ORIGINAL ARTICLE

Therapeutic Effect of Levodopa/Carbidopa/Entacapone on Sleep Disturbance in Patients with Parkinson's Disease

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ABSTRACT

Objective To investigate the efficacy of levodopa/carbidopa/entacapone (LCE) at bedtime for treating sleep disturbance in patients with Parkinson's disease (PD) with motor fluctuations.

Methods Participants included 128 PD patients with motor fluctuations. All patients were assessed for motor, nonmotor, and sleep-specific symptoms using the United Parkinson's Disease Rating Scale (UPDRS), the Korean version of the Nonmotor Symptom Scale, the Parkinson's Disease Sleep Scale (PDSS), the Epworth Sleepiness Scale, and the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ). We compared the baseline characteristics of patients with sleep disturbance (PDSS score < 120) and those without sleep disturbance (PDSS score ≥ 120). Thirty-nine patients with sleep disturbance who agreed to take LCE at bedtime completed 3-month follow-ups. We analyzed changes in the scores of motor, nonmotor, and sleep symptom scales over the 3 months.

Results PD patients with sleep disturbance were at more advanced disease stages and had more severe motor, nonmotor, and sleep symptoms than those without sleep disturbance. Patients who took LCE at night showed improvements in motor (UPDRS part III, $p = 0.007$) and sleep symptoms (total PDSS, $p < 0.001$). Sleep features that benefitted from LCE included not only nocturnal motor components but also insomnia (PDSS items 2 and 3, $p = 0.005$ and $p < 0.001$) and rapid eye movement behavior disorder (PDSS item 6, $p = 0.002$; and RBDSQ, $p < 0.001$).

Conclusion The use of LCE at bedtime may be a useful treatment for sleep disturbance in advanced PD patients with motor fluctuations.

Key Words Levodopa; Parkinson's disease; Sleep wake disorders.

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is characterized by the cardinal motor symptoms of bradykinesia, rigidity, resting tremors, and postural instability. PD patients also manifest nonmotor symptoms. Nonmotor symptoms in PD patients have a substantial impact on their quality of life. Sleep disturbance is a common symptom of PD and is a major contributor to exhaustion.[1,2]

The clinical features of sleep disturbance in PD patients are highly diverse, including insomnia, excessive daytime sleepiness (EDS), rapid eye movement sleep behavior disorder (RBD), restless leg syndrome, and others.[2] Neurodegeneration due to PD is observed in sleep-related brainstem structures and struc-

tures associated with circadian regulation.[3] Some sleep symptoms are indirectly caused by motor complications induced by advanced PD, such as the overnight re-emergence of parkinsonian motor symptoms as an "off" state. Frequent nocturia, anxiety, and the worsening of visual hallucinations at night also affect sleep quality in PD patients. Thus, the pathophysiology underlying sleep and circadian disruption in PD is complex and influenced by multiple factors.[4]

Several strategies have been used to treat sleep symptoms in patients with PD.[4,5] A common pharmacological option is to administer an additional dopaminergic agent before going to bed. This strategy is frequently prescribed for patients who experience motor fluctuations at night, anticipating that relieving nighttime motor symptoms could improve sleep quality. In addition, dopamine plays an essential role in regulating the sleep-wake cycle. Thus, the dopaminergic agent is intended to correct sleep-wake cycle disruptions caused by PD-related dopamine depletion.[6] However, a limited body of research has endeavored to systematically analyze the effects of dopaminergic agents on sleep quality in individuals with PD.

In this open-label study, we aimed to investigate the effects of using levodopa at bedtime on sleep quality in PD patients with motor fluctuations using the triple combination agent levodopa/carbidopa/entacapone (LCE). To do so, we 1) compared baseline motor, sleep, and other nonmotor features between PD patients who did or did not experience sleep disturbance; 2) observed which components of sleep, motor and nonmotor PD features improved with the use of LCE at bedtime; and 3) compared the baseline features of PD patients who showed improvements in sleep disturbance due to the use of LCE at bedtime with those who did not show improvements.

