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# The Effect of Rotigotine on Cognitive Function, Daytime Sleepiness, and Sleep Problems in Parkinson Disease: An Open-Label Pilot Study

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**Background:** We hypothesized that rotigotine may have a positive effect on cognitive function in patients with Parkinson disease (PD) by improving daytime motor function and sleep status.

**Methods:** Fifteen PD patients with sleep disturbances, defined as a PD Sleep Scale (PDSS)-2 score of 15 or greater, were included in this single-center, 3-month open-label study. Participants received 2 to 4 mg/24 h (patch content: 4.5–9 mg) rotigotine for a 3-month period. At baseline and 3 months, the patients were evaluated on the Movement Disorder Society Revision of the Unified PD Rating Scale (MDS-UPDRS) parts III and IV and cognitive assessments, such as the Mini-Mental State Examination, frontal assessment battery, and Montreal Cognitive Assessment (MoCA). The Epworth Sleepiness Scale (ESS) and PDSS-2 were administered at baseline and at 1, 2, and 3 months.

**Results:** At 3 months, the MDS-UPDRS part III ( $-11.1$ ,  $P < 0.0001$ ) and MDS-UPDRS part IV ( $-1.1$ ,  $P = 0.0013$ ) scores significantly decreased, and off time significantly decreased ( $-34.6$  minutes,  $P = 0.0085$ ) from baseline. The PDSS-2 scores significantly decreased from baseline at 1 month ( $-4.2$ ,  $P < 0.01$ ), 2 months ( $-7.7$ ,  $P < 0.0001$ ), and 3 months ( $-7.3$ ,  $P < 0.0001$ ). The ESS also decreased at 1 month ( $-2.5$ ,  $P < 0.05$ ) and 3 months from baseline ( $-4.5$ ,  $P < 0.01$ ). The MoCA scores ( $1.6$ ,  $P = 0.0029$ ) significantly improved, but the Mini-Mental State Examination or frontal assessment battery scores did not significantly change. The mean changes from baseline to 3 months in the MoCA were negatively correlated with mean changes in the ESS scores.

**Conclusions:** We suggest that rotigotine could improve cognitive function by improving motor symptoms, sleep disturbance, and daytime sleepiness in patients with PD.

**Key Words:** Parkinson disease, rotigotine, sleep disturbances, cognitive function, motor symptoms

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Parkinson disease (PD) is characterized not only by classic motor signs due to degeneration of nigrostriatal dopaminergic neurons but also by high rates of nonmotor symptoms, including

sleep disorders, cognitive impairment, depression, and autonomic symptoms, due to impairments in nondopaminergic systems such as noradrenergic, serotonergic, and cholinergic systems.<sup>1</sup> At the onset of motor symptoms, dopaminergic neurons in the midbrain substantia nigra are decreased by 60%, and dopamine content in the striatum is reduced by 80%.<sup>2</sup> Therefore, dopamine replacement treatment with dopamine receptor agonists and levodopa is the mainstay of treatment for motor symptoms of PD. On the other hand, available treatment for nonmotor symptoms, such as sleep disturbances and cognitive impairment, is still limited.<sup>1</sup>

Rotigotine is a 24-hour long-acting transdermal dopamine agonist that is effective in improving motor symptoms and wearing-off phenomena. It is commonly used in combination with levodopa and has been reported to be effective in PD patients younger than 70 years<sup>3</sup> as well as in advanced-stage PD.<sup>4</sup> In a double-blind, placebo-controlled trial (dose titration period of 1–8 weeks and maintenance period of 4 weeks), rotigotine improved motor symptoms and sleep disturbances as evaluated by the PD Sleep Scale (PDSS)-2,<sup>5</sup> and improvements in sleep disturbances lasted for 43 weeks following the long-term open trial.<sup>6</sup> In a study using axial inertial sensors, rotigotine improved nocturnal immobility and difficulty turning in bed in PD patients.<sup>7</sup> In addition, rotigotine has been reported to be effective for pain,<sup>8</sup> restless legs syndrome, and nocturia.<sup>6</sup> A multicenter, observational, retrospective study using nonmotor symptom questionnaires reported that rotigotine treatment improved sleep and mood/cognition domains after 6 months.<sup>9</sup> However, few studies have evaluated cognitive function in detail before and after the administration of rotigotine.

