Circadian Melatonin Rhythm and Excessive Daytime Sleepiness in Parkinson Disease

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**IMPORTANCE** Diurnal fluctuations of motor and nonmotor symptoms and a high prevalence of sleep-wake disturbances in Parkinson disease (PD) suggest a role of the circadian system in the modulation of these symptoms. However, 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** 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, SETTING, AND PARTICIPANTS** A cross-sectional study from January 1, 2009, through December 31, 2012, of 20 patients with PD receiving stable dopaminergic therapy and 15 age-matched control participants. Both groups underwent blood sampling for the measurement of serum melatonin levels at 30-minute intervals for 24 hours under modified constant routine conditions at the Parkinson's Disease and Movement Disorders Center of Northwestern University.

**INTERVENTIONS** Twenty-four hour monitoring of serum melatonin secretion.

**MAIN OUTCOMES AND MEASURES** Clinical and demographic data, self-reported measures of sleep quality (Pittsburgh Sleep Quality Index) and daytime sleepiness (Epworth Sleepiness Scale), and circadian markers of the melatonin rhythm, including the amplitude, area under the curve (AUC), and phase of the 24-hour rhythm.

**RESULTS** Patients with PD had blunted circadian rhythms of melatonin secretion compared with controls; the amplitude of the melatonin rhythm and the 24-hour AUC for circulating melatonin levels were significantly lower in PD patients (P < .001). Markers of the circadian phase were not significantly different between the 2 groups. Compared with PD patients without excessive daytime sleepiness, patients with excessive daytime sleepiness (Epworth Sleepiness Scale score ≥10) had a significantly lower amplitude of the melatonin rhythm and 24-hour melatonin AUC (P = .001). Disease duration, Unified Parkinson's Disease Rating Scale scores, levodopa equivalent dose, and global Pittsburgh Sleep Quality Index score in the PD group were not significantly related to measures of the melatonin circadian rhythm.

**CONCLUSIONS AND RELEVANCE** Circadian dysfunction may underlie excessive sleepiness in PD. The nature of this association needs to be explored further in longitudinal studies. Approaches aimed to strengthen circadian function, such as timed exposure to bright light and exercise, might serve as complementary therapies for the nonmotor manifestations of PD.
Disturbances of sleep and wake are among the most common and disabling nonmotor manifestations of Parkinson disease (PD), affecting as many as 90% of patients.\textsuperscript{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.\textsuperscript{3-5} Current treatment options for disturbed sleep and alertness in PD are very limited and are associated with undesirable adverse effects. Therefore, the need to understand the mechanisms leading to sleep-wake dysfunction in PD and to develop innovative treatment modalities is great. The exact pathophysiological features of sleep-wake disturbances in PD remain largely unknown, but the cause is likely to be multifactorial, including the effect of motor symptoms on sleep, primary sleep disorders (sleep apnea and Rapid Eye Movement Sleep Behavioral Disorder), adverse effects of medications, and neurodegeneration of central sleep-wake regulatory systems.\textsuperscript{6-9}

Circadian rhythms are physiological and behavioral cycles with a periodicity of approximately 24 hours and are generated by an endogenous biological clock, the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus.\textsuperscript{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.\textsuperscript{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 the plasma melatonin level is a reliable marker of the endogenous circadian rhythm.\textsuperscript{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 biological factors in PD, including suppressed daily motor activity,\textsuperscript{19-21} loss of the normal circadian rhythm of blood pressure and heart rate,\textsuperscript{22-24} impaired sleep and daytime alertness,\textsuperscript{25-28} and fluctuations in levels of catecholamines,\textsuperscript{29} cortisol,\textsuperscript{30,31} and melatonin.\textsuperscript{32-34} Although these investigations suggest modifications of the circadian system in PD, the observed results reflect influences of endogenous and exogenous factors. In this study, we aimed to examine the endogenous circadian rhythm of melatonin secretion in participants with PD and healthy control individuals using a modified constant routine protocol, which is an experimental protocol designed to assess the human endogenous rhythmicity accurately 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 the Parkinson’s Disease and Movement Disorders Center of Northwestern University. Controls were recruited via advertising throughout the Chicago area and from the Aging Research Registry of healthy individuals interested in participating in research within the Northwestern Buehler Center on Aging. The study was approved by the Northwestern University institutional review board. Written consent was obtained from all participants.

