Published in final edited form as:
JAMA Neurol. 2014 April ; 71(4): 463–469. doi:10.1001/jamaneurol.2013.6239.

Circadian melatonin rhythm and excessive daytime sleepiness in Parkinson's disease

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Authors' Conflict of Interest Disclosures:

Dr. Videnovic received research grant support from the American Academy of Neurology Foundation, Parkinson's Disease Foundation, National Institutes of Health (K23 NS072283) and Michael J. Fox Foundation for Parkinson's Research.
Mr. Noble has nothing to disclose.
Dr. Reid received grant support from the American Waterway Operators, and Philips Consumer Lifestyles, and is a consultant for the American Waterways Operators.
Ms. Peng has nothing to disclose.
Dr. Turek is a consultant for Merck Inc, Servier, Vanda Pharmaceuticals, Philips Respironics, Ingram Barge Company, and received research support from National Institutes of Health (P01 AG011412, R01AA020216), Merck Inc, Servier, American Waterways Operators, March of Dimes, and Department of Defense.
Ms. Marconi has nothing to disclose.
Dr. Rademaker received honoraria from serving as an external Advisory Board member for Georgetown University, and research support form National Institutes of Health.
Dr. Simuni is a consultant for Novartis, Ibsen, General Electric, UCB Pharma, TEVA, Boehringer Ingelheim, and received grant support from National Institutes of Health (U01 NS050324-01A1, U01 NS050095-03, U10 NS053377-02), Michael J Fox Foundation for Parkinson's Research, TEVA, and Takeda.
Dr. Zadikoff is a consultant for Teva, Ipsen, Merz, Abbott, and received honoraria for speaking engagements from Teva, UCB Pharma and GSK.
Dr. Zee is a consultant for Sanofi-Aventis, UCB, Johnosn&Johnson, Merck, Takeda, Phillips, Purdue, Jazz, Vanda, Ferring, has stock ownership with Teva, and received research support from National Institutes of Health (R01 HL090873, R01 HL105549, P01 AG11412, UM1HL112856).

Authors' Contributions

Dr. Videnovic: study concept and design; acquisition of data; analysis and interpretation; critical revision of the manuscript for important intellectual content; study supervision.
Mr. Noble: analysis and interpretation; critical revision of the manuscript for important intellectual content.
Dr. Reid: analysis and interpretation; critical revision of the manuscript for important intellectual content.
Ms. Peng: analysis and interpretation; critical revision of the manuscript for important intellectual content.
Dr. Turek: analysis and interpretation; critical revision of the manuscript for important intellectual content.
Ms. Marconi: acquisition of data; analysis and interpretation; critical revision of the manuscript for important intellectual content.
Dr. Rademaker: analysis and interpretation; critical revision of the manuscript for important intellectual content.
Dr. Simuni: analysis and interpretation; critical revision of the manuscript for important intellectual content.
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Abstract

Importance—Diurnal fluctuations of motor and non-motor symptoms and high prevalence of sleep/wake disturbances in Parkinson's disease (PD) suggest a role of the circadian system in the modulation of these symptoms. Yet, surprisingly little is known regarding circadian function in PD, and whether circadian dysfunction is involved in the development of sleep/wake disturbances in PD.

Objective—The objective of this study was to determine the relationship between the timing and amplitude of the 24-hour melatonin rhythm, a marker of endogenous circadian rhythmicity, with self-reported sleep quality, the severity of daytime sleepiness and disease metrics.

Design—A cross-sectional study, (2009–2012).

Setting—PD and Movement Disorders Center, Northwestern University, Chicago.

Participants—Twenty PD patients on stable dopaminergic therapy and 15 age-matched controls underwent blood sampling for the measurement of serum melatonin levels at 30-minute intervals for 24 hours under *modified constant routine* conditions.

