In the largest survey of nonmotor symptoms of Parkinson disease (PD), 64% of patients reported sleep problems, representing the second most common nonmotor complaint. Such problems are typically attributed to motor impairment, nocturia, sleep-disordered breathing, neuropsychiatric symptoms, and medications but may be an intrinsic feature of the disease itself.

Sleep is governed by the intricate interplay between sleep-wake homeostasis and circadian rhythms in the body. These rhythms are largely controlled by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and tuned to the 24-hour day by environmental cues such as light, motor activity, and food intake. Clock genes form the molecular machinery of this circadian system, operating via autoregulatory feedback loops. The key loop involves the proteins BMAL1 and CLOCK, which form a heterodimer to regulate the expression of clock-controlled genes, thus driving SCN circadian output. The BMAL1/CLOCK complex also activates the expression of Period (Per) and Cryptochrome (Cry) genes, whose products (PER and CRY) represent negative elements in the loop and inhibit the activity of BMAL1/CLOCK (and hence their own expression). In a separate stabilizing loop, the Rev-Erbα and retinoic orphan receptor genes fine-tune the oscillations generated by the main loop. Unlike other PER proteins, PER2 can directly interact with REV-ERBα to regulate Bmal1 expression.

The SCN transmits its circadian signal to peripheral tissues via neural and hormonal mechanisms, synchronizing circadian oscillations throughout the body. Endocrine parameters, such as melatonin and cortisol profiles, can be used as surrogate markers of the central clockwork in vivo, since their rhythmic output is generated by the SCN. It has also been shown that circadian clock gene expression can be readily measured in peripheral blood mononuclear cells and displays significant circadian rhythmicity, making it possible to study central (serum cortisol and melatonin levels) and peripheral (clock gene expression) circadian markers using human blood samples.
In this study we set out to define the sleep and circadian phenotype of patients with early-stage Parkinson disease.

Methods

We began by studying patients newly diagnosed with PD who were recruited to a community-based incidence study in Cambridgeshire, England (Parkinsonism–Incidence and Cognitive Heterogeneity in Cambridgeshire [PICNICS]). The study was approved by the Cambridgeshire Research Ethics Committee (REC 09/H0308/7) and performed according to the Declaration of Helsinki, with all participants providing written informed consent. Patients completed the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Parkinson’s Disease Questionnaire (PDQ-39) and underwent a range of other assessments (eAppendix in Supplement).

To further investigate sleep dysfunction, we carried out more comprehensive analyses on a subgroup of 30 patients with PD (16 men, 14 women) recruited consecutively from the PICNICS study, as well as 15 healthy age- and sex-matched controls (recruited via local advertising).

Sleep Questionnaires

Sleep complaints were assessed using the Parkinson’s Disease Sleep Scale (PDSS), Rapid Eye Movement (REM) Sleep Behavior Disorder Questionnaire (RBDQ-HK), and ESS.

Actigraphy Assessment

Along with keeping sleep diaries, all participants wore an activity monitor (Actiwatch; Cambridge Neurotechnology) on the nondominant wrist continuously during the 14-day period prior to their polysomnography assessment.

Polysomnography

Participants were admitted for 2 consecutive nights of polysomnographic recording based on their habitual bed times (first night was an acclimatization night and not analyzed). Sleep recordings were scored visually by trained raters using the American Academy of Sleep Medicine guidelines. See eAppendix in Supplement for more information on the polysomnography protocol, parameters measured, and diagnostic criteria for primary sleep diagnoses.

Circadian Rhythm Analysis

A peripheral venous cannula was inserted prior to the start of sampling at 1 PM. Over the next 24 hours, patients adhered to their habitual bed times and blood was collected through a long catheter to prevent sleep disruption. Subjects remained sedentary apart from bathroom visits. Meal times were fixed and no daytime naps were allowed. Temperature was constant at approximately 21°C. Patients were not strictly shielded from external light but lighting levels were less than 5 lux once lights were turned off.

