subjective daytime sleepiness. Surprisingly, we also found in a subsample of 38 subjects that gold-standard, sleep laboratory-based nocturnal polysomnography and MSLTs did not discriminate PD patients with subjective insomnia or daytime sleepiness from PD patients who did not report these problems.

In general, depressed mood is one of the leading causes of insomnia, and insomnia is one of core symptoms of depression. Delayed sleep onset, disrupted sleep continuity, decreased slow wave sleep, and alterations in REM sleep are often reported in patients diagnosed as having depression.²² Insomnia is reported as a risk factor for the progression of depression, suicidal ideation, and recurrence of depression. Depressed mood in PD may be associated with dopaminergic dysfunction, as dopamine agonist medication can improve depressive symptoms,²³ and depressed mood can occur after discontinuation of these agents in PD patients. However, depressed mood in PD patients is usually under-recognized, perhaps because relevant symptoms may be confused with other conditions. Depressive symptoms in PD patients should be managed as effectively as possible, only in part because this may enhance control of sleep disturbances and improve quality of life.

Autonomic dysfunction can influence the severity of insomnia in PD patients.²⁴ Autonomic dysfunction such as urinary problems and gastrointestinal symptoms could give rise to sleep complaints. Nocturia, particularly in elderly people, is often overlooked as a cause of sleep disturbance.⁴ In the current study, the ISI score was significantly correlated with urinary problems and constipation (individual items within part I of the MDS-UPDRS, data not shown). Some authors have speculated that the anatomical proximity and concomitant degeneration of

sleep and autonomic regulatory centers in the brain stem may explain this correlation.^{24,25}

We also found that the ISI score shows an independent, inverse association with age. In contrast, outside the context of PD, the prevalence of insomnia increases with age.²⁶ However, previous studies have suggested that the severity of insomnia is less affected by age than by anxiety, depression, fatigue, dysfunctional belief toward sleep, and personality.^{27,28} Parkinson symptom severity could conceivably contribute to the inverse association we identified, but in fact age correlated directly with Hoehn and Yahr stages ($\rho = 0.32$, $p < 0.0001$), part II ($\rho = 0.29$, $p = 0.001$) and part III ($\rho = 0.21$, $p = 0.02$) of the MDS-UPDRS. Among individual symptom items of MDS-UPDRS, there was no item except sleep problems ($\rho = -0.27$, $p = 0.004$) that improved with age (data not shown).

We observed that fatigue is associated with subjective insomnia in PD patients. Fatigue is a common condition in chronically ill PD patients, and the reported prevalence of fatigue in PD ranges from 33% to ~58%,²⁹ depending on its definition. Fatigue itself can decrease physical activity during the daytime in PD patients, and therefore could significantly influence the frequency and severity of insomnia. In addition, fatigue is usually associated with depressed mood, although fatigue is a symptom that should be distinguished from depressed mood. However, our cross-sectional analysis does not allow us to exclude the likely possibility that for some patients, poor nocturnal sleep augments fatigue, or that a third variable fosters both fatigue and insomnia.

In our data, fatigue was also associated with daytime sleepiness. In PD patients, daytime sleepiness and fatigue are often considered to arise from sleep disturbance, disease progression, depressive symptoms, or the presence of other comorbid illness.³⁰ In particular, medications have been suspected to contribute to insomnia or daytime sleepiness in PD patients.³¹

as dopaminergic agents can have daytime sleepiness or sudden-onset sleep attacks as an adverse effect. We observed that high doses of medications were associated with daytime sleepiness in accordance with other previous studies.^{32,33} Although daytime sleepiness followed by nocturnal sleep disturbance has a large impact on quality of life in PD, control of medication-related daytime sleepiness may not be simple because high doses of antiparkinsonian medication may be necessary to reduce severe motor symptoms.

Among our 38 PD patients who underwent nocturnal polysomnography, longer sleep latency was associated with increased autonomic symptoms and the part I subcategory of the UPDRS. We previously found, among a larger set of PD subjects (including those who had polysomnography in the current study), that the total UPDRS score correlated with sleep efficiency rather than sleep latency,¹⁰ and we believe that the difference in the sample as well as the current focus on separate UPDRS parts is likely to explain this difference. Decreased sleep efficiency was associated only with increased autonomic symptoms. In contrast, previous investigators found something that we could not confirm with objective measures, namely that PD duration was correlated with increased subjective sleep latency or decreased sleep efficiency.³⁴ In our study, subjective insomnia severity was not reflected by any polysomnographic results. Overall, our data suggest that polysomnography is useful to assess comorbid sleep disorders and OSA in particular in PD patients.³⁵ However, PSG cannot explain subjective symptoms of sleepiness and insomnia specific to PD. The MSLTs did not reflect subjective daytime sleepiness as measured by the ESS. Previous studies also have documented little or no correlation between subjective sleepiness and MSLT results,³⁶ even among PD patients.³⁷