Main Outcome Measure(s)—Clinical and demographic data, self-reported measures of sleep quality (Pittsburgh Sleep Quality Index (PSQI)) and daytime sleepiness (Epworth Sleepiness Scale (ESS)), circadian markers of the melatonin rhythm, including the amplitude, area-under-the-curve (AUC), and phase of the 24-hour rhythm.

Results—Participants with PD had a blunted circadian rhythms of melatonin secretion compared to controls; both the amplitude of the melatonin rhythm and the 24-hour AUC for circulating melatonin levels were significantly lower in PD participants compared with controls ($p<0.001$). Markers of circadian phase were not significantly different between the two groups. Among PD participants, those with excessive daytime sleepiness (ESS score ≥10) had a significantly lower amplitude of the melatonin rhythm and the 24-hour melatonin AUC compared with PD participants without excessive sleepiness ($p=0.001$). Disease duration, UPDRS scores, levodopa equivalent dose and global PSQI scores in the PD group were not significantly related to measures of the melatonin circadian rhythm.

Conclusion and Relevance—These results indicate that circadian dysfunction may underlie excessive sleepiness in PD. The nature of this association needs to be further explored in longitudinal studies. Approaches aimed to strengthen circadian function, such as timed bright light and exercise, might potentially serve as complementary therapies for the non-motor manifestations of PD.

Introduction

Disturbances of sleep and wake are one of the most common and disabling non-motor manifestations of Parkinson's disease (PD), affecting as many as 90% of patients.[1,2] Disrupted sleep-wake cycles contribute to poor quality of life and increased risk for

accidents, leading to increased morbidity and mortality in the PD population.[3–5] Current treatment options for disturbed sleep and alertness in PD are very limited and associated with undesirable adverse effects. Therefore, there is a great need to understand the mechanisms leading to sleep-wake dysfunction in PD, and to develop innovative treatment modalities. The exact pathophysiology of sleep-wake disturbances in PD remains largely unknown, but the etiology is likely to be multifactorial, including the impact of motor symptoms on sleep, primary sleep disorders, (sleep apnea and REM Sleep Behavior Disorder), adverse effects of medications, and neurodegeneration of central sleep-wake regulatory systems.[6–9]

Circadian rhythms are physiological and behavioral cycles with a periodicity of approximately 24 hours, generated by an endogenous biological clock, the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus.[10–12] The SCN actively promotes arousal during the day by stimulating neural circuits mediating arousal and/or inhibiting neural circuits mediating sleep. Circadian rhythms can be characterized by their period, phase and amplitude. Changes in circadian amplitude and/or phase can reduce nighttime sleep quality, daytime alertness and cognitive performance.[13–16] Although the sleep-wake cycle represents the most apparent circadian rhythm, other processes such as core body temperature, hormone secretion, cognitive performance, cardiometabolic function and mood are also regulated by the SCN. For example, the timing of melatonin release from the pineal gland is regulated by the SCN, and plasma melatonin is a reliable marker of the endogenous circadian rhythm.[17,18]

Despite the alerting function of the SCN, little is known about the role of the circadian system in the regulation of sleep-wake cycles in PD. Several studies have reported daily fluctuations of clinical and biologic factors in PD, including suppressed daily motor activity[19–21], loss of the normal circadian rhythm of blood pressure and heart rate[22–24], impaired sleep and daytime alertness[25–28], as well as fluctuations in catecholamines[29], cortisol[30,31] and melatonin levels.[32–34] While these investigations suggest modifications of the circadian system in PD, the observed results reflect influences of both endogenous and exogenous factors. In this study we aimed to examine endogenous circadian rhythm of melatonin secretion in participants with PD and healthy controls using a modified constant routine protocol, which is an experimental protocol designed to allow for the accurate assessment of the human endogenous rhythmicity by controlling the effects of exogenous variables.