MATERIALS & METHODS

Patients

PD patients were diagnosed based on the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria and were recruited from March 2016 to February 2018. The inclusion criteria were as follows: 1) age between 20−79 years old, 2) Hoehn and Yahr (H&Y) stage 1−4, 3) presence of wearing-off phenomenon, 4) absence of significant cognitive impairment as determined by a Montreal Cognitive Assessment (MoCA) score ≥ 15,[7] 5) absence of significant depression as determined by a Geriatric Depression Scale (GDS) score ≤ 24,[8] and 6) consent to participate in the study. Patients with atypical parkinsonism, including multiple system atrophy, corticobasal syndrome, and progressive supranuclear palsy, were excluded from the study, as were patients who previously experienced side effects due to LCE. This study was approved by the local Institutional Review Board (IRB) (IRB number: 2015-0241). Written informed consent was obtained from all participants.

Clinical assessment

All patients were assessed using the United Parkinson's Disease Rating Scale (UPDRS), H&Y stage, the Schwab and England Activities of Daily Living (SE-ADL) scale, the Parkinson's Disease Sleep Scale (PDSS),[9] the Epworth Sleepiness Scale (ESS), the Korean versions of RBD screening questionnaire (RBDSQ), MoCA, the Parkinson's Disease Quality of Life Questionaire-39 (PDQ-39), the Nonmotor Symptom Scale for Parkinson's Disease (NMSS),[10] and the GDS at baseline. All scales were rated during the 'on' state, i.e., at a time when the patient reported optimal or partial relief of parkinsonian symptoms due to dopaminergic medications. The total PDSS score was used to evaluate the overall quality of sleep, and a total PDSS score below 120 indicated sleep disturbance.[9] The 15 items of the PDSS that cover the entire spectrum of sleep disturbance in PD are as follows: overall quality of night sleep (item 1), insomnia sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (items 8 and 9), nocturnal motor symptoms (items 10−13), sleep refreshment (item 14), and daytime dozing (item 15).

Among patients experiencing sleep disturbance (PDSS score < 120), those who agreed to take additional levodopa were started on LCE (Stalevo®, Novartis Pharmaceuticals Corp., East Hanover, NJ, USA) at bedtime for 3 months, with the dosage adjusted based on each patient's previous levodopa-equivalent daily dose (LEDD). The dose of anti-Parkinson drugs and (if applicable) the doses of hypnotics, anxiolytics, antipsychotics, and antidepressants were fixed until the end of the 3-month follow-up. None of the patients were taking nighttime levodopa prior to this trial. Each patient underwent a follow-up assessment using the scales described above, including the individual items of the PDSS, at 1 and 3 months to assess the interval change in the scale scores.

Statistical analysis

We compared the clinical features of PD patients experiencing sleep disturbance (PDSS score < 120) to those of patients who were not experiencing sleep disturbance (PDSS score ≥ 120) at baseline according to various motor, nonmotor, and sleep features of PD. Second, we analyzed changes in sleep and other motor and nonmotor PD features caused by the use of LCE at bedtime during the 3-month follow-up. Last, we compared baseline features between PD patients who experienced overall sleep improvement (PDSS improvement > 15%) due to the use of LCE at bedtime (i.e., responders) and those who did not experienced overall sleep improvement (i.e., nonresponders). Continuous variables were compared using Student's t-tests, and categorical

variables were compared using chi-square tests. A repeated measures analysis of variance was used to compare changes in scores on each scale at baseline, 1 month, and 3 months. A p value < 0.05 was considered statistically significant. For the analysis of individual PDSS items, a false discovery rate (FDR) was applied to correct for multiple comparisons.

RESULTS

Clinical characteristics of PD patients who do and do not experience sleep disturbance

A total of 128 PD patients participated in the study. Among them, 85 (66%) patients experienced sleep disturbance (PDSS score < 120), and 43 (34%) did not experience sleep disturbance (PDSS score ≥ 120) (Figure 1, Table 1). Compared to PD patients who did not experience sleep disturbance, those who did had longer mean disease durations (p = 0.015), were at more advanced H&Y stages (p = 0.045), and had higher LEDD (p = 0.031) at baseline. They also had worse relative baseline scores on the full UPDRS (p = 0.005), UPDRS part IV (p < 0.001), PDQ-39 (p < 0.001), NMSS (p < 0.001), and GDS (p < 0.001). Overall, these results are indicative of worse motor and nonmotor symptoms in patients experiencing sleep disturbance. In terms of sleep scales, scores on all 15 PDSS items (data not shown) as well as the ESS (p < 0.001) and the RBDSQ (p = 0.005) were lower in patients experiencing sleep disturbance. This indicates that all components of sleep are affected in PD patients experiencing sleep disturbance.