Serum melatonin and cortisol levels were measured every 90 minutes by enzyme-linked immunosorbent assays (eAppendix in Supplement). Bmal1, Per2, and Rev-Erbα gene expression was reported as a relative ratio to the constitutively expressed nonrhythmic β-actin gene every 3 hours by 1-step real-time quantitative reverse-transcription polymerase chain reactions (eAppendix in Supplement). All samples were analyzed in triplicate and averaged.

Statistical Analysis

Full details of the statistical analyses performed are given in eAppendix in Supplement.

Results

Clinical Characteristics

Two hundred thirty-nine patients newly diagnosed with PD were recruited to the PICNICS study (Table 1). One hundred ninety-two patients (80%) returned the PSQI, 170 patients (71%) returned the ESS, and 206 patients (86%) returned the PDQ-39. Age, sex, Movement Disorders Society–Unified Parkinson’s Disease Rating Scale; PICNICS, Parkinsonism—Incidence and Cognitive Heterogeneity in Cambridgeshire; PSQI, Pittsburgh Sleep Quality Index; PDQ-39, Parkinson’s Disease Questionnaire.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>62</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>68 (9)</td>
</tr>
<tr>
<td>Time since diagnosis, mo</td>
<td>2.2 (2.9)</td>
</tr>
<tr>
<td>Receiving dopaminergic therapy, %</td>
<td>42</td>
</tr>
<tr>
<td>LEDD in treated patients, mg</td>
<td>316 (209)</td>
</tr>
<tr>
<td>MDS-UPDRS Part III score</td>
<td>32 (12)</td>
</tr>
<tr>
<td>Hoehn and Yahr score</td>
<td>1.8 (0.8)</td>
</tr>
<tr>
<td>ACE-R score</td>
<td>90 (7)</td>
</tr>
<tr>
<td>Global PSQI score</td>
<td>6.1 (3.9)</td>
</tr>
<tr>
<td>Total PDQ-39 score</td>
<td>26.1 (20.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-R, Addenbrooke’s Cognitive Examination; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorders Society–Unified Parkinson’s Disease Rating Scale; PICNICS, Parkinsonism—Incidence and Cognitive Heterogeneity in Cambridgeshire; PSQI, Pittsburgh Sleep Quality Index; PDQ-39, Parkinson’s Disease Questionnaire.

*Twenty-four percent, levodopa; 16%, dopamine agonist; 5%, amantadine, and 4%, rasagiline. Twenty-nine patients (12%) were also taking antidepressants, 10 patients (4%) were taking opiates, 7 patients (3%) were taking benzodiazepines, and 3 patients (1%) were taking zopiclone.
amantadine. Four patients (13%) were taking antidepressants and 2 patients (7%) were taking benzodiazepines.

Sleep Complaints and Quality of Life
In the incident PICNICS cohort, global PSQI scores ranged from 0 to 20, with 94 patients (49%) classified as poor sleepers (global PSQI score greater than 5). Poor sleepers were significantly more likely to have problems with nonmotor activities of daily living, low mood, apathy, and impaired cognition (eTable 3 in Supplement). Moreover, the PSQI score was found to be an independent risk factor for increased PDQ-39 score (β = 0.170, P = .007).

In the intensive sleep subgroup, patients with PD had lower total PDSS scores compared with controls (β = −0.373, P = .01), reflecting their greater subjective sleep complaints. Specifically, they scored lower on subscores relating to sleep quality (β = −0.372, P = .01), sleep refreshment (β = −0.422, P = .005), and nocturnal motor impairment (β = −0.408, P = .007). Using the suggested RBDQ-HK cutoff score of 19, 9 patients (30%) and 1 control (7%) reported symptoms suggestive of REM parasomnia. The ESS scores were not significantly different between the groups.

