Sleepiness and Depression in Parkinson's Disease Patients Treated with Ropinirole and Levodopa

Suk Yun Kang,¹ Ho-Sung Ryu,² Mun-Kyung Sunwoo,³ Sang-Jin Kim,⁴ Jong-Sam Baik,⁵ Mee-Young Park,⁶ Hyung-Eun Park,⁷ Joong-Seok Kim,⁷ Kyum-Yil Kwon,⁸ Seong-Beom Koh,⁹ Young-Eun Kim,¹⁰ Mi-Kyong Lee,¹¹ Jong-Min Kim,¹¹ Sun Ju Chung,² Young-Ho Sohn¹²

¹Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Korea
²Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
³Department of Neurology, Bundang Jeesaeng General Hospital, Seongnam, Korea
⁴Department of Neurology, Inje University College of Medicine, Busan, Korea
⁵Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea
⁶Department of Neurology, Yeungnam University Medical Center, Daegu, Korea
⁷Department of Neurology Seoul St. Mary’s Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
⁸Department of Neurology, Soonchunhyang University Seoul St. Mary's Hospital, Soonchunhyang University School of Medicine, Seoul, Korea
⁹Department of Neurology, Korea University College of Medicine, Korea University Guro Hospital, Seoul, Korea
¹⁰Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea
¹¹Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
¹²Department of Neurology, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Objective: We aimed to investigate the effect of ropinirole on excessive daytime sleepiness (EDS) and depression in Parkinson's disease (PD) with a large population.

Methods: We conducted a cross-sectional observational study at nine hospitals in Korea between April 24, 2013, and April 22, 2015. We analyzed the demographic and clinical features, other medical history, history of antiparkinsonian medication within 6 months, Hoehn and Yahr stage (HY stage), Unified Parkinson's Disease Rating Scale (UPDRS) part II and III, Epworth Sleepiness Scale (ESS), and 30-item Geriatric Depression Scale (GDS-30).

Results: Four-hundred-thirteen patients with PD (mean age: 65.2 ± 9.0 years; men: 227 patients) were analyzed. Multivariate logistic regression analysis showed that age at examination, UPDRS II, and GDS-30 were independent risk factors for EDS and that sex, UPDRS II, and ESS were independent risk factors for depression.

Conclusion: Our large group study did not find any significant associations of ropinirole with EDS and depression in Korean PD patients.

Key Words: Parkinson's disease; ropinirole; levodopa; sleepiness; mood; excessive daytime sleepiness; depression.
study showed that EDS is related to low doses of levodopa and high doses of DA.\(^4,5\) Ropinirole, a DA, has also been suggested to be associated with EDS,\(^6\) but there are conflicting results.\(^7-11\)

Clinically significant depressive symptoms have been reported in 35% of PD patients.\(^2\) Depression is common and even precedes the onset of motor manifestation by many years.\(^12\) The serotonergic and/or noradrenergic system is known to be important in the pathogenesis of depression. In addition, the dopaminergic system may also play a role in the development of depression in PD.\(^12\) Depression is improved by dopaminergic medication, and depressive symptoms appear as medication wears off.\(^13\) It has been reported that ropinirole improves depressive symptoms,\(^8,10\) but there is still not enough evidence to support these findings.

Therefore, the aim of this study was to evaluate the effect of ropinirole on EDS and depression in PD patients. We also analyzed the effect of ropinirole on EDS through stratification of dopaminergic medication.