Changes in motor, nonmotor, and sleep features of PD due to the use of LCE at bedtime

Among the 85 patients with sleep disturbance, 54 patients agreed to take LCE at bedtime in addition to their regular daytime medication (Figure 1). Thirty-nine patients (72%) completed the 3-month follow-up. Eight patients withdrew due to various side effects from LCE, and seven were lost to follow-up for unspecified reasons.

As expected, patients who took an additional dose of LCE showed statistically significant improvements in motor features, reflected by the improvement of total UPDRS (p = 0.017), UPDRS part III (p = 0.007), and UPDRS part IV (p = 0.006) scores (Table 2). There was no overall improvement in nonmotor symptom severity, as shown by NMSS scores (p = 0.059) (Table 2). In terms of sleep, patients showed an overall improvement in sleep quality, as shown by an improvement in the total PDSS score (p < 0.001), scores for PDSS item 1 (overall sleep quality, p < 0.001), and scores for PDSS item 14 (sleep refreshment, p = 0.018) (Table 2, Figure 2A). Patients also showed improvements in sleep onset (PDSS item 2, p = 0.005), sleep maintenance (PDSS items 3, p < 0.001), distressing dreams (PDSS item 6, p = 0.002), nocturia (PDSS item 8, p < 0.001), and RBD (RBDSQ, p < 0.001) (Table 2, Figure 2A).

Clinical comparison of PD patients who did and did not experience improved sleep due to the use of LCE at bedtime

Although patients who used LCE at bedtime showed an overall improvement in sleep, the degree of improvement was highly heterogeneous (the change in PDSS scores ranged from -46% to
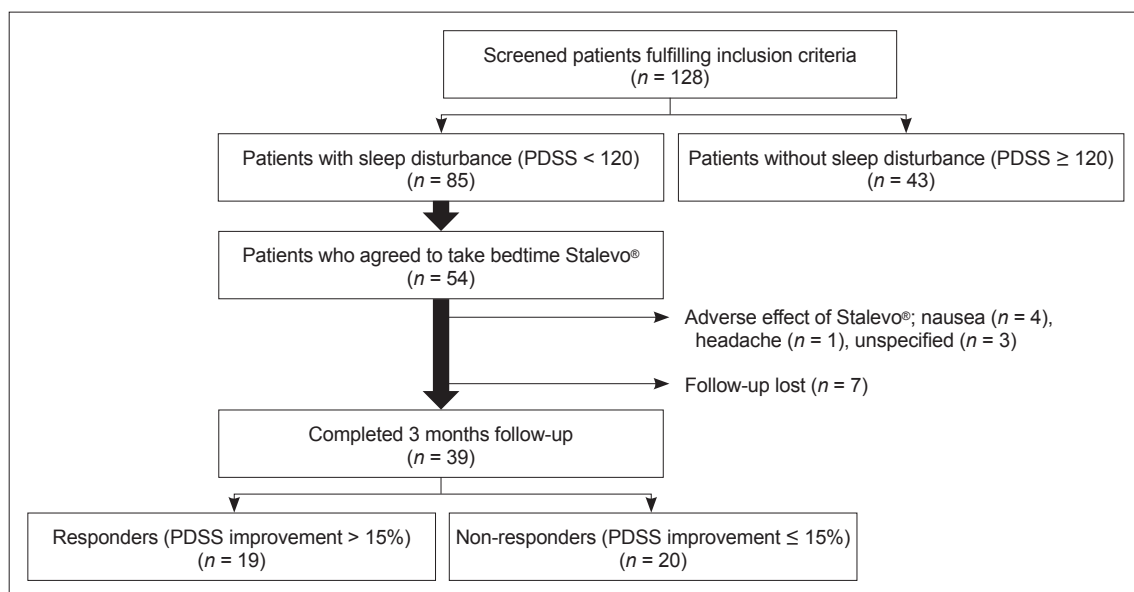

Figure 1. Study flow chart. PDSS: Parkinson's Disease Sleep Scale.