Methods

Recruitment, protocol approval, and consent

The PD group was represented by a convenience sample of PD patients recruited from Northwestern University Parkinson's Disease and Movement Disorders Center. Control participants were recruited via advertising throughout the Chicago land area as well as from the Aging Research Registry of healthy individuals interested to participate in research within the Northwestern Buehler Center on Aging. The study was approved by the Northwestern Institutional Review Board. Written consent was obtained from all participants.

Study participants

Inclusion criteria were: 1) Diagnosis of idiopathic PD as defined by the United Kingdom Parkinson's Disease Society Brain Bank Criteria[35], 2) PD Hoehn and Yahr stage 2–4, 3) Stable dose of PD medications for at least 4 weeks prior to the study screening and throughout the study period.

Exclusion criteria were: 1) Atypical or secondary forms of parkinsonism, 2) Cognitive impairment as determined by the Mini-Mental State Examination (MMSE) score of ≤ 26, 3) Presence of depression defined as the Beck Depression Inventory (BDI) score >14, 4) Untreated hallucinations or psychosis (drug-induced or spontaneous), 5) Use of hypnotic, sedative or stimulant medications, 6) Use of antidepressants, unless the participant has been on a stable dose for at least 3 months prior to enrollment; tricyclics, trazodone, nefazodone, and mirtazapine were not allowed due to their soporific properties, 7) Use of medications known to affect melatonin secretion, such as lithium, alpha- and beta-adrenergic antagonists, 8) High sleep apnea risk, as assessed by the Berlin Questionnaire, 9) Shift work, 10) Travel through two or more time zones within 90 days prior to study screening, 11) Unstable/ serious medical illness. The same exclusion criteria were used for control participants who were matched for age with the PD participants.

Study protocol

PD severity was assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) in the ON condition at the time of study enrollment. Sleep quality and daytime sleepiness were assessed by the Pittsburg Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), respectively. Mini-Mental State Examination (MMSE) and Beck Depression Inventory (BDI) were administered to all participants. All assessments were performed by a movement disorders specialist (A.V.). Demographic characterization of the study cohort included age, gender, education, race, smoking status and caffeine consumption.

Each participant was instructed to maintain a regular (±30 minutes) sleep schedule for 14 days prior to testing, which was confirmed by sleep diaries. The experimental protocol was conducted in the Clinical Research Unit (CRU) at Northwestern Memorial Hospital. Participants were admitted to the CRU in the evening hours. Lights-out time was determined based on the averaged habitual sleep-time, calculated from sleep diaries. Upon awakening on day 1 (circadian time (CT) 0), participants were fitted with an IV catheter in the forearm vein for repeated blood sampling, and maintained in a modified constant routine condition for the 24-hour blood sampling. They remained in a semi-recumbent position with their head at a 45-degree angle during waking hours, received 150–250 Kcal snacks depending on their normal food intake at 2-hour intervals while awake. Blood (2 ml) was sampled every 30 minutes from CT 3 until the next CT 3 (total of 24 hours) for assay of melatonin. Participants were not sleep deprived for the duration of the 24-hour blood sampling period due to safety concerns for PD participants, and were allowed 8 hours of sleep/time in bed; therefore this was a modified constant routine protocol. In order not to disrupt participants' sleep overnight, the indwelling catheter was connected to long plastic tubing that extended into an adjacent room. During the modified CR routine protocol light levels in the CRU were maintained ≤ 10 lux during waking hours and reduced to < 3 lux during sleep periods.

Plasma melatonin levels were measured by a radioimmunoassay (LDN, Nordhorn, Germany); the sensitivity of the assay = 2 pg/mL, intra assay coefficient of variation = 9.8% for a concentration of 50 pg/ml, and inter-assay coefficient of variation = 9.6% for a concentration of 40 pg/ml. Plasma levels were expressed in picograms per milliliter.