### MATERIALS & METHODS

**Study design**

This was a cross-sectional observational study conducted at nine hospitals in Korea between April 24, 2013, and April 22, 2015. Participants were evaluated during one visit. We collected their demographic and clinical features, other medical history, history of antiparkinsonian medication within 6 months, Hoehn and Yahr stage (HY stage), and scores on the Unified Parkinson’s Disease Rating Scale (UPDRS) part II and III, Epworth Sleepiness Scale (ESS), and 30-item Geriatric Depression Scale (GDS-30). Patients with an ESS score > 10 were classified as having EDS. Patients with GDS-30 > 17 were classified as having depression. Levodopa equivalent daily doses (LEDD) were calculated according to the usual formula.\(^13\)

**Patients**

The inclusion criteria were 1) diagnosis of idiopathic PD as defined by the UK Parkinson’s Disease Society Brain Bank Criteria;\(^14\) 2) patients who had taken antiparkinsonian medications, including ropinirole and levodopa, for more than six months at the time of enrollment; and 3) no changes of the doses of ropinirole and levodopa for more than one month at the time of enrollment. The exclusion criteria were 1) Alzheimer’s dementia and Vascular dementia, clinically diagnosed using the Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria; 2) patients who participated in other clinical trials at the time of enrollment; 3) chronic use of a sedative; 4) history of alcohol abuse; 5) severe comorbid disorders that can affect sleep (i.e., chronic obstructive pulmonary disease, ischemic heart disease, stroke, and painful joint disease, etc.); and 6) having taken pramipexole or other DAs (rotigotine, bromocriptine) within six months of the time of enrollment.

**Standard protocol approvals, registrations, and patient consents**

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. This study protocol was approved by the Institutional Review Board of all nine centers (IRB No. 2013-007). All participants provided written, informed consent prior to enrollment.

**Statistical analysis**

Data are expressed as the means ± standard deviation. Measurements were compared between patients with EDS and without EDS. Measurements were compared between patients with depression and without depression. For univariate analysis, we used the independent t-test and chi-square test. Multivariate logistic regression with the use of backward elimination was performed on variables that were associated with \(p < 0.20\) according to univariate logistic regression. We chose \(p = 0.20\) as the threshold of significance in multivariate analysis as suggested elsewhere as an appropriate threshold.\(^15\) Because the ranges of the total LEDD were very wide, we thought that it might be a bias for the comparison. Therefore, we classified patients into three groups according to the total LEDD, less than the 32nd percentile; 33rd to 66th percentile; and greater than the 67th percentile, and compared the dosage of ropinirole between patients without and with EDS in each group. All statistical analyses were performed using SAS Proprietary Software 9.4 (SAS Institute, Inc., Cary, NC, USA). Values of \(p < 0.05\) were regarded as significant.

**RESULTS**

Four-hundred-thirteen of 426 patients who provided informed consent were enrolled. Thirteen
patients were excluded; 12 patients did not meet the inclusion criteria, and the other patient’s ESS was missing. The demographic and clinical features are summarized in Table 1.

Comparison between patients without and with EDS

Patients with EDS were more likely to be men, had higher UPDRS II & III scores, have more frequent motor fluctuation and dyskinesia, and have more severe depression. There was a significant difference in the laterality of motor symptoms at the time of evaluation. In patients with EDS, the larger proportion of lateralized motor symptoms occurred on the left side. There was no significant difference of the total LEDD between patients without EDS and with EDS. Moreover, there was no significant difference of the levodopa and ropinirole doses (Table 2).

Multivariate logistic regression analysis revealed that age at examination, UPDRS II, and depression were independent risk factors for EDS. Total LEDD, levodopa and ropinirole doses were not associated with EDS (Table 3).

Comparison between patients without and with depression

Patients with depression were more likely to be women; had a higher HY stage as well as UPDRS II and UPDRS III scores; had more severe ESS; and had a higher GDS-30 score. Total LEDD, levodopa dose, and ropinirole dose were not different between patients without and with depression (Table 4).

Multivariate logistic regression analysis showed that sex, UPDRS II, and ESS were independently associated with depression. Total LEDD, levodopa dose, and ropinirole dose were not significant risk factors (Table 5).

Comparison of the ropinirole dose between patients without and with EDS after total LEDD stratification

Four-hundred-thirteen patients were divided into three groups according to the percentiles of total LEDD. There were larger doses of ropinirole in patients with EDS than in patients without EDS in the lowest 33rd percentile group \( (p = 0.009) \). In the other groups, the ropinirole dose was not significantly different between patients without and with EDS (Table 6).