84%). For this reason, we divided the patients into two groups according to their degree of improvement at 3 months: patients who had PDSS improvements of over 15% (i.e., responders, *n* = 19, average PDSS increment 34%) and patients who had improvements of less than 15% (i.e., nonresponders, *n* = 20, average PDSS increment -1.7%) (Figure 1). At baseline, responders had

Table 1. Baseline characteristics of the study participants

	PD with sleep disturbance (PDSS < 120) (*n* = 85)	PD without sleep disturbance (PDSS ≥ 120) (*n* = 43)	*p* value
Age (years)	65.9 ± 7.9	65.4 ± 7.9	0.700
Age at onset (years)	56.6 ± 8.4	58.3 ± 8.5	0.297
Disease duration (years)	9.3 ± 5.0	7.1 ± 4.5	0.015*
Female	50 (59)	19 (44)	0.135
Patients on hypnotics/anxiolytics	14 (16)	9 (21)	0.535
Patients on antipsychotics	0 (0)	2 (5)	0.111
Patients on antidepressants	4 (5)	0 (9)	0.300
H&Y stage	2.6 ± 0.6	2.3 ± 0.5	0.045*
LEDD (mg)	903 ± 321	770 ± 335	0.031*
MoCA	24.7 ± 3.9	24.7 ± 3.1	0.863
UPDRS, total	45.1 ± 18.8	34.0 ± 13.9	0.005*
UPDRS, part I	5.5 ± 4.9	4.6 ± 4.1	0.319
UPDRS, part II	16.0 ± 11.6	19.4 ± 11.4	0.119
UPDRS, part III	26.9 ± 12.2	25.5 ± 10.9	0.525
UPDRS, part IV	4.7 ± 2.8	1.8 ± 2.1	< 0.001*
SE-ADL	82.3 ± 10.7	85.8 ± 10.1	0.090
PDQ-39	41.8 ± 22.2	22.4 ± 20.9	< 0.001*
PDSS	95.8 ± 18.8	134.5 ± 7.6	< 0.001*
ESS	8.1 ± 4.2	5.2 ± 2.4	< 0.001*
RBDSQ	5.9 ± 2.8	4.4 ± 3.0	0.005*
NMSS	57.6 ± 31.8	30.0 ± 23.1	< 0.001*
GDS	13.7 ± 6.4	7.8 ± 6.9	< 0.001*

Data are shown as the mean ± standard deviation or *n* (%). *statistically significant. PD: Parkinson's disease, H&Y: Hoehn and Yahr, LEDD: levodopa-equivalent daily dose, MoCA: Montreal Cognitive Assessment, UPDRS: Unified Parkinson's Disease Rating Scale, SE-ADL: Schwab and England Activities of Daily Living, PDQ-39: Parkinson's Disease Quality of Life Questionaire-39, PDSS: Parkinson's Disease Sleep Scale, ESS: Epworth Sleepiness Scale, RBDSQ: Rapid Eye Movement Behavior Disorder Screening Questionnaire, NMSS: the Nonmotor Symptom Scale, GDS: Geriatric Depression Scale.

Table 2. Changes in motor, nonmotor, and sleep scale scores at baseline, 1 month, and 3 months after the use of LCE at bedtime in 39 patients

	Baseline	1 month	3 months	*p* value
H&Y stage	2.6 ± 0.5	2.6 ± 0.5	2.6 ± 0.5	0.767
UPDRS, total	49.3 ± 18.8	45.7 ± 17.2	44.1 ± 19.7	0.017*
UPDRS, part I	3.1 ± 2.0	2.9 ± 1.7	3.4 ± 2.0	0.166
UPDRS, part II	11.2 ± 6.4	10.6 ± 6.0	11.6 ± 6.9	0.556
UPDRS, part III	29.3 ± 11.4	27.0 ± 10.5	25.9 ± 10.3	0.007*
UPDRS, part IV	5.7 ± 2.9	5.1 ± 2.9	5.0 ± 3.0	0.006*
SE-ADL	80.0 ± 11.2	79.6 ± 11.0	79.4 ± 11.4	0.442
PDQ-39	44.5 ± 23.5	44.0 ± 24.5	47.1 ± 27.5	0.348
PDSS	92.2 ± 19.6	102.5 ± 21.3	105.2 ± 20.9	< 0.001*
ESS	3.3 ± 4.4	7.5 ± 4.3	7.4 ± 4.5	0.260
RBDSQ	6.4 ± 2.8	4.7 ± 3.0	4.3 ± 2.5	< 0.001*
NMSS	69.5 ± 33.7	63.1 ± 31.4	63.6 ± 34.6	0.059