Actigraphy Assessment
Patients with PD had reduced light to dark ratio (β = −0.393, P = .01), as well as higher intradaily variability (β = 0.355, P = .02) showing that they had more fragmented motor activity during the 24-hour period compared with controls. Apart from later sleep onset time (β = 0.316, P = .04), there were no actigraphy differences in nocturnal motor activity between patients with PD and controls (eTable 3 in Supplement).

Primary Sleep Diagnoses
Eight patients with PD had evidence of REM sleep behavior disorder (RBD) (Table 2). Ten patients with PD had periodic limb movements of sleep (defined as a periodic limb movement index greater than 15 per hour) compared with 5 controls. Two patients with PD had central sleep apnea (CSA), while 5 patients and 5 controls had evidence of moderate or severe obstructive sleep apnea (OSA) (moderate = 2 and severe = 3 in both groups). In all cases, individuals had not been diagnosed with these conditions prior to the sleep study. Patients with moderate or severe OSA were more likely to have increased body mass index (unpaired t test, P < .001).

Changes in Sleep Architecture
On detailed polysomnography studies, patients with PD exhibited increased sleep latency (β = 0.333, P = .04), reduced sleep efficiency (β = −0.411, P = .008), increased stage 1 sleep (β = 0.307, P = .03), and reduced REM sleep (β = −0.363, P = .02) (Table 3). Two patients with PD exhibited no REM sleep whatsoever. These aspects of the sleep architecture were similarly affected in patients with and without OSA (eTable 4 in Supplement).

In patients with PD, there was no significant correlation between sleep efficiency and total PDSS score (Pearson correlation, r = 0.156, P = .42). The RBDQ-HK was poor at correctly identifying patients with polysomnography-confirmed RBD (positive predictive value, 33%), but significantly better at correctly excluding the condition (negative predictive value, 76%).

To investigate the effect of dopaminergic medications on sleep architecture, patients with PD were divided into subgroups according to whether they were taking levodopa, dopamine agonists, or neither. Accepting the small subgroup sizes, differences between groups were not statistically significant (eTable 5 in Supplement).

Excessive Daytime Sleepiness
Patients with PD had a tendency towards hypersomnolence compared with controls, considering both mean sleep latency (MSL) (β = −0.259, P = .09) and individual nap opportunities (repeated-measures 2-way analysis of variance, F_{1,38} = 3.985, P = .053). All 4 of the patients with severe excessive daytime sleepiness (MSL less than 5 minutes) were in the PD group. No sleep-onset REM episodes were observed. There was a strong correlation between ESS score and reduced MSL (Spearman correlation, r = −0.548, P = .002). Reduced MSL was associated with dopamine agonist use (unpaired t test, P = 0.04).

Table 2. Primary Sleep Diagnoses in Patients With PD vs Controls

<table>
<thead>
<tr>
<th>Primary Sleep Disorder</th>
<th>Patients With PD (n=30)</th>
<th>Controls (n=15)</th>
<th>Univariatea</th>
<th>Multivariateb</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBD</td>
<td>27</td>
<td>0</td>
<td>.04c</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>PLMSd</td>
<td>33</td>
<td>33</td>
<td>&gt;.99</td>
<td>.56</td>
</tr>
<tr>
<td>RLS</td>
<td>3</td>
<td>0</td>
<td>&gt;.99</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>OSAe</td>
<td>17</td>
<td>33</td>
<td>.47</td>
<td>.33</td>
</tr>
<tr>
<td>CSA</td>
<td>7</td>
<td>0</td>
<td>&gt;.99</td>
<td></td>
</tr>
<tr>
<td>EDSf</td>
<td>30</td>
<td>13</td>
<td>.28</td>
<td>.40</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, central sleep apnea; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea; PD, Parkinson disease; PLMS, periodic limb movements of sleep; RBD, rapid eye movement sleep behavior disorder; RLS, restless legs syndrome.

a Fisher exact test used.