Melatonin levels (pg/ml) were adjusted to a percentage of maximum (average of the 3 highest values). The data were subsequently smoothed with the Lowess (Cleveland) curve-fitting procedure[36] and interpolated at 1-min intervals (Graphpad Software, Inc.). Melatonin acrophase and nadir was defined as the level corresponding to the maximum and minimum of the best fit curve, and amplitude was defined as 50% of the difference between the acrophase and nadir values. The area-under-the-curve (AUC) was calculated as a measure of the secreted amount of melatonin over 24-hour period using the trapezoid method. Circadian phase was assessed by 1) dim light melatonin onset (DLMO) calculated as 2 standard deviations (2SD) above the average baseline samples (baseline = the average of three lowest points between CT 3 – CT 10), 2) DLMO 50% (time that melatonin level rose to 50% of the maximum level), 3) DLMO 50% off (time that melatonin level declined to 50% of maximum levels) and 4) melatonin midpoint, defined as the average of DLMO 50% and DLM 50% off.[37]

Data analysis

Descriptive summary statistics were calculated and exploratory graphical displays obtained for all variables of interest. Group differences were analyzed using Kruskal-Wallis test and Fisher's exact test. Spearman correlation was used to assess the relationship between demographic/disease characteristics and parameters of melatonin circadian rhythm. *p* values less than 0.05 were considered significant. Statistical analyses were performed using SAS for Windows (Version 9.3, SAS Institute Inc., Cary, NC, USA).

Results

Twenty participants with PD on dopaminergic therapy and 15 controls completed the study protocol. Demographics of the study cohort, and disease characteristics are outlined in Table 1. Demographic variables did not differ between PD participants and controls. Global PSQI score was (mean±SE) 6.1 ± 0.7 in the PD group and 6.7 ± 1.1 in the control group (p=0.50), indicating similar self-reported sleep quality between PD participants and controls. The mean ESS score was 10.9 ± 1.1 in the PD group and 6.1 ± 1.0 in the control group (p=0.006), indicating presence of excessive daytime sleepiness among participants with PD. Twelve PD participants (60%) and four controls (27%) had excessive sleepiness, as defined by ESS score ≥10 (p=0.09).

Circadian variations of melatonin secretion are presented in Table 1. There was a preserved circadian rhythm of melatonin secretion in both groups. Participants with PD had a blunted circadian rhythm of melatonin secretion (Figure 1A) compared to controls: both the amplitude of the circadian rhythm of melatonin (p<0.001) and the 24-hour AUC for circulating melatonin levels (p<0.001) was diminished significantly (four-fold) in PD participants compared with controls. Both daytime AUC (CT 0–16) and nighttime AUC (CT 16–24) were significantly diminished in the PD group compared with controls (p<0.001).

Markers of circadian phase, 2SD, DLMO 50%, DLMO 50%off, and melatonin midpoint were not significantly different between the two groups (Table 1).

Among PD participants, those with excessive daytime sleepiness had a significantly lower amplitude of the melatonin rhythm compared with PD participants without excessive sleepiness (p=0.001) (Table 1; Figure 2B). Similarly, the 24-hour melatonin AUC was significantly lower in PD participants with excessive daytime sleepiness (p=0.001). Demographics, disease duration, total and part III UPDRS scores, total levodopa equivalent dose and total PSQI scores were not significantly different in PD participants with or without daytime sleepiness.

The amplitude of the melatonin rhythm as well as the 24-hour melatonin AUC were inversely associated with the age of the PD participants (r=−0.54, p=0.01 and r=−0.47, p=0.04, respectively). Disease duration, age at onset of PD, total and part III UPDRS scores, total levodopa equivalent dose and global PSQI scores in the PD group were not significantly related to measures of the melatonin circadian rhythm.

The amplitude of the melatonin rhythm and the 24-hour melatonin AUC were not associated with the age of the control participants (r=−0.24, p=0.38 and r=−0.15, p=0.57, respectively). Control participants with (n=4) and without (n=11) excessive daytime somnolence did not differ in demographic variables, self-reported sleep quality, and circadian markers of melatonin rhythm (p>0.39).