Obstructive sleep apnea was frequently observed in our PD patients. A previous study found OSA in 43% of 49 PD patients and implicated OSA as a cause of daytime sleepiness and tiredness.³⁸ The OSA may arise in part from upper airway muscle dysfunction caused by nocturnal akinesia or dyskinesia. However, a recent report suggested that the frequency of OSA in PD is not different from that seen in the general population.³⁹ Our previous study also showed that neither serotonergic nor dopaminergic neuron degeneration play a key role in OSA among our PD patients.¹⁰ In the current study, the variables that predicted the apnea-hypopnea index in PD patients were BMI and objective daytime sleepiness, rather than motor or non-motor symptoms of PD. Our findings support the lack of direct association between OSA and disease status or progression in PD patients.

Several limitations in this study should be considered. First, objective sleep measures including nocturnal polysomnography and daytime MSLTs were obtained for only 30% of the subjects, though those who volunteered for these studies did not differ from remaining subjects on key PD or sleep measures. Second, Hoehn and Yahr scores of the subjects in this study suggested early to moderate PD, when motor symptoms may not yet have made a large contribution to insomnia or daytime sleepiness. Third, our data on depression and ability to discern its association with sleep problems may have been limited by use of antidepressants among 19 (21%) of the 90 subjects who did not have sleep studies. However, Beck Depression Inventory

scores were higher (not lower) among patients who took antidepressants than among those who did not ($p = 0.03$, data not shown). Fourth, the MDS-UPDRS part II does not capture all motor issues related to sleep. For example, nocturnal and early morning dystonia are not addressed, though limitations to turning in bed and getting out of bed are addressed. Perhaps most importantly, our study was cross-sectional, and results cannot be used to confirm cause-and-effect relationships.

We did observe that non-motor features such as mild depressive symptoms, fatigue, and autonomic symptoms are associated with insomnia ratings among PD patients, whereas fatigue and dopaminergic medication dose are associated with subjective sleepiness. Our findings suggest that clinicians should pay particular attention to uncontrolled non-motor features as potential causes or results of insomnia or daytime sleepiness among patients diagnosed with Parkinson disease. Subjective rating scales may be useful to assess routinely for insomnia and daytime sleepiness in PD patients, and laboratory-based sleep studies may be informative when evaluation for OSA and associated, objective daytime sleepiness is desired.

REFERENCES

1. Tandberg E, Larsen JP, Karlsen K. A community-based study of sleep disorders in patients with Parkinson's disease. *Mov Disord* 1998;13:895-9.
2. Lees AJ, Blackburn NA, Campbell VL. The nighttime problems of Parkinson's disease. *Clin Neuropharmacol* 1988;11:512-9.
3. Louter M, Munneke M, Bloem BR, Overeem S. Nocturnal hypokinesia and sleep quality in Parkinson's disease. *J Am Geriatr Soc* 2012;60:1104-8.
4. Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. Nocturia and disturbed sleep in the elderly. *Sleep Med* 2009;10:540-8.
5. Zesiewicz TA, Gold M, Chari G, Hauser RA. Current issues in depression in Parkinson's disease. *Am J Geriatr Psychiatry* 1999;7:110-8.
6. Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 2008;23:183-9; quiz 313.
7. Borek LL, Kohn R, Friedman JH. Mood and sleep in Parkinson's disease. *J Clin Psychiatry* 2006;67:958-63.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181-4.
9. Bohnen NI, Albin RL, Koeppe RA, et al. Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson disease. *J Cereb Blood Flow Metab* 2006;26:1198-212.
10. Lelieveld IM, Muller ML, Bohnen NI, et al. The role of serotonin in sleep disordered breathing associated with Parkinson disease: a correlative [(11)C] DASB PET imaging study. *PLoS One* 2012;7:e40166.
11. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23:2129-70.
12. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297-307.
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-5.
14. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695-9.
15. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996;67:588-97.
16. Spielberger C. State-Trait Anxiety Inventory for Adults: Mindgarden Inc., 2008.
17. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121-3.
18. Zilliox L, Peltier AC, Wren PA, et al. Assessing autonomic dysfunction in early diabetic neuropathy: the Survey of Autonomic Symptoms. *Neurology* 2011;76:1099-105.

19. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 1997;26:353-7.
20. Iber C, Ancoli-Israel S, Chesson A, Quan S. *The AASM manual of the scoring of sleep and associated events: rules, terminology and technical specifications*. Westchester, IL: American Academy of Sleep Medicine, 2007.
21. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113-21.
22. Fleming J. Sleep architecture changes in depression: interesting finding or clinically useful. *Prog Neuropsychopharmacol Biol Psychiatry* 1989;13:419-29.
23. Leentjens AF, Koester J, Fruh B, Shephard DT, Barone P, Houben JJ. The effect of pramipexole on mood and motivational symptoms in Parkinson's disease: a meta-analysis of placebo-controlled studies. *Clin Ther* 2009;31:89-98.
24. Tijero B, Somme J, Gomez-Esteban JC, et al. Relationship between sleep and dysautonomic symptoms assessed by self-report scales. *Mov Disord* 2011;26:1967-8.
25. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
26. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
27. Park JH, An H, Jang ES, Chung S. The influence of personality and dysfunctional sleep-related cognitions on the severity of insomnia. *Psychiatry Res* 2012;197:275-9.
28. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601-8.
29. Beiske AG, Svensson E. Fatigue in Parkinson's disease: a short update. *Acta Neurol Scand Suppl* 2010;78-81.
30. Schapira AH. Excessive daytime sleepiness in Parkinson's disease. *Neurology* 2004;63:S24-7.
31. Happe S, Berger K. The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease—a prospective study. *J Neurol* 2001;248:1062-7.
32. Poryazova R, Benninger D, Waldvogel D, Bassetti CL. Excessive daytime sleepiness in Parkinson's disease: characteristics and determinants. *Eur Neurol* 2010;63:129-35.
33. Verbaan D, van Rooden SM, Visser M, Marinus J, van Hilten JJ. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. *Mov Disord* 2008;23:35-41.
34. Diederich NJ, Vaillant M, Mancuso G, Lyen P, Tiete J. Progressive sleep 'destructuring' in Parkinson's disease. A polysomnographic study in 46 patients. *Sleep Med* 2005;6:313-8.
35. Cronlein T, Geisler P, Langguth B, et al. Polysomnography reveals unexpectedly high rates of organic sleep disorders in patients with prediagnosed primary insomnia. *Sleep Breath* 2012;16:1097-103.
36. Chervin RD, Aldrich MS. The Epworth Sleepiness Scale may not reflect objective measures of sleepiness or sleep apnea. *Neurology* 1999;52:125-31.
37. Shpirer I, Miniovitz A, Klein C, et al. Excessive daytime sleepiness in patients with Parkinson's disease: a polysomnography study. *Mov Disord* 2006;21:1432-8.
38. Diederich NJ, Vaillant M, Leischen M, et al. Sleep apnea syndrome in Parkinson's disease. A case-control study in 49 patients. *Mov Disord* 2005;20:1413-8.
39. Trotti LM, Bliwise DL. No increased risk of obstructive sleep apnea in Parkinson's disease. *Mov Disord* 2010;25:2246-9.

ACKNOWLEDGMENTS

The authors thank C. Minderovic for expert assistance with execution of this protocol.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication April, 2013

Submitted in final revised form June, 2013

Accepted for publication July, 2013

Address correspondence to: Seockhoon Chung, M.D., Ph.D., Michael S. Aldrich Sleep Disorders Laboratory, University of Michigan Health System, C728 Med Inn Bldg. 1500 E Medical Center Dr., Ann Arbor, MI 48109-5845; Tel: (734) 647-9064; Fax: (734) 647-9065; E-mail: chung@amc.seoul.kr

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Chung is supported by University of Ulsan College of Medicine and Asan Medical Center in South Korea. Dr. Bohnen has received funding from the NIH, Department of Veterans Affairs, and the Michael J. Fox Foundation. Dr. Albin receives research support from the NIH, Department of Veterans Affairs, and the Cure Huntington Disease Initiative. He served on DSMBs for the HORIZON and QE3 trials. He receives reimbursement for medical-legal consulting. Dr. Frey has received support from the NIH and General Electric (GE Healthcare). He is a consultant to AVID Radiopharmaceuticals (a subsidiary of Eli Lilly & Co), Bayer-Schering pharmaceuticals and MIM Software. He holds common stock in Bristol-Myers Squibb, General Electric, Johnson & Johnson and Novo Nordisk. Dr. Müller has received support from the NIH and Department of Veterans Affairs. Dr. Chervin has received support from the NIH, the University of Michigan Health System, Respiroics, and Fisher Paykel. He receives honoraria from the American Academy of Sleep Medicine and UpToDate.