Data are shown as the mean ± standard deviation. *statistically significant by repeated measure ANOVA. LCE: levodopa/carbidopa/entacapone, H&Y: Hoehn and Yahr, UPDRS: Unified Parkinson's Disease Rating Scale, SE-ADL: Schwab and England Activities of Daily Living, PDQ-39: Parkinson's Disease Quality of Life Questionaire-39, PDSS: Parkinson's Disease Sleep Scale, ESS: Epworth Sleepiness Scale, RBDSQ: Rapid Eye Movement Behavior Disorder Screening Questionnaire, NMSS: the Nonmotor Symptom Scale.

worse PDSS scores than nonresponders ($p = 0.003$), but there was no difference in other motor, nonmotor, or sleep features of PD except for slightly lower ADL scores in responders (Table 3). For individual PDSS items, responders had worse scores only on PDSS item 12 (morning off dystonia, $p = 0.002$) after FDR correction.

We also assessed changes in motor, nonmotor, and sleep fea-tures in PD for each group during the 3-month follow-up (Table 3, Figure 2B). Responders showed improvement in most as-pects of sleep, including total PDSS scores, scores on 9 of the 15 PDSS items (after FDR correction), and RBDSQ scores. Notably, nonresponders showed significant improvements in RBDSQ scores at the 3-month follow-up ($p = 0.007$), although no other features showed improvement over this period (Table 3).
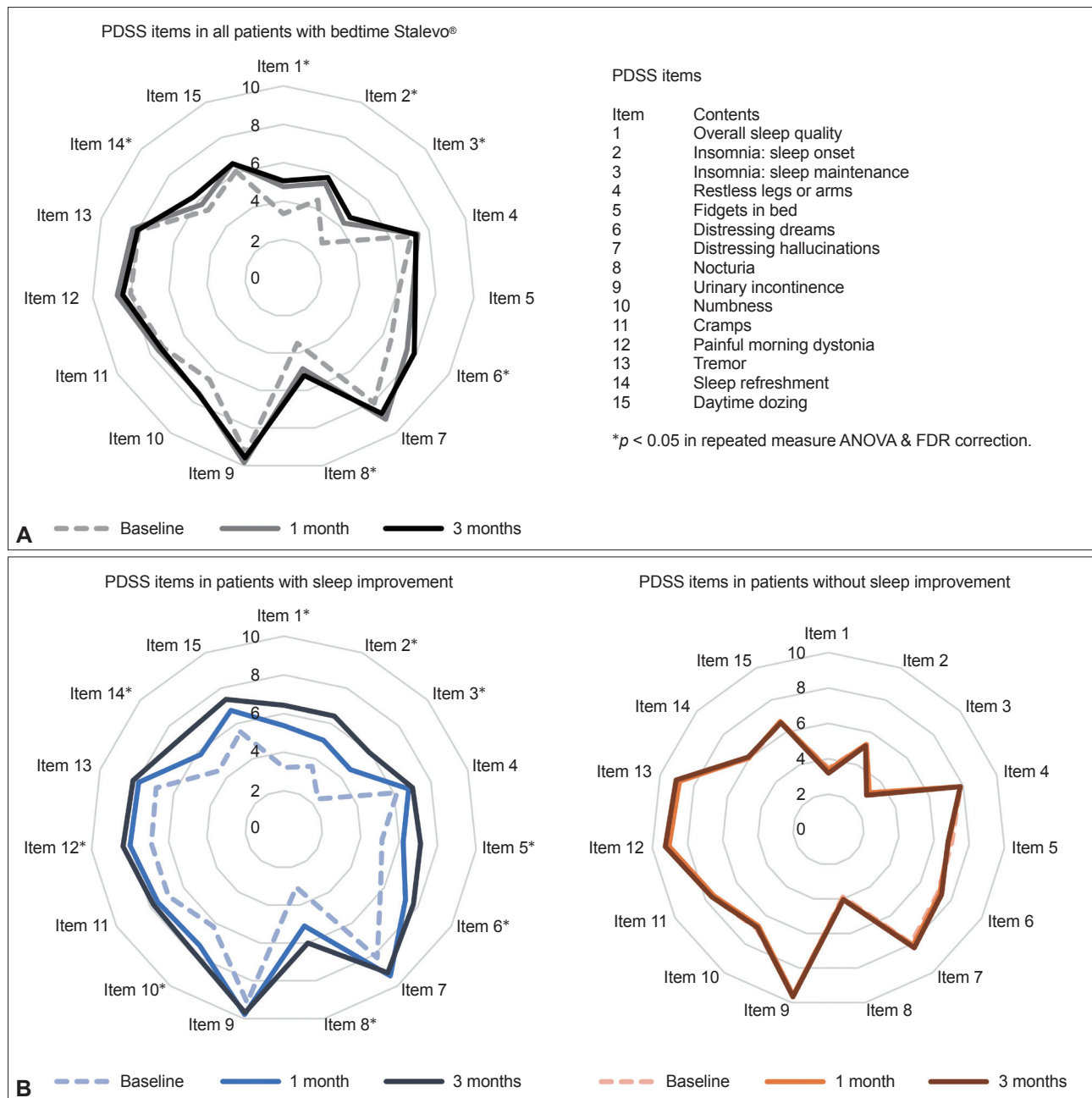