We hypothesized that rotigotine would have a positive effect on cognitive function by improving daytime motor function and sleep status due to its 24-hour sustained properties, and we designed a study to assess cognitive function and sleep status before and after rotigotine treatment in PD patients who experienced sleep disturbances.

## METHODS

We performed a single-center, 3-month open-label study between July 2018 and June 2021. The participants received 2 to 4 mg/24 hours (patch content, 4.5–9 mg) rotigotine for a 3-month period. The dose of rotigotine was increased from 2 to 4 mg/24 hours after 1 month of treatment according to the physician's judgment on motor performances and sleep problems. The inclusion criteria were PD patients who experienced sleep disturbances. Parkinson disease was diagnosed by board-certified neurologists according to the Movement Disorder Society (MDS) clinical diagnostic criteria for PD.<sup>10</sup> Excluded patients included those with atypical Parkinsonian syndrome, vascular parkinsonism, or drug-induced parkinsonism who were carefully differentiated by brain magnetic resonance imaging and neurological examination in combination with clinical markers, such as olfactory testing, dopamine transporter scan, and cardiac metaiodobenzylguanidine scintigraphy. Patients with psychosis or dementia, defined as scores of 20 or

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The relevant data are within the article, but the data sets from this study are available from the corresponding author upon reasonable request.

All authors have read and approved the final manuscript. K.S. contributed to the study design, method, data acquisition, and statistical analysis and drafted the manuscript. K.F. and H.F. were involved in the study design, method, and data acquisition. K.H. contributed to the study design, review, and supervision.

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**TABLE 1.** Patient Background at Baseline

	Patients With PD
Sex, M/F	7/8
Age, y	71.6 ± 5.7
Disease duration, y	4.6 ± 3.9
HY stage on state	2.8 ± 0.6
HY stage off state	3.3 ± 0.8
MMSE	25.6 ± 3.1
FAB	13.8 ± 2.3
MoCA	19.0 ± 2.8
MDS-UPDRS part III	41.9 ± 12.4
MDS-UPDRS part IV	2.7 ± 2.3
Off time, min	115.5 ± 128.3
PDSS-2	27.6 ± 12.6
ESS	13.7 ± 7.0
Levodopa, mg/d	316.7 ± 70.7

PD, Parkinson Disease. Data are expressed as the mean ± SD (range).

lower on the Mini-Mental State Examination (MMSE), were excluded. Disease severity was evaluated by the Hoehn and Yahr (HY) staging.<sup>11</sup> At baseline and 3 months, patients were assessed by the Japanese version of the MDS revision of the Unified PD Rating Scale (MDS-UPDRS) parts III (motor examination) and IV (motor complication),<sup>12</sup> and cognitive functions were assessed by the MMSE, frontal assessment battery (FAB), and the Montreal Cognitive Assessment (MoCA).<sup>13</sup> Motor performance was rated in the on state. The PDSS-2 was used to evaluate PD-related sleep disturbances.<sup>14</sup> All patients included in this study had sleep disturbance, defined as a PDSS-2 score of 15 or greater, which has been reported to be useful in detecting poor sleepers among patients with PD.<sup>15</sup> Nocturnal restlessness was evaluated by the sum of PDSS-2 subitems 4 and 5. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).<sup>16</sup> The ESS and PDSS-2 were administered to the patients at baseline and at 1, 2, and 3 months. This study was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of Dokkyo Medical

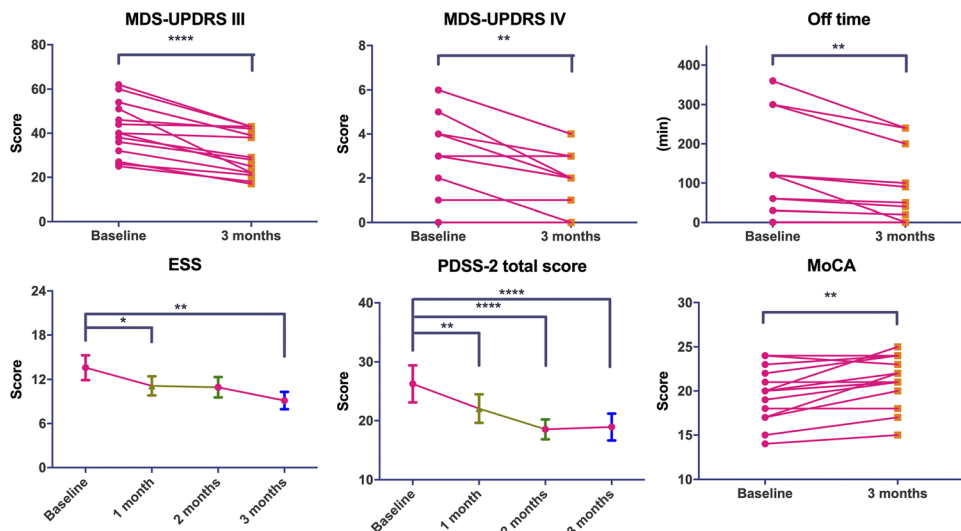
University Hospital. All participants gave written informed consent to participate in this study.