Discussion

Disruption of sleep-wake cycles in PD negatively affects the quality of life and safety of PD patients. Mechanisms that underlie poor sleep and alertness in PD are not fully elucidated and treatment options remain limited. The main finding from this study is a significantly diminished amplitude and amount of melatonin secretion in PD participants compared to controls. Among PD patients, those with daytime sleepiness exhibit the most prominent impairment in circadian melatonin secretion. These findings suggest an important and novel role of circadian regulation in the manifestation of the excessive sleepiness associated with PD.

The results of this investigation differ from observations reported in several prior studies which examined 24-hour melatonin profiles in PD. Fertl and colleagues reported diurnal secretion curves of melatonin among nine PD patients treated with levodopa in combination with benserazide or carbidopa, nine *de novo* untreated PD patients, and 14 age-matched controls.[33,34] They did not find a difference in the amount of melatonin secreted nor in the amplitude of the melatonin rhythm between PD and control groups. Similar to our observations, the motor UPDRS score and the duration of disease were not significantly associated with the amplitude and AUC of the melatonin rhythm. In another study, Bordet and colleagues compared melatonin rhythms across different disease stages in eight untreated and 18 treated PD patients with and without levodopa-related motor complications.[32] While there were no significant differences in the amount of melatonin secretion across the three PD groups, a progressive, although non-significant, trend to a

decrease in amplitude of the melatonin rhythm during evolution of PD was observed. In contrast to the lack of significant changes in the amplitude of melatonin rhythms, studies by Fertl and Bordet found changes in the phase of the melatonin rhythm.[32–34] Fertl et al. reported an earlier nocturnal melatonin peak in PD patients on levodopa than in the control group. This advanced phase was, however, not observed in de novo, untreated PD patients. Similarly, Bordet et al. reported earlier acrophase of melatonin secretion in treated compared with untreated PD patients. These observations raised the possibility that levodopa or decarboxylase inhibitors (benserazide and carbidopa) may have phase shifting properties. In our study, there was no difference in the timing of the melatonin rhythm between the groups.

Differences in the methodology used in our study compared with those in the prior studies may explain the discordant results. We assayed melatonin in 30-minute intervals over the 24-hour period, compared to 1–2 hours in prior studies. More frequent sampling increased our ability to more accurately determine the timing of the melatonin rhythm. In addition, experimental protocols employed in the prior studies did not control for environmental conditions and behaviors (light exposure, temperature, meal schedules, activity level) that are known to influence the timing and amplitude of circadian rhythms. Therefore, it is important to point out that the alterations in melatonin amplitude and phase reported in prior studies may have been influenced by external factors. To our knowledge, this is the first study that has examined circadian function in PD using a modified constant routine experimental design. In the prior studies, sleep quality and daytime sleepiness of the study participants were not measured. Therefore, observed differences in the amplitude and phase of the melatonin rhythms may be reflective of different sleep quality and alertness profiles between the study cohorts. Furthermore, these differences may be due to medication regimens, in particular the timing of dopaminergic medications. It has been proposed that administration of levodopa late in the evening may lead to stimulation of endogenous melatonin secretion, which may influence melatonin phase.[33,38]

The results of this study raise questions about the mechanism underlying the blunted circadian melatonin rhythm in PD. A potential confounder may be the effects of dopaminergic treatment on melatonin secretion. Due to safety and feasibility issues, we decided to study PD participants on their stable PD medication regimen. While we did not find associations between the dose of dopaminergic medications and the amplitude/AUC of the melatonin rhythm, the impact of dopaminergic therapy on circadian function needs to be further explored in PD patients naive to dopaminergic medications. We propose that the decreased amplitude of the melatonin rhythm in PD may result from dysfunction of the SCN and/or its afferent and efferent pathways. For example, reduced light exposure and/or impaired light transmission, partly due to dopaminergic retinal degeneration[39], may affect the circadian rhythm of melatonin in the PD population. While the structure and function of the SCN in PD has not been rigorously examined to date, degeneration of the central circadian pacemaker itself represents another possible mechanism leading to impaired circadian rhythmicity in PD. Finally, autonomic dysfunction, frequently seen in PD, may negatively affect melatonin secretion due to a dysfunction within the sympathetic ganglionic chain that is involved in the SCN regulation of the pineal melatonin rhythm of synthesis and release.[40]