b Logistic regression used, adjusting for age and sex (and, in the case of OSA, the effect of body mass index).

c Significant difference at .05 level.

d Periodic limb movement index greater than 15 per hour.
e Moderate or severe OSA (apnea-hypopnea index greater than 15 events per hour).
f Defined as mean sleep latency less than 8 minutes.
Table 3. Polysomnography Findings in Patients With PD vs Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) Patients With PD (n=29)</th>
<th>Mean (SD) Controls (n=15)</th>
<th>P Value</th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep, h:min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start</td>
<td>21:30 (04:11)</td>
<td>20:55 (05:47)</td>
<td>.80</td>
<td>.58</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>End</td>
<td>06:55 (00:29)</td>
<td>06:44 (00:38)</td>
<td>.33</td>
<td>.32</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>407 (69)</td>
<td>420 (48)</td>
<td>.52c</td>
<td>.49</td>
<td>.27</td>
<td></td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>13 (13)</td>
<td>6 (4)</td>
<td>.13</td>
<td>.04d</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>REM latency, min</td>
<td>117 (100)</td>
<td>77 (42)</td>
<td>.26</td>
<td>.12</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>78 (10)</td>
<td>85 (7)</td>
<td>.005&lt;0d</td>
<td>.008&lt;0d</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>AI, arousals/h</td>
<td>21 (7)</td>
<td>24 (17)</td>
<td>.94</td>
<td>.16</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>PLMI, events/h</td>
<td>17 (29)</td>
<td>16 (25)</td>
<td>.92</td>
<td>.51</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>11 (17)</td>
<td>18 (22)</td>
<td>.09</td>
<td>.20</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>DI, events/h</td>
<td>8 (15)</td>
<td>15 (21)</td>
<td>.004&lt;0d</td>
<td>.012&lt;0d</td>
<td>.33</td>
<td></td>
</tr>
<tr>
<td>Minimum oxygen saturation, %</td>
<td>86 (4)</td>
<td>80 (7)</td>
<td>.002&lt;0d</td>
<td>&lt;0.01&lt;0d</td>
<td>.86</td>
<td></td>
</tr>
<tr>
<td>MSL, min</td>
<td>11 (5)</td>
<td>14 (4)</td>
<td>.06</td>
<td>.09</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>Time in sleep stages, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake</td>
<td>21 (11)</td>
<td>15 (7)</td>
<td>.08</td>
<td>.03</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>10 (5)</td>
<td>7 (3)</td>
<td>.01c&lt;0d</td>
<td>.02&lt;0d</td>
<td>1.67</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>49 (10)</td>
<td>51 (10)</td>
<td>.46</td>
<td>.35</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Stages 3 and 4</td>
<td>8 (6)</td>
<td>11 (6)</td>
<td>.23</td>
<td>.33</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>REM</td>
<td>12 (6)</td>
<td>16 (6)</td>
<td>.02c&lt;0d</td>
<td>.01&lt;0d</td>
<td>1.10</td>
<td></td>
</tr>
</tbody>
</table>

**Reduced Melatonin Production**

The time-dependent variation in melatonin concentration was statistically significant in controls ($F_{1,46,776} = 1.873, P = .09$) but not in patients with PD ($F_{1,3,290} = 0.738, P = .47$) (Figure 1A). Patients with PD had a reduced area under the curve ($β = -0.341, P = .048$) and a reduced melatonin nadir ($β = -0.461, P = .004$) (eTable 6 in Supplement). There was a significant main group effect on melatonin concentration ($F_{1,3,3} = 4.532, P = .04$). There was no change in the timing of melatonin onset or offset. Cosinor analysis confirmed a robust circadian melatonin profile in the majority of participants—only 5 patients (18%) and 1 control (7%) were arrhythmic—and there was no evidence of a melatonin phase shift in patients with PD compared with controls (Mann-Whitney test, $P = .45$).