Figure 2. Changes in the 15 PDSS items at baseline, 1 month, and 3 months. A: PDSS items for all 39 patients who completed a 3-month follow-up with LCE. B: PDSS items for patients with sleep improvement (responders, total PDSS improvement > 15%) and patients without sleep improvement (nonresponders, total PDSS improvement < 15%) due to LCE. PDSS: Parkinson's Disease Sleep Scale, LCE: levodo-pa/carbidopa/entacapone, ANOVA: analysis of variance, FDR: false discovery rate.

Table 3. Clinical characteristics of patients according to their responsiveness to LCE for sleep disturbance

	Responders (n = 19) (PDSS improvement > 15%)			Nonresponders (n = 20) (PDSS improvement ≤ 15%)			p value
Levodopa dose of LCE (mg)	150 [100–200]			150 [100–200]			0.667
Age (years)	66.0 ± 6.7			64.5 ± 9.4			0.477
Age at onset (years)	57.3 ± 8.6			55.6 ± 8.9			0.183
Disease duration (years)	8.7 ± 5.9			8.9 ± 3.7			0.294
Female	13 (68)			12 (60)			0.741
Patients on hypnotics/anxiolytics	4 (21)			5 (25)			1.000
Patients on antipsychotics	0 (0)			0 (0)			1.000
Patients on antidepressants	1 (5)			1 (5)			1.000
H&Y stage	2.6 ± 0.2			2.6 ± 0.3			0.587
LEDD (mg)	875 ± 347			951 ± 297			0.467
MoCA	24.6 ± 4.1			25.2 ± 3.2			0.512
	Baseline	3 months	p value†	Baseline	3 months	p value†	p value‡
UPDRS, total	53.1 ± 20.0	44.3 ± 21.8	0.002*	45.6 ± 17.2	43.9 ± 18.0	0.589	0.126
UPDRS, part I	3.7 ± 2.2	3.5 ± 1.9	0.170	2.5 ± 1.7	3.2 ± 1.9	0.021	0.058
UPDRS, part II	12.7 ± 6.7	12.0 ± 7.0	0.192	9.8 ± 6.0	11.2 ± 6.8	0.191	0.158
UPDRS, part III	30.2 ± 11.9	26.3 ± 10.3	0.001*	28.4 ± 11.0	25.6 ± 10.6	0.127	0.443
UPDRS, part IV	5.9 ± 3.3	5.0 ± 3.3	0.007*	5.4 ± 2.5	4.9 ± 2.6	0.225	0.572
SE-ADL	76.8 ± 11.5	77.8 ± 11.3	0.270	83.0 ± 10.3	80.7 ± 11.5	0.119	0.049*
PDQ-39	46.5 ± 27.5	45.8 ± 30.0	0.783	42.5 ± 19.5	48.2 ± 25.5	0.219	0.494
PDSS	83.6 ± 19.6	112.2 ± 23.1	< 0.001*	100.3 ± 16.5	98.6 ± 16.5	0.576	0.003*
ESS	8.0 ± 3.8	6.1 ± 3.4	0.362	8.1 ± 4.8	8.6 ± 5.1	0.545	0.728
RBDSQ	6.0 ± 2.4	3.7 ± 2.1	0.001*	6.7 ± 3.2	4.8 ± 2.6	0.007*	0.686
NMSS	74.3 ± 35.6	59.0 ± 32.8	0.004*	64.9 ± 31.9	67.9 ± 36.5	0.378	0.321