### Statistical Analysis

Paired *t* tests were used to compare the MDS-UPDRS III and IV scores, off time, and cognitive assessments (MMSE, FAB, and MoCA) at baseline and at 3 months. Repeated measures analysis of variance followed by Dunnett multiple comparison test was used to analyze differences in the PDSS-2 and ESS scores at baseline and at 1, 2, and 3 months. Spearman rank correlation was used to assess correlations between changes in the MoCA and MDS-UPDRS III, MDS-UPDRS IV, off time, PDSS-2 total score, and PDSS-2 subitems 4 and 5 from baseline to 3 months. Two-tailed *P* values less than 0.05 were considered to be statistically significant. GraphPad Prism for Mac (Version 8; GraphPad Software, San Diego) was used for statistical analyses and figure creation.

### RESULTS

Fifteen PD patients with sleep disturbances (7 M/8 F; age, 71.6 ± 5.7 years; disease duration, 4.6 ± 3.9 years) were enrolled, and all completed the study. The HY stages in the on and off states were 2.8 ± 0.6 and 3.3 ± 0.8, respectively (Table 1). At the end of the study, 9 patients (60.0%) received 2 mg/24 hours of rotigotine, and 6 received 4 mg/24 hours of rotigotine. Two were drug naive, 12 were being treated with levodopa, and 5 (33.3%) were on zonisamide at baseline. The mean levodopa dose was 316.7 ± 70.7 mg/d. At 3 months, the MDS-UPDRS part III (−11.1, *P* < 0.0001) and part IV (−1.1, *P* = 0.0013) scores were significantly decreased, and off time was significantly reduced (−34.6 minutes, *P* = 0.0085) from baseline (Fig. 1). The PDSS-2 scores significantly decreased from baseline at 1 month (−4.2, *P* < 0.01), 2 months (−7.7, *P* < 0.0001), and 3 months (−7.3, *P* < 0.0001). The ESS score also decreased at 1 month (−2.5, *P* < 0.05) and 3 months from baseline (−4.5, *P* < 0.01). Nocturnal restlessness, as measured by the PDSS-2 subitems 4 and 5, significantly improved at 2 months (−2.2, *P* < 0.0001) and 3 months (−2.3, *P* < 0.0001) from baseline. Regarding cognitive function, the MoCA scores (1.6, *P* = 0.0029) significantly improved and the MMSE scores (0.6, *P* = 0.065) tended to improve. However, the FAB scores (−0.3, *P* = 0.57) did not significantly change after rotigotine treatment.



**FIGURE 1.** Changes in the MDS-UPDRS III and IV, off time, ESS, PDSS-2 and MoCA scores after rotigotine treatment. \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001, \*\*\*\**P* < 0.0001. Error bars represent standard errors of the mean.

The mean changes from baseline to 3 months in the MoCA were significantly correlated with changes in the ESS ( $r = -0.75$ ,  $P = 0.0012$ ), but not with changes in the MDS-UPDRS III ( $r = -0.09$ ,  $P = 0.73$ ), MDS-UPDRS IV ( $r = -0.46$ ,  $P = 0.09$ ), off time ( $r = -0.39$ ,  $P = 0.15$ ), PDSS-2 ( $r = -0.29$ ,  $P = 0.29$ ), or PDSS-2 subitems 4 and 5 ( $r = 0.11$ ,  $P = 0.71$ ).