The majority of scholarly work on melatonin in neurodegenerative disorders has been focused on its potential antioxidant properties and on its therapeutic role for sleep dysfunction commonly associated these disorders. Circadian disruption, including melatonin imbalance, has been associated with disorders other that PD, such as cognitive impairment, Alzheimer's disease, Huntington's disease, major depression, bipolar disorder, and headache disorders.[41–44] These disorders are frequently associated with impaired alertness and poor sleep and favorably respond to circadian-directed interventions such as increased environmental light, daytime activity and exogenous administration of melatonin.

Based on our findings, we propose that circadian dysfunction may be a novel mechanism involved in impaired alertness and perhaps in the development of other non-motor symptoms of PD. Furthermore, therapeutic approaches aimed at strengthening circadian function, such as timed bright light exposure, melatonin administration and modifications of physical activity, may have potential as complementary therapies for impaired sleep-wake cycles in the PD population. Future studies are needed to further explore our observations in larger cohorts of patients where objective measures of daytime sleepiness and sleep quality are utilized.

Acknowledgments

This study was supported by the NIH/NINDS (K23 NS072283), the American Brain Foundation / Parkinson's Disease Foundation Clinician Scientist Development Award, NIH/NIA (5P01AG011412-17) and the National Center for Advancing Translational Sciences (8UL1TR000150).

The authors thank Elizabeth B. Klerman, MD, PhD, for review of the manuscript.

Aleksandar Videnovic had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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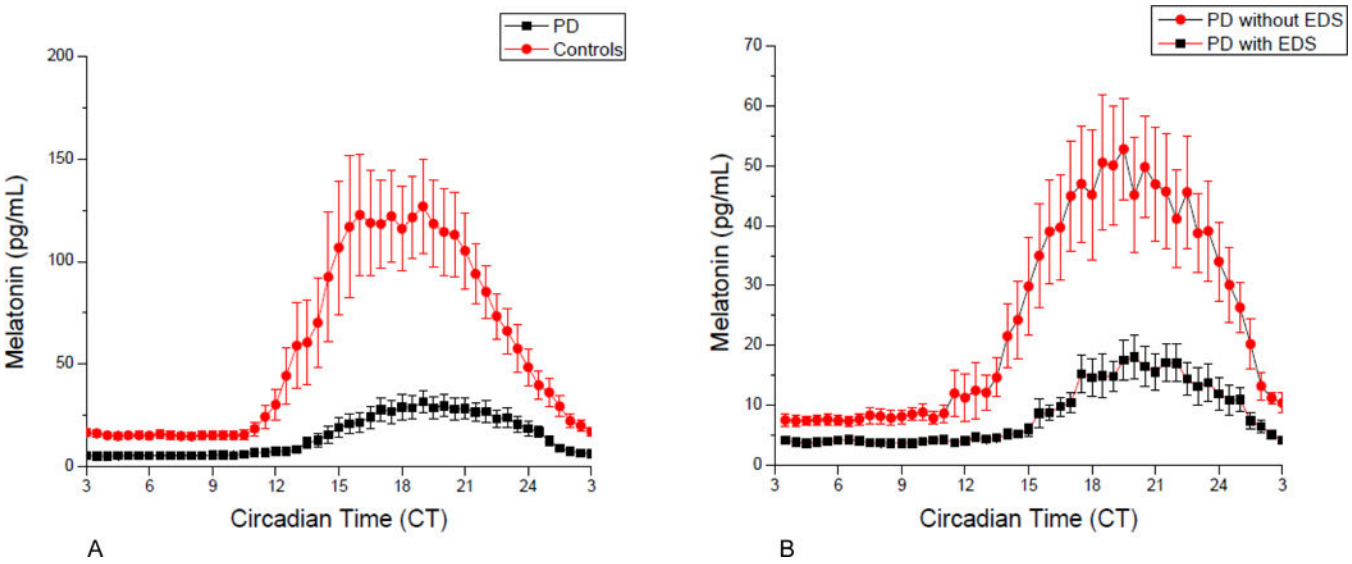