Table 2. Comparison of Parkinson’s disease patients without and with EDS

| Variables                      | Without EDS \( (n = 288) \) | With EDS \( (n = 125) \) | p value |
|--------------------------------|-------------------------------|--------------------------|---------|
| Age, years                     | 65.7 ± 8.9                    | 64.1 ± 9.1               | 0.1167  |
| Men, n (%)                     | 147 (51.0)                    | 80 (64.0)                | 0.0150  |
| HY stage\*                     | 2.2 ± 0.7                     | 2.3 ± 0.8                | 0.1935  |
| UPDRS II\*                     | 7.6 ± 5.2                     | 11.0 ± 6.6               | < 0.0001|
| UPDRS III\*                    | 18.9 ± 10.4                   | 21.9 ± 11.2              | 0.0080  |
| Motor fluctuation, n (%)       | 60 (20.8)                     | 48 (38.4)                | 0.0002  |
| Dyskinesia, n (%)              | 90 (31.3)                     | 53 (42.4)                | 0.0287  |
| ESS                            | 5.5 ± 2.8                     | 15.1 ± 3.7               | < 0.0001|
| GDS-30\‡                       | 11.1 ± 7.0                    | 13.7 ± 7.8               | 0.0020  |
| Laterality\#, n (%)            | 153 (37.5)                    | 47 (38.5)                | 0.0024  |
| Right                          | 77 (26.9)                     | 50 (41.0)                |         |
| Left                           | 127 (31.1)                    | 25 (20.5)                |         |
| Symmetric                      | 103 (36.0)                    | 25 (20.5)                |         |
| Total LEDD                     | 829.2 ± 378.7                 | 853.3 ± 390.7            | 0.4060  |
| Levodopa                       | 481.2 ± 254.6                 | 504.0 ± 276.5            | 0.4150  |
| Ropinirole\§                   | 8.2 ± 5.7                     | 8.9 ± 4.9                | 0.2240  |

Table 3. Demographics and clinical features of 413 patients with Parkinson’s disease

| Variables                      | Patients \( n = 413 \) |
|--------------------------------|-------------------------|
| Age, years                     | 65.2 ± 9.0              |
| Men, n (%)                     | 227 (55.0)              |
| HY stage\*                     | 2.2 ± 0.7               |
| UPDRS II\*                     | 8.6 ± 5.8               |
| UPDRS III\*                    | 19.8 ± 10.7             |
| Motor fluctuation, n (%)       | 108 (26.2)              |
| Dyskinesia, n (%)              | 143 (34.6)              |
| ESS                            | 8.4 ± 5.4               |
| GDS-30\‡                       | 11.9 ± 7.3              |
| Laterality\#, n (%)            | 153 (37.5)              |
| Right                          | 127 (31.1)              |
| Left                           | 128 (31.4)              |
| Total LEDD                     | 829.5 ± 388.2           |
| Levodopa                       | 488.1 ± 261.3           |
| Ropinirole\§                   | 8.4 ± 5.5               |

*data missing from two patients, †data missing from seven patients, §data missing from one patient, ¶data missing from six patients, ‡data missing from five patients, §the mean value of ropinirole is presented as LEDD. HY stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson’s Disease Rating Scale, ESS: Epworth Sleepiness Scale, GDS-30: 30-item Geriatric Depression Scale, LEDD: levodopa equivalent daily dose.
DISCUSSION

This observational study did not find any influence of ropinirole on EDS and depression in Korean PD patients. Younger age at visit, lower activities of daily life (ADL), and depression were independent risk factors for EDS. Women, lower ADL and EDS were independent risk factors for depression.