Data are shown as the median [range], mean ± standard deviation, or n (%). *statistically significant, †comparison between baseline, 1 month, and 3 months follow-up in each group by repeated measure analysis of variance, ‡comparison between responders and nonresponders at baseline. LCE: levodopa/carbidopa/entacapone, H&Y: Hoehn and Yahr, LEDD: levodopa-equivalent daily dose, MoCA: Montreal Cognitive Assessment, UPDRS: Unified Parkinson's Disease Rating Scale, SE-ADL: Schwab and England Activities of Daily Living, PDQ-39: Parkinson's Disease Quality of Life Questionaire-39, PDSS: Parkinson's Disease Sleep Scale, ESS: Epworth Sleepiness Scale, RBDSQ: Rapid Eye Movement Behavior Disorder Screening Questionnaire, NMSS: the Nonmotor Symptom Scale.

DISCUSSION

The present study investigated the characteristics of PD patients who have sleep disturbance, identified clinical features that could be improved with the use of LCE at bedtime, and characterized the patients whose sleep would benefit from the use of LCE at bedtime. First, it was found that PD patients with poorer sleep quality had more advanced disease stages and more severe symptoms, as measured by motor, nonmotor, and sleep scales, than those with better sleep quality. Second, LCE improved sleep by improving nonmotor as well as motor symptoms. Specifically, sleep onset, sleep maintenance, and RBD were improved by the use of LCE. We also found that those with lower PDSS scores at baseline responded more favorably to LCE in terms of sleep improvements.

The disruption of sleep and circadian rhythms is highly prevalent in patients with PD.[4,11] Interestingly, impaired sleep was one of the first recognized symptoms of PD, as stated in the earliest description of the disease by James Parkinson in his 1817 essay "An Essay on the Shaking Palsy."[11] Although there have been tremendous advancements in treating the motor symptoms of PD over the last two centuries, little advancement has been made in regards to treating sleep disturbance in patients with PD. Nevertheless, sleep disturbance is one of the most troublesome and irritating symptoms for patients with PD. It has been shown that poor sleep quality in patients with PD is associated with diminished quality of life, depression, increased burden for caregivers, and more advanced motor symptoms.[12-14] Patients from our study population who had poor sleep quality had worse motor, nonmotor, and sleep symptoms (Table 1). Notably, the GDS score was significantly higher in patients with lower PDSS scores even though we excluded patients with overt depression (GDS > 24) in the screening, thus reflecting the strong association between depression and sleep disturbance in PD. Thus, the treatment of patients with PD should take sleep symptoms into account to optimally improve quality of life.