**Study Participants**

Inclusion criteria were (1) diagnosis of idiopathic PD as defined by the UK Parkinson’s Disease Society Brain Bank Criteria,\textsuperscript{35} (2) PD at Hoehn and Yahr Scale stages 2 to 4,\textsuperscript{36,37} and (3) a stable dose of PD medications for at least 4 weeks before the study screening and throughout the study period. Exclusion criteria were (1) atypical or secondary forms of parkinsonism; (2) cognitive impairment as determined by a Mini-Mental State Examination score of no greater than 26; (3) presence of depression defined as a Beck Depression Inventory score of greater than 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 had been receiving a stable dose for at least 3 months before enrollment (tricyclics, trazodone, nefazodone, and mirtazapine were not allowed owing to their soporific properties); (7) use of medications known to affect melatonin secretion, such as lithium and α- and β-adrenergic antagonists; (8) high risk for sleep apnea as assessed by the Berlin Questionnaire;\textsuperscript{38} (9) shift work; (10) travel through 2 or more time zones within 90 days before study screening; and (11) unstable/serious medical illness. The same exclusion criteria were used for controls, who were matched for age with the PD patients.

**Study Protocol**

Severity of PD was assessed by the Unified Parkinson’s Disease Rating Scale (UPDRS)\textsuperscript{38} in the ON condition at the time of study enrollment. Sleep quality and daytime sleepiness were assessed by the Pittsburgh Sleep Quality Index (PSQI)\textsuperscript{39} and Epworth Sleepiness Scale,\textsuperscript{40} respectively. The Mini-Mental State Examination\textsuperscript{41} and Beck Depression Inventory\textsuperscript{42} were administered to all participants. All assessments were performed by a movement disorders specialist (A.V.). Demographic characterization of the study cohort included age, sex, educational level, race, smoking status, and caffeine consumption.

Each participant was instructed to maintain a regular (±30 minutes) sleep schedule for 14 days before testing, which was confirmed by sleep diaries. The experimental protocol was conducted in the clinical research unit at Northwestern Memorial Hospital. Participants were admitted to the clinical research unit in the evening hours. Lights-out time was determined from the mean habitual sleep time calculated from sleep diaries. On awakening on day 1 (circadian time [CT] 0), participants were fitted with an intravenous catheter in the forearm vein for repeated blood sampling and maintained in a modified constant routine condition for the 24-hour blood sampling. Each participant remained in a semirectumbent position with his or her head at a 45-degree angle during waking hours and received 150- to 250-kcal snacks, depending on his...
or her 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 levels. Participants were not sleep deprived for the duration of the 24-hour blood sampling period owing to safety concerns for the PD patients and were allowed 8 hours of sleep and/or time in bed, representing a modified constant routine protocol. To avoid disrupting participants’ sleep overnight, the indwelling catheter was connected to long plastic tubing that extended into an adjacent room. During the modified constant routine protocol, light levels in the clinical research unit were maintained at 10 lux or less during waking hours and reduced to less than 3 lux during sleep periods.

Plasma melatonin levels were measured by a radioimmunoassay from LDN. The sensitivity of the assay was 2 pg/mL; intra-assay coefficient of variation, 9.8% for a concentration of 50 pg/mL; and interassay coefficient of variation, 9.6% for a concentration of 40 pg/mL.

Melatonin levels were adjusted to a percentage of maximum (mean of the 3 highest values). The data were subsequently smoothed with the Lowess (Cleveland) curve-fitting procedure and interpolated at 1-minute intervals (GraphPad Prism; GraphPad Software, Inc). Melatonin acrophase and nadir were defined as the levels corresponding to the maximum and minimum of the best-fit curve, respectively, 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 during a 24-hour period using the trapezoidal method. Circadian phase was assessed by (1) dim-light melatonin onset (DLMO) calculated as 2 SDs above the mean baseline samples (DLMO 2SD) (baseline indicates the mean of the 3 lowest points from CT 3 to CT 10); (2) the time that the melatonin level rose to 50% of the maximum level (DLMO 50%); (2) the time that the melatonin level declined to 50% of the maximum level (DLMO 50% off); and (4) the melatonin level midpoint, defined as the mean of the DLMO 50% and DLMO 50% off values.

Data Analysis
We calculated descriptive summary statistics and obtained exploratory graphical displays for all variables of interest. We analyzed group differences using the Kruskal-Wallis and Fisher exact tests. Spearman correlation was used to assess the relationship between demographic and disease characteristics and the measures of melatonin circadian rhythm. P < .05 was considered significant. Statistical analysis was performed using commercially available software (SAS for Windows, version 9.3; SAS Institute, Inc).