The relationship between DAs and EDS has been controversial. In 1999, sleep attacks of ropinirole and pramipexole were first introduced, but later, other studies showed that there was no difference among DAs where EDS was concerned. It was suggested that total LEDD, rather than specific DAs, might be more important in the pathogenesis of EDS. The opposite results were also reported. There was no correlation found between total LEDD and EDS, and a higher levodopa dose was associated with greater vigilance. In our study, the total LEDD, levodopa dose, and ropinirole dose were not associated with EDS. We do not know the exact reason why these results are contradictory. Heterogeneous populations among studies might be a reason. A variety of clinical features may affect EDS in PD. In addition to DA

Table 3. Excessive daytime sleepiness; univariate and multivariate logistic regression analyses

| Variables          | Univariate       | Multivariate     |
|--------------------|------------------|------------------|
| Age                | 0.1173           | 0.025            |
| Sex (men)          | 0.0155           | 0.075            |
| HY stage           | 0.1680           | 0.002            |
| UPDRS II           | <0.0001          | 0.055            |
| UPDRS III          | 0.0090           | 0.055            |
| Motor fluctuation  | 0.0002           | 0.055            |
| Dyskinesia         | 0.0233           | 0.055            |
| GDS-30             | 0.0020           | 0.055            |
| Laterality         | 0.1306           | 0.051            |
| Symmetric          | 0.0336           | 0.051            |
| Total LEDD         | 0.4050           | 0.051            |
| Levodopa           | 0.4150           | 0.051            |
| Ropinirole         | 0.2250           | 0.051            |

HY stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson’s Disease Rating Scale, GDS-30: 30-item Geriatric Depression Scale, LEDD: levodopa equivalent daily dose, OR: odds ratio, CI: confidence interval.

Table 4. Comparison of Parkinson’s disease patients without and with depression

| Variables          | Without depression (n = 310) | With depression (n = 97) | p value |
|--------------------|------------------------------|--------------------------|---------|
| Age, years         | 63.1 ± 9.0                   | 66.6 ± 9.3               | 0.6280  |
| Men, n (%)         | 180 (58.1)                   | 42 (43.3)                | 0.0110  |
| HY stage*          | 2.2 ± 7.0                    | 2.4 ± 7.1                | 0.0170  |
| UPDRS II           | 7.6 ± 4.9                    | 11.8 ± 7.1               | <0.0001 |
| UPDRS III          | 19.1 ± 10.6                  | 22.1 ± 11.2              | 0.0160  |
| Motor fluctuation, n (%) | 77 (24.8)                 | 29 (29.9)                | 0.3220  |
| Dyskinesia, n (%)  | 102 (32.9)                   | 39 (40.2)                | 0.1870  |
| ESS                | 7.7 ± 5.2                    | 10.6 ± 5.6               | <0.0001 |
| GDS-30             | 8.6 ± 4.7                    | 22.4 ± 2.9               | <0.0001 |
| Laterality*, n (%) |                              |                          | 0.4520  |
| Right              | 119 (38.6)                   | 33 (34.7)                |         |
| Left               | 96 (31.3)                    | 27 (28.4)                |         |
| Symmetric          | 92 (30.0)                    | 35 (36.8)                |         |
| Total LEDD         | 820.8 ± 392.1                | 847.7 ± 356.7            | 0.5460  |
| Levodopa           | 482.6 ± 266.6                | 493.6 ± 246.2            | 0.7190  |
| Ropinirole*        | 8.4 ± 5.4                    | 8.7 ± 6.0                | 0.5860  |

*data missing from one patient with depression, †data missing from seven patients (one without depression, the other with depression), ‡data missing from one in patients without depression, ††data missing from five patients (three without depression, the other with depression), the mean value of ropinirole is presented as LEDD. HY stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson’s Disease Rating Scale, ESS: Epworth Sleepiness Scale, GDS-30: 30-item Geriatric Depression Scale, LEDD: levodopa equivalent daily dose.
use, age, gender, disease severity, poor nighttime sleep, cognition, hallucination, dyskinesia, antihypertensive medications, body mass index, and pain are associated with higher EDS.