We found that the use of levodopa at bedtime may improve sleep quality in patients with advanced PD. Dopamine, the key

neurotransmitter that is deficient in the PD brain, is an emerging key factor for circadian regulation.[6,11,15] Studies have shown the existence of dopamine-mediated circadian-like activity in major areas of the central nervous system, including the striatum, olfactory bulb, midbrain, hypothalamus, and retina.[1,6] The factors for sleep disturbances in PD can be categorized into three groups: 1) primary sleep disorders in PD due to altered circadian regulation, including insomnia, RBD, and EDS; 2) secondary sleep disorders in PD due to nocturnal motor symptoms, including nocturnal akinesia and morning dystonia; and 3) other miscellaneous causes, including nocturnal psychiatric symptoms and treatment-related nocturnal disturbances.[4,16,17] Traditionally, levodopa has been recommended for secondary sleep disorders due to motor symptoms worsening at night.[4] Given the recent finding that dopamine is a key neurotransmitter for circadian regulation, its utility for treating primary sleep disorders in PD should be reconsidered. We recruited advanced PD patients with motor fluctuations to encompass both the primary and secondary sleep disorders of PD. The triple combination drug Stalevo® (levodopa/carbidopa/entacapone) was chosen because the agent is indicated for advanced PD patients with motor fluctuations. In addition, few trials have been conducted to examine the efficacy of such triple combination regimens for sleep disturbance in patients with PD. Our results showed a fair amount of improvement not only in nocturnal motor symptoms but also in RBD scores, even in the subgroup that did not display a significant improvement in total PDSS scores. There are several other reports showing improvements in RBD due to levodopa therapy.[18-20] These findings reflect the possible role of levodopa as a treatment option for all types of sleep disturbance in PD.

Nevertheless, for several reasons, we suggest that more well-designed trials are warranted to examine the efficacy of levodopa, to determine the optimal regimen of levodopa and to identify potential better responders of levodopa for the treatment of sleep disturbance in PD. First, the dropout rate of our study was relatively high (15 out of 54, 28%). This could have biased the results due to the exclusion of poor responders. Second, contrary to our study, some previous trials that studied the efficacy of using levodopa at night did not identify objective improvements in the sleep parameters of PD patients.[21,22] Unlike our study, these trials used controlled-releasing levodopa formula. The difference in the peak dose effect might have affected the controversial clinical results. The efficacy of different formulas or regimens of levodopa for sleep disturbance in PD has yet to be elucidated. Third, the patients' responses to levodopa were highly heterogeneous in our study population. We tried to determine the clinical factors that affect responses to levodopa by comparing the baseline characteristics of responders and nonresponders. However, we only found that those who showed improvement in sleep quality as a result of LCE had relatively worse PDSS scores at baseline. Additional studies with more objective parameters (e.g., polysomnographic parameters, genetic variants of circadian and clock genes) may provide a better understanding of who would show improvements in sleep symptoms due to the use of levodopa at bedtime.

There are several limitations to this study. Most importantly, the study was an open-label study without a placebo group. The size of the placebo effect on the overall improvement resulting from LCE is hard to quantify. Furthermore, our study was based on clinical scales that were subjectively completed by clinicians and patients. Although these scales are well validated and reliable, our study lacks objective polysomnographic parameters to evaluate changes in sleep.

In conclusion, we investigated the characteristics of PD patients with sleep disturbance and their clinical response to the use of LCE at bedtime. Sleep disturbance is associated with more severe motor and nonmotor symptoms, and the use of LCE at bedtime is a possible treatment option for patients with PD who are experiencing sleep disturbance. Further clinical trials with objective sleep parameters and various regimens of levodopa to treat sleep disturbance of PD should be conducted.

Author Contributions

Conceptualization: Kye Won Park, Ho-Sung Ryu, Sun Ju Chung. Data curation: Kye Won Park, Dagyo Lee. Formal analysis: Kye Won Park. Funding acquisition: Sun Ju Chung. Investigation: Kye Won Park, Dagyo Lee, Ho-Sung Ryu. Methodology: Kye Won Park, Ho-Sung Ryu, Sun Ju Chung. Project administration: Sun Ju Chung. Resources: Kye Won Park, Dagyo Lee, Ho-Sung Ryu, Sun Ju Chung. Software: Kye Won Park. Supervision: Sun Ju Chung. Validation: Sungyang Jo, Seung Hyun Lee, Yun Su Hwang. Visualization: Kye Won Park. Writing—original draft: Kye Won Park. Writing—review & editing: Sungyang Jo, Seung Hyun Lee, Yun Su Hwang, Dagyo Lee, Sun Ju Chung.

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