Results
Twenty patients with PD who were receiving dopaminergic therapy and 15 controls completed the study protocol from January 1, 2009, through December 31, 2012. Demographics of the study cohort and disease characteristics are outlined in the Table. Demographic variables did not differ between PD patients and controls. The mean (SE) global PSQI score was 6.1 (0.7) in the PD group and 6.7 (1.1) in the control group (P = .50), indicating similar self-reported sleep quality between groups. The mean (SE) Epworth Sleepiness Scale score was 10.9 (1.1) in the PD group and 6.1 (1.0) in the control group (P = .006), indicating the presence of excessive daytime sleepiness among the PD patients. Twelve PD patients (60%) and 4 controls (27%) had excessive sleepiness, as defined by an Epworth Sleepiness Scale score of at least 10 (P = .09).

Circadian variations of melatonin secretion are presented in the Table. A preserved circadian rhythm of melatonin secretion occurred in both groups. Patients with PD had a blunted circadian rhythm of melatonin secretion (Figure, A) compared with controls; the amplitude of the circadian rhythm of melatonin (P < .001) and the 24-hour AUC for circulating melatonin levels (P < .001) were diminished significantly (4-fold) in PD patients compared with controls. The daytime (CT 0-16) and nighttime (CT 16-24) AUCs were significantly diminished in the PD group compared with controls (P < .001). Markers of the circadian phase were not significantly different between the 2 groups (Table).

Among PD patients, those with excessive daytime sleepiness had a significantly lower amplitude of the melatonin rhythm compared with those without excessive sleepiness (P = .001) (Table and Figure, B). Similarly, the 24-hour melatonin AUC was significantly lower in PD patients with excessive daytime sleepiness (P = .001). Demographics, disease duration, total and part III UPDRS scores, total levodopa equivalent dose, and total PSQI score were not significantly different in PD patients with or without daytime sleepiness.

The amplitude of the melatonin rhythm and the 24-hour melatonin AUC were inversely associated with the age of the PD patients (r = −0.54 [P = .01] and r = −0.47 [P = .04], respectively). Disease duration, the age at onset of PD, total and part III UPDRS scores, total levodopa equivalent dose, and global PSQI score 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 = .38] and r = −0.15 [P = .57], respectively). Controls 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 > .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 patients compared with 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 that examined 24-hour melatonin profiles in PD. Fertl and colleagues reported diurnal secretion curves of melatonin among 9 PD patients treated with levodopa in combination with benzserazide or carbidopa, 9 de novo untreated PD patients, and 14 age-matched controls. They did not find a difference in the amount of melatonin secreted or in the amplitude of the melatonin rhythm between the PD and control groups. Similar to our observations, the motor UPDRS score and 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 8 untreated and 18 treated PD patients with and without levodopa-related motor complications. Although no significant differences in the amount of melatonin secretion were observed across the 3 PD groups, a progressive, although nonsignificant, 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 et al and Bordet et al found changes in the phase of the melatonin rhythm. Fertl et al reported an earlier nocturnal melatonin level peak in PD patients receiving levodopa than in the control group. This advanced phase was, however, not observed in their untreated patient group. Similarly, Bordet et al reported an 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, no difference was observed in the timing of the melatonin rhythm between the groups.

Differences in the methods used in our study compared with those in the prior studies may explain the discordant results. We assayed melatonin levels in 30-minute intervals during a 24-hour period compared with 1- to 2-hour periods in prior studies. More frequent sampling increased our ability to determine the timing of the melatonin rhythm more accurately.

