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# Daytime sleep in Parkinson's disease measured by episodes of immobility

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ABSTRACT

Excessive daytime sleepiness (EDS) is common in Parkinson's Disease (PD). Actigraphy uses periods of immobility as surrogate markers of nighttime sleep but there are no examples of its use in assessing EDS of PD. A commercial wrist worn system for measuring bradykinesia and dyskinesia also detects 2 min periods of immobility, which have a 85.2% concordance with the detection of sleep by ambulatory daytime polysomnography, ($p < 0.0001$ Chi Squared). High Epworth Sleepiness Scores (ESS) were associated with a proportion of time immobile (PTI) ($p = 0.01$ Mann–Whitney U). The median PTI between 0900 and 1800 h w in 30 age matched control subjects was 2%, representing 10 min and PTI at or above the 75th percentile (5% or 27 min) was taken as a high level. PD patients had higher PTI (median 4.8%) than controls ($p < 0.0001$, Mann–Whitney U). PD subjects with a high PTI had more bradykinesia, less dyskinesia and higher PDQ39 scores than those with low PTI. There was no relationship between PTI and dose or type of PD medications. However, in 53% of subjects, PTI increased in the 30–60 min after levodopa confirming that in some subjects levodopa results in increased sleepiness. In summary, immobility is a surrogate marker of daytime sleep in PD, confirmed by correlation with PSG and ESS. PD subjects measured this way are more likely to be sleepy and sleepy PD subjects are more likely to be bradykinetic and have a higher PDQ39. Levodopa leads to an increase in sleepiness in more than half of subjects post dosing.



## 1. Introduction

Excessive daytime sleepiness (EDS) is common in Parkinson's Disease [1–4], occurring in 20–50% of subjects [3,5] and is considered to be present when the score from the Epworth Sleepiness Scale (ESS) is 10 or greater [6,7]. Anti-parkinsonian therapies may contribute to EDS [8], especially dopamine D2–D3 agonists [9–12], apomorphine [13] and levodopa monotherapy [10]. While the dose of antiparkinsonian medications was related to EDS in some studies [14,15], this has not been a universal finding [8,16–18]. Indeed, in some studies, higher levodopa doses have been associated with increased vigilance [8,18]. EDS may also be associated with severity of PD [5,15] and the evidence for a correlation with severity of striatal dopamine denervation has been summarized by Arnulf [5]. On the other hand, others claim that fatigue, rather than EDS, may correlate better with disease severity [19].

Night-time sleep deprivation and fragmentation caused by nocturnal motor symptoms, sleep apnea, periodic leg movements, REM sleep behavioral disorder or disruption to the sleep-wake system [2,20] also contribute to EDS in PD. These night time factors have received greater attention than EDS itself, in part because studying EDS in PD is hampered by existing methods of detection which are largely based on self/spouse reporting through diaries or other subjective measures. Under reporting is common, with more than one third of PD patients failing to perceive daytime naps lasting minutes and involving slow wave sleep [21]. While daytime polysomnography (PSG) accurately measures sleep state, the

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equipment lacks practicality in the optimal recording environment of normal daily activities. Multiple Sleep Latency Testing (MSLT) is also used to measure daytime sleepiness but also does not assess subjects in a naturalistic setting and does not always correlate with ESS [22]. While absence of movement, as measured for example by actigraphy, has proved to be a good proxy of night time sleep quality and correlates with PSG and subjective sleep measures [23], there are no studies that use it to measure daytime sleep in PD.

Recently, we described a system consisting of algorithms that operate on wrist accelerometry obtained in an ambulatory setting to quantify bradykinesia and dyskinesia (the Parkinson's Kinetigraph or PKG, Global Kinetics Corporation) [24]. During these recordings, many PD subjects had episodes of complete immobility. The PKG produces scores every 2 min, representing the briefest of these episodes, but some were prolonged (i.e. hours). On direct questioning of subjects and spouses, the most important reason for immobility appeared to be daytime drowsiness or sleep. While the PKG is similar to actigraphy in using accelerometry to detect absence of movement [25], it differs by providing simultaneous measures of bradykinesia and dyskinesia over the recording period and by recording the timing of levodopa consumption. Thus, the PKG provides the opportunity of linking these episodes of immobility to bradykinesia, dyskinesia and PD medications.

## 2. Methods

Subjects with idiopathic levodopa responsive PD were recruited from the Movement Disorder Clinic at St Vincent's Hospital. Control subjects were recruited from the spouses of PD subjects. The study was approved by the St Vincent's Health Human Research & Ethics Committee. All subjects provided consent. Control subjects all wore the PKG and 10 also had ESS performed. All PD subjects wore the PKG and had ESS scores, UPDRS III motor scores and daily levodopa equivalent dose (LED) recorded. A significant but variable proportion of PD patients also had modified Abnormal Involuntary Movements (AIMS), PDQ39 and Addenbrooke's Cognitive Examination (ACE) scores. All clinical rating scales were performed in the "on state" prior to wearing the PKG.

### 2.1. Recording protocol

The PKG system was used to provide bradykinesia and dyskinesia scores (BKS and DKS respectively) [24]. This device is worn on the wrist of the most severely affected side and contains a rechargeable battery, a triaxial accelerometer, memory, a reminder of medications due, a means for recording when medications were taken, as well as a capacitive sensor to detect removal from the wrist. Subjects wore the device for 10 consecutive days, from first arising until retiring at night, except when washing. At the end of the recording period, data was downloaded and analyzed using a proprietary algorithm to calculate BKS and DKS [24]. The BKS and DKS are continuous variables. In the case of the BKS, the scores can range from movements that are made with normal acceleration to those that have very low or no acceleration. The correlation between BKS