The mean gap between sleep and circadian assessments was 5.8 months (SD, 3.6), but habitual sleep times were not significantly different between these visits (Mann-Whitney test, $P = .68$). We found that reduced slow-wave sleep was associated with reduced melatonin area under the curve in patients with PD (Spearman correlation, $r = 0.483, P = .02$), while reduced sleep latency was associated with reduced melatonin area under the curve (Spearman correlation, $r = 0.446, P = .02$) and reduced melatonin area under the curve (Spearman correlation, $r = 0.479, P = .02$). Lower melatonin onset concentration was associated with increased sleep latency in patients with PD (Pearson correlation, $r = -0.323, P = .04$). Melatonin parameters were not associated with disease characteristics such as motor phenotype or treatment status (de novo vs treated patients).

**Elevated Serum Cortisol Levels**

The time-dependent variation in cortisol concentration was not statistically significant in either group owing to large interindividual variation (Figure 1B). Patients with PD had an increased acrophase ($β = 0.502, P = .001$), increased amplitude ($β = 0.485, P = .002$), and increased area under the curve ($β = 0.615, P < .001$) (eTable 7 in Supplement). There was a significant main group effect on cortisol concentration ($F_{1,3,30} = 15.720, P < .001$). There was no change in the timing of cortisol onset or offset. Cosinor analysis revealed that 11 patients (41%) and 1 control (7%) had arrhythmic cortisol profiles, and there was no evidence of a cortisol phase shift in patients with PD compared with controls (Mann-Whitney test, $P = .36$). There was no correlation between cortisol and objective sleep measures.

**Peripheral Clock Gene Expression Differences**

The main finding was a lack of time-dependent variation in *Bmal1* expression in patients ($F_{7,175} = 0.794, P = .59$) compared with controls ($F_{7,84} = 2.229, P = .04$) (Figure 2A). Neither Per2 or Rev-Erb showed statistically significant time-dependent variation in patients or controls, despite visually similar 24-hour expression profiles in both groups (Figure 2B and C). No interaction was found between group and time for any of the 3 genes studied; however, patients with PD did have increased expression of Per2 and Rev-Erb at 4 AM (unpaired t test, $P = .04$ and $P = .03$, respectively). There was no evidence of a phase shift in *Bmal1*, Per2, or Rev-Erb on cosinor analysis (Mann-Whitney test, $P = .86$, $P = .44$, and $P = .84$, respectively). Overall, few patients showed peripheral clock gene expression profiles that were rhythmic: 2 patients (7%) and no controls (0%) for *Bmal1*, 3 patients (10%) and 3 controls (20%) for Per2, and 5 patients (22%) and 3 controls (20%) for Rev-Erb. There were no significant differences in sleep architecture in patients with rhythmic vs nonrhythmic clock gene profiles.

**Abbreviations:** AH1, apnea-hypopnea index; AI, arousals index; DI, desaturation index; MSL, mean sleep latency; PD, Parkinson disease; PLMI, periodic limb movement index; REM, rapid eye movement.

*e Not possible to distinguish electroencephalography wakefulness from individual sleep stages in 1 patient with PD; therefore, these data are excluded from the analysis.

$f Linear regression used, adjusting for age and sex (and, in the case of AHI, the effect of body mass index).

$t* Unpaired t test; other wise Mann-Whitney test used.

$ Significant difference at .05 level.

$ In 2 patients with PD, MSL is based on 4 rather than 5 Multiple Sleep Latency Test nap opportunities.
In this study, we have confirmed that sleep complaints are common in patients newly diagnosed with PD and correlate significantly with poorer quality of life. We have found that patients with PD have an abnormal sleep macro-architecture including increased sleep latency, reduced sleep efficiency, and reduced sleep duration compared to controls.