Figure 1.

Mean (± SD) 24-hour plasma melatonin concentration for: panel A – participants with PD and controls, panel B – PD participants without and with EDS

CT – circadian time (time since wake); EDS – excessive daytime sleepiness

Table 1

Demographics, disease characteristics, and parameters of circadian variations of melatonin secretion in controls and participants with PD.

Variable	PD	Controls	p-value	PD without EDS	PD with EDS	p-value
Demographics / Disease characteristics						
N	20	15		8	12	
Age	64.1±1.8	64.5±1.5	0.88	59.8±1.6	66.9±2.5	0.075
Gender	9M/11F	3M/12F	0.163*	3M/5F	6M/6F	0.67*
Education			0.58*			0.72*
College 4yrs or >	16	7		6	10	
College 1–3 yrs	3	2		2	1	
Grade 12 or <	1	2		0	1	
Smoking status (Y/N)	1/19	1/14	1.0	1/7	0/12	0.40
Caffeine consumption (cups/day)	1.3±0.2	1.5±0.3	0.42	1.22±0.4	1.30±0.2	0.75
PD duration (yrs)	6.7±1.4			5.4±1.4	7.5±2.1	0.48
LED (mg)	436.6±70.5			378.1±87.2	475.4±103.5	0.59
UPDRS total score	34.1±2.1			30.4±2.8	36.5±2.8	0.23
UPDRS-III score	22.7±1.1			21.3±2.0	23.6±1.2	0.35
ESS score	10.9±1.1	6.1±1.0	0.006	5.6±0.8	14.3±0.9	<0.001
PSQI score	6.1±0.7	6.7±1.1	0.50	6.4±0.5	5.9±1.1	0.56
Circadian markers						
Melatonin amplitude (pg/ml)	18.6±3.0	77.2±15.2	<0.001	30.2±4.6	10.8±1.6	0.001
Melatonin AUC (total)	332.7±52.4	1322.7±218.9	<0.001	574.2±81.5	189.7±20.6	0.001
Melatonin AUC (day)	161.6±20.6	490.8±72.4	<0.001	248.3±27.6	103.9±12.1	<0.001
Melatonin AUC (night)	171.1±34.3	831.9±161.0	<0.001	298.9±60.6	85.9±13.6	0.002
DLMO 2SD (CT)	6.6±0.4	7.3±0.6	0.42	6.3±0.8	6.8±0.5	0.61
DLMO 50% (CT)	15.3±0.8	14.3±0.4	0.12	15.2±0.7	15.3±1.2	0.44
DLMO 50% off (CT)	24.0±0.4	22.9±0.5	0.069	23.8±0.5	24.1±0.5	0.74
Midpoint melatonin secretion (CT)	19.8±0.4	18.6±0.4	0.074	19.5±0.5	20.1±0.7	0.56

All values are mean ± SE. p-values in this table were generated by the Kruskal-Wallis test, with the exception of the asterisked p-values that were generated by the Fisher's exact test. LED – levodopa equivalent dose; UPDRS – Unified Parkinson Disease Rating Scale; ESS – Epworth Sleepiness Scale; PSQI – Pittsburgh Sleep Quality Index; AUC – area under curve; CT–circadian time.