In our study, younger age, poorer ADL, and higher GDS-30 were associated with higher EDS. It is not clear whether depression is a risk factor. In our study, depression was a risk factor for EDS, but other studies reached inconsistent conclusion. One study reported that depression was correlated with severe EDS, but another study reported that depression was correlated with less EDS. A different study showed that there was no association between depression and EDS. Another possible reason was suggested: a non-dopaminergic system might be more responsible for EDS. In an animal study, dopamine and serotonin played roles in the regulation of sleep and waking. Therefore, studies with more comprehensive clinical features (i.e., fatigue) are needed to understand EDS.

One possible interesting finding of our study is that patients who displayed EDS had taken a larger dose of ropinirole in the lowest 33rd percentile group of total LEDD (Table 6). Considering that most patients in the lowest 33rd percentile group of total LEDD may be early PD, this observation suggests that close attention might be needed when starting ropinirole in early PD.

We did not find any effect of dopaminergic medication on depression. Only gender, ADL and EDS were risk factors for depression in PD. DAs may alleviate depressive symptoms in PD. Pramipexole is known to have a direct antidepressant effect. It seems that there is not sufficient evidence for the effect of ropinirole, although it has been shown to lead to some improvement of depression in various disorders, including PD.

| Table 5. Depression, univariate and multivariate logistic regression analysis |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Variables                    | Univariate | | | Multivariate | |
|                              | p value    | OR   | 95% CI    | p value    | OR   | 95% CI    |
| Age                          | 0.6270     | 1.006 | 0.981–1.032 | 0.0003     | 0.383 | 0.228–0.644 |
| Sex (men)                    | 0.0110     | 0.552 | 0.348–0.874 | 0.0120     | 0.793 | 0.571–1.111 |
| HY stage                     | 0.0180     | 1.489 | 1.071–2.071 | < 0.0001   | 1.129 | 1.079–1.182 |
| UPDRS II                     | < 0.0001   | 1.133 | 1.085–1.183 | < 0.0001   | 1.129 | 1.079–1.182 |
| UPDRS III                    | 0.0170     | 1.026 | 1.005–1.047 | 0.3230     | 1.290 | 0.779–2.139 |
| Motor fluctuation            | 0.3230     | 1.290 | 0.779–2.139 | 0.1880     | 1.371 | 0.857–2.194 |
| Dyskinesia                   | 0.8180     | 1.371 | 0.857–2.194 | 0.0001     | 1.099 | 1.054–1.145 |
| ESS                          | < 0.0001   | 1.099 | 1.054–1.145 | 0.0002     | 1.092 | 1.043–1.143 |
| Laterality                   |            |      |            |            |      |            |
| Left                         | 0.9620     | 1.014 | 0.571–1.803 |            |      |            |
| Symmetric                    | 0.2580     | 1.372 | 0.793–2.373 |            |      |            |
| Total LEDD                   | 0.5460     | 1.000 | 1.000–1.001 |            |      |            |
| Levodopa                     | 0.7180     | 1.000 | 0.999–1.001 |            |      |            |
| Ropinirole                   | 0.5850     | 1.011 | 0.971–1.053 |            |      |            |

HY stage: Hoehn and Yahr stage, UPDRS: Unified Parkinson’s Disease Rating Scale, ESS: Epworth Sleepiness Scale, LEDD: levodopa equivalent daily dose, OR: odds ratio, CI: confidence interval.

| Table 6. Comparison of the ropinirole dose between Parkinson’s disease without and with EDS (following total LEDD stratification*) |
|-------------------------------------------------------------------------------------------------------------------------|
| Without EDS (n = 288) | With EDS (n = 125) | p value |
|------------------------|--------------------|---------|
| Group 1                |                    | 0.009   |
| Cases                  | 96                 | 41      |
| Ropinirole (mg/d)      | 5.5 ± 3.4          | 7.2 ± 3.8 |
| Group 2                |                    | 0.343   |
| Cases                  | 102                | 36      |
| Ropinirole (mg/d)      | 8.0 ± 5.2          | 8.9 ± 5.0 |
| Group 3                |                    | 0.357   |
| Cases                  | 90                 | 48      |
| Ropinirole (mg/d)      | 11.4 ± 6.5         | 10.4 ± 5.2 |