### Table. Demographics, Disease Characteristics, and Circadian Variations of Melatonin Secretion in Controls and Patients With PD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Groupa</th>
<th>PD Patient Groupa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD Patients (n = 20)</td>
<td>Controls (n = 15)</td>
</tr>
<tr>
<td>Demographics/Disease Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.1 (1.8)</td>
<td>64.5 (1.5)</td>
</tr>
<tr>
<td>Sex, No. of participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Completed college, ≥4 y</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Some college, 1-3 y</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>High school, ≤12 y</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Smoking status, No. yes/no</td>
<td>1/19</td>
<td>1/14</td>
</tr>
<tr>
<td>Caffeine consumption, cups/d</td>
<td>1.3 (0.2)</td>
<td>1.5 (0.3)</td>
</tr>
<tr>
<td>PD duration, y</td>
<td>6.7 (1.4)</td>
<td>NA</td>
</tr>
<tr>
<td>LED, mg</td>
<td>436.6 (70.5)</td>
<td>NA</td>
</tr>
<tr>
<td>UPDRS total score</td>
<td>34.1 (2.1)</td>
<td>NA</td>
</tr>
<tr>
<td>UPDRS III score</td>
<td>22.7 (1.1)</td>
<td>NA</td>
</tr>
<tr>
<td>ESS score</td>
<td>10.9 (1.1)</td>
<td>6.1 (1.0)</td>
</tr>
<tr>
<td>PSQI score</td>
<td>6.1 (0.7)</td>
<td>6.7 (1.1)</td>
</tr>
<tr>
<td>Circadian Markers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melatonin amplitude, pg/mL</td>
<td>18.6 (3.0)</td>
<td>77.2 (15.2)</td>
</tr>
<tr>
<td>Total</td>
<td>332.7 (52.4)</td>
<td>1322.7 (218.9)</td>
</tr>
<tr>
<td>Daytime</td>
<td>161.6 (20.6)</td>
<td>490.8 (72.4)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>171.1 (34.3)</td>
<td>831.9 (161.0)</td>
</tr>
<tr>
<td>DLMO 2SD, CTd</td>
<td>6.6 (0.4)</td>
<td>7.3 (0.6)</td>
</tr>
<tr>
<td>DLMO 50%, CTd</td>
<td>15.3 (0.8)</td>
<td>14.3 (0.4)</td>
</tr>
<tr>
<td>DLMO 50% off, CTd</td>
<td>24.0 (0.4)</td>
<td>22.9 (0.5)</td>
</tr>
<tr>
<td>Midpoint melatonin secretion, CTd</td>
<td>19.8 (0.4)</td>
<td>18.6 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CT, circadian time; DLMO, dim-light melatonin onset; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; LED, levodopa equivalent dose; NA, not applicable; PD, Parkinson disease; PSQI, Pittsburgh Sleep Quality Index; UPDRS, Unified Parkinson's Disease Rating Scale.

a Unless otherwise indicated, data are expressed as mean (SE).
b Unless otherwise indicated, generated by the Kruskal-Wallis test.
c Indicates generated by the Fisher exact test.
d Described in the “Study Protocol” subsection of the “Methods” section.
In addition, experimental protocols used in the prior studies did not control for environmental conditions and behaviors (light exposure, temperature, meal schedules, and activity level) that are known to influence the timing and amplitude of circadian rhythms. Therefore, we must 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 study is the first to examine 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 reflect different sleep quality and alertness profiles between the study cohorts. Furthermore, these differences may be caused by medication regimens, in particular the timing of dopaminergic medication administration. Administration of levodopa late in the evening has been proposed to lead to stimulation of endogenous melatonin secretion, which may influence melatonin phase.33,45

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 medication.
gic treatment on melatonin secretion. Owing to safety and feasibility issues, we studied the PD patients with a stable PD medication regimen. Although we did not find associations between the dose of dopaminergic medications and the amplitude/AUC of the melatonin rhythm, the effect of dopaminergic therapy on circadian function needs to be explored further 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 resulting from dopaminergic retinal degeneration, may affect the circadian rhythm of melatonin in the PD population. Although the structure and function of the SCN in PD has not been rigorously examined to date, degeneration of the central circadian pacemaker represents another possible mechanism leading to impaired circadian rhythmicity in PD. Finally, autonomic dysfunction, frequently seen in PD, may have a negative effect on melatonin secretion because of a dysfunction within the sympathetic ganglionic chain that is involved in the SCN regulation of the pineal melatonin rhythm of synthesis and release. 47

Most scholarly work on melatonin in neurodegenerative disorders has focused on its potential antioxidant properties and therapeutic role in sleep dysfunction commonly associated with these disorders. Circadian disruption, including melatonin imbalance, has been associated with disorders other than PD, such as cognitive impairment, Alzheimer disease, Huntington disease, major depression, bipolar disorder, and headache disorders. 48–51 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.

**Conclusions**

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 nonmotor symptoms of PD. Furthermore, therapeutic approaches aimed at strengthening circadian function, such as timed exposure to bright light, 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 using objective measures of daytime sleepiness and sleep quality.
Circadian Melatonin Rhythm in Parkinson Disease