These graphs show the mean (SEM) serum melatonin and cortisol concentrations at each time point. In healthy individuals, melatonin levels typically rise in the late evening while cortisol levels peak in the early morning. A, Significant group effect on melatonin concentration on repeated-measures 2-way analysis of variance and lack of a statistically significant time-dependent variation in melatonin concentration over the 24-hour sampling period. Patients with PD also had a reduced area under the curve and a reduced melatonin nadir. There were individual missing melatonin data points in 6 patients with PD (1.1% of total dataset) and 1 control (0.4% of total dataset). B, Significant group effect on cortisol concentration on repeated-measures 2-way analysis of variance. Patients with PD also had an increased acrophase, increased amplitude, and increased area under the curve. There were individual missing cortisol data points in 7 patients with PD (1.3% of total data set) and 4 controls (1.6% of total data set).

These graphs show the mean (SEM) normalized gene expression levels for the 3 clock genes studied at each time point in peripheral blood mononuclear cells. We sought to investigate whether patients with PD exhibited the same peripheral clock gene expression oscillations as one would expect in healthy individuals. Loss of the time-dependent variation in Bmal1 was seen in patients with PD over the 24-hour period (A), together with higher expression of Per2 and RevErbα at 4 AM (B and C, respectively). There were individual missing data points in 2 patients with PD (0.8%) and no controls.

Discussion

In this study, we have confirmed that sleep complaints are common in patients newly diagnosed with PD and correlate significantly with poorer quality of life. We have found that patients with PD have an abnormal sleep macro-architecture including increased sleep latency, reduced sleep efficiency, and reduced sleep duration compared to controls.
REM sleep and that this relates to alterations in relevant circulating hormone profiles. These abnormalities are also linked to differences in peripheral clock gene expression.

Almost half of our newly diagnosed PD cohort were poor sleepers according to the PSQI, a validated sleep questionnaire that has been recommended for PD research. In the population-based Norwegian Park West study, only 17.8% of patients with early untreated PD were found to have sleep problems based on the Neuropsychiatric Inventory sleep subscore.9 In the population-based Norwegian Park West study, only 17.8% of patients with early untreated PD were found to have sleep problems reported in prevalent cohorts.11 There was discordance between subjective and objective sleep measures in our study, suggesting that other factors may influence patients’ perceived sleep quality. For instance, we found that poor sleepers were more likely to exhibit low mood, apathy, and impaired cognition.

We found that 8 patients in our intensive sleep subgroup had RBD, which is not surprising since RBD can predate the typical motor features of PD by many years.22 In line with other studies,23,24 OSA was no more common in nonobese patients with PD than in the general population. Similarly, CSA was uncommon in idiopathic PD and its presence should raise the possibility of an atypical parkinsonian syndrome such as multiple system atrophy.24 Finally, we replicated our previous findings, showing that significant excessive daytime sleepiness can be present from the earliest stages of disease and is associated with dopamine agonist use.15

Pooled analysis has not been undertaken on previous case-control studies investigating sleep architecture in PD owing to differences in methods and parameters measured.16 Bušková and colleagues17 compared 15 patients with early untreated PD vs 15 matched controls and found that patients with PD had a tendency for reduced sleep efficiency, increased wakefulness, and reduced REM sleep. Yong and colleagues18 reported similar findings in their prevalent cohort and Diederich and colleagues19 concluded that there was a progressive destructuring of the sleep architecture in patients with more advanced PD.

We hypothesized that the sleep-wake disturbances in early PD might reflect a disruption to the neural circuitry controlling circadian rhythms. Decline in SCN activity is already believed to be responsible for reduced melatonin output and sleep-wake disruption in older healthy adults.20,21 There is evidence from neuropathological22 and imaging23 studies that the hypothalamus is affected in PD. Moreover, it has been shown that mice overexpressing a-synuclein or sleep disorder and Diederich and colleagues19 concluded that there was a progressive destructuring of the sleep architecture in patients with more advanced PD.

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12. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16 year update on a previously reported series. Sleep Med. 2013;14(8):744-748.