*groups were divided into three percentile categories of total LEDD: group 1 (n = 137, 487.2 ± 127.3 mg/d); group 2 (n = 138, 845.3 ± 109.6 mg/d); group 3 (n = 138, 1510.5 ± 444.9 mg/d). EDS: excessive daytime sleepiness, LEDD: levodopa equivalent daily dose.
ported to be severe motor symptoms, disease duration, advanced disease stage, poor ADL, high LEDD, hallucination, sleep disturbance, dysautonomia, and dementia. Our univariate analysis results showed that there were several different factors, including advanced disease stage and severe motor symptoms, between patients without depression and with depression, but in the multivariate analysis, the independent risk factors were women, lower ADL, and higher ESS. This is noteworthy for EDS. Previous studies have reported that sleep disturbances might be a risk factor for depression, but they did not check EDS.

Our study has some limitations. First, this was an observational study. We could not determine the effect of ropinirole alone on EDS and depression because enrolled patients had taken combined anti-parkinsonian medications that included ropinirole and levodopa. Second, the demographics between PD patients without and with EDS were not matched. Although we adjusted these variables with multivariate logistic regression, these differences might be biased. Third, another sleep problem (i.e., REM sleep behavior disorder, insomnia) may affect EDS, but we did not check for other sleep problems.

**Conflicts of Interest**
The authors have no financial conflicts of interest.

**Acknowledgments**
This study was supported by GlaxoSmithKline Korea (study no.116404). We would like to thank anonymous reviewers for their valuable comments and suggestions, and Kang, Seung-Min (Dream CIS CRO) for statistical analysis.

All of the authors were investigators in this study and, as such, received research funding from GSK for the study and report no conflicts of interest.