## DISCUSSION

Our study showed beneficial effects of rotigotine on motor symptoms and motor fluctuation, as with previous studies.<sup>3,4</sup> Our study included PD patients with sleep disturbances and showed significant improvements in the PDSS-2 scores after rotigotine treatment at 1, 2, and 3 months. This finding is in agreement with a previous study<sup>5</sup> and a meta-analysis of 21 articles that found efficacy with rotigotine on sleep disturbances, as evaluated by the PDSS or PDSS-2 scores.<sup>17</sup> Of note, we also observed significant decrease in the ESS scores at 1 and 3 months from baseline. Considering obvious improvement of PDSS-2 total score and nocturnal restlessness (PDSS-2 subitems 4 and 5), improvement of daytime sleepiness by rotigotine may be attributed to the improvement of nocturnal sleep problems. Daytime sleepiness is a problem associated with dopamine agonists; however, in an open study, daytime sleepiness did not increase in 13 PD patients who were switched from other dopamine agonists, such as pramipexole, cabergoline, and ropinirole, to equivalent doses of rotigotine, and the overall clinical impression was significantly improved.<sup>18</sup> Furthermore, we observed significant improvement in the MoCA scores after rotigotine treatment but not in the FAB or MMSE scores. A significant correlation found between changes in the MoCA and ESS suggests improved sleepiness may contribute to enhancement of cognitive function. The MoCA is considered a more specific and sensitive test to detect changes in cognitive function in patients with PD and is a recommended scale for screening cognitive impairment in clinical trials in patients with PD.<sup>19</sup> In contrast, Brusa et al<sup>20</sup> did not find positive effect of rotigotine or other dopamine agonists on cognitive symptoms in the early-mild PD patients. This difference may be due to difference in evaluation method of cognition (MMSE, Rey Auditory Verbal Learning Test, Trail Making Test, etc) and different patient background such as younger with shorter duration than our study.

Sleep is important in memory consolidation, and changes in sleep quality and architecture can cause cognitive decline.<sup>21</sup> A relationship between cognitive impairment and insomnia in older adults has been reported by epidemiological studies.<sup>22</sup> Increased sleep fragmentation could accelerate neurodegeneration via the accumulation of abnormal proteins such as tau and amyloid beta in the brain, leading to dementia.<sup>23</sup> In older people, better cognitive performance was related to having profiles of sleep metrics observed in younger people.<sup>24</sup> Insomnia is associated with impairments in cognitive performance, and thus, relieving insomnia could potentially improve cognitive outcome.<sup>25</sup> A recent systematic review and meta-analysis showed that obstructive sleep apnea was associated with significantly lower MoCA scores in patients with PD.<sup>26</sup> Increased sleep fragmentation and nocturnal hypoxia are important mechanisms, contributing to impair cognition.<sup>23</sup>

Rotigotine is described as not only a D<sub>3</sub>/D<sub>2</sub>/D<sub>1</sub> receptor agonist but also an antagonist of  $\alpha_{2B}$  adrenergic receptors and an agonist of 5-HT<sub>1A</sub> receptors.<sup>27</sup> In animal models, a selective postsynaptic 5-HT<sub>1A</sub> receptor agonist improved cognitive function.<sup>28</sup> Furthermore, single intraperitoneal injection of rotigotine enhanced cholinergic transmission in the mouse medial prefrontal cortex.<sup>29</sup> Therefore, in our study, the modulation of 5HT<sub>1A</sub> receptors or cholinergic transmission may have had a favorable effect on cognitive function.

Our study has several limitations. First, the sample size was small, which was partly because of the single-center study setting in which limited numbers of patients who scored 15 or higher on the PDSS-2 were available. Second, polysomnography was not performed, and sleep disturbances were assessed by questionnaire. However, the PDSS-2 can screen PD-related sleep problems and has been validated and widely used.<sup>30</sup> Third, the placebo effect on sleep and motor outcomes should be considered, given the open-label design of the study. Fourth, change in the MoCA may be related to practice effect.<sup>31</sup> Further multicenter, large-sample studies are needed to confirm whether rotigotine has beneficial effects on cognition by improving daytime motor symptoms and sleep disturbances.

In conclusion, our preliminary findings suggest that low-dose rotigotine could improve motor symptoms, sleep disturbances and daytime sleepiness as well as cognitive function in patients with PD.

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