**REFERENCES**

1. Arnulf I. Excessive daytime sleepiness in Parkinsonism. Sleep Med Rev 2005;9:185-200.
2. 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;23:183-189; quiz 313.
3. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson’s disease. Neurology 2001;57:1392-1396.
4. Blahs DL, Trotti LM, Wilson AG, Green SA, Wood-Silverio C, Juncos JF, et al. Daytime alertness in Parkinson’s disease: potentially dose-dependent, divergent effects by drug class. Mov Disord 2012;27:1118-1124.
5. Irnanzo A. Sleep in neurodegenerative diseases. Sleep Med Clin 2016;1:11-18.
6. Razmy A, Lang AE, Shapiro CM. Predictors of impaired daytime sleep and wakefulness in patients with Parkinson disease treated with older (ergot) vs newer (nonergot) dopamine agonists. Arch Neurol 2004;61:97-102.
7. Emmanu, Samii A, Takkouche B, Rochon PA. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson’s disease: a meta-analysis of randomised controlled trials. Drugs 2001;62:679-686.
8. Pacula R, Stacy MA, Factor SA, Lyons KE, Stocchi F, Hersh BP, et al. Ropinirole 24-hour prolonged release: randomised, controlled study in advanced Parkinson disease. Neurology 2007;68:1108-1115.
9. Paus S, Brecht HM, Köster J, Seeger G, Klockgether T, Wülser U. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson’s disease. Mov Disord 2003;18:659-667.
10. Rektorova I, Balaz M, Svatova J, Zarubova K, Honig I, Dostal V, et al. Effects of ropinirole on nonmotor symptoms of Parkinson disease: a prospective multicenter study. Clin Neuropharmacol 2008;31:261-266.
11. Roth T, Rye DB, Borchert LD, Bartlett C, Blahs DL, Cantor C, et al. Assessment of sleepiness and unintended sleep in Parkinson’s disease patients taking dopamine agonists. Sleep Med 2003;4:275-280.
12. Castrioto A, Thobois S, Carnicella S, Maillet A, Krack P. Emotional manifestations of PD: neurobiological basis. Mov Disord 2016;31:1103-1113.
13. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson’s disease. Mov Disord 2010;25:2649-2653.
14. Hughes AJ, Daniel SE, Kiflord L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson’s disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-184.
15. Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. Regression methods in biostatistics, linear, logistic, survival, and repeated measures models, 2nd ed. New York: Springer, 2012.
16. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908-1910.
17. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks and Parkinson’s disease treatment. Lancet 2001:7;355:1333-1334.
18. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson’s disease and sleepiness: an integral part of PD. Neurology 2002;58:1019-1024.
19. Cochen De Cock V, Bayard S, Jaussent I, Charfi M, Grini M, Langenier MC, et al. Daytime sleepiness in Parkinson’s disease: a reappraisal. PLoS One 2014;9:e107278.
20. Tholens IK, Larsen JP, Schulz J, Tysnes OB, Gjerstad MD. Development of excessive daytime sleepiness in early Parkinson disease. Neurology 2015;85:162-168.
21. Zhu K, van Hilten JJ, Marinus J. Course and risk factors for excessive daytime sleepiness in Parkinson’s disease. Parkinsonism Relat Disord 2016;24:34-40.
22. Hoglund A, Broman JE, Pålham S, Fredrikson S, Hagell P. Is excessive daytime sleepiness a separate manifestation in Parkinson’s disease? Acta Neurol Scand 2015;132:97-104.
23. Ataide M, Franco CM, Lins OG. Daytime sleepiness in Parkinson’s disease: perception, influence of drugs, and mood disorder. Sleep Disord 2014;2014:59713.
24. Távora DG, de Bruin VM, Lopes Gama R, Lopes EM, Jorge IF, de Bruin PE. The nature of excessive sleepiness and sudden sleep onset in Parkinson’s disease. Sleep Sci 2014;7:13-18.
25. Monti JM, Jantos H. The roles of dopamine and serotonin,
and of their receptors, in regulating sleep and waking. Prog Brain Res 2008;172:625-646.

26. Kang SY, Ma HI, Lim YM, Hwang SH, Kim YJ. Fatigue in drug-naïve Parkinson’s disease. Eur Neurol 2013;70:59-64.

27. Barone P, Poewe W, Albrecht S, Debieuvre C, Massey D, Rascol O, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson’s disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:573-580.

28. Smith KM, Eyal E, Weintraub D; ADAGIO Investigators. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. JAMA Neurol 2015;72:88-95.

29. Thobois S, Lhomme E, Klinger H, Ardouin C, Schmitt E, Bichon A, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain 2013;136:1568-1577.

30. Benes H, Mattern W, Peglau I, Dreykluft T, Bergmann L, Hansen C, et al. Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study. J Neurol 2011;258:1046-1054.

31. Cassano P, Lattanzi L, Fava M, Navari S, Battistini G, Abelli M, et al. Ropinirole in treatment-resistant depression: a 16-week pilot study. Can J Psychiatry 2005;50:357-360.

32. Kvernmo T, Hårtter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. Clin Ther 2006;28:1065-1078.

33. Leentjens AF, Moonen AF, Dujardin K, Marsh L, Martinez-Martín P, Richard IH, et al. Modeling depression in Parkinson disease: disease-specific and nonspecific risk factors. Neurology 2013;81:1036-1043.

34. Riedel O, Heuser I, Klotsche J, Dodel R, Wittchen HU; GEPAD Study Group. Occurrence risk and structure of depression in Parkinson disease with and without dementia: results from the GEPAD Study. J Geriatr Psychiatry Neurol 2010;23:27-34.

35. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Risk of incident depression in patients with Parkinson disease in the UK. Eur J Neurol 2011;18:448-453.

36. Dissanayaka NN, Sellbach A, Silburn PA, O’Sullivan JD, Marsh R, Mellick GD. Factors associated with depression in Parkinson’s disease. J Affect Disord 2011;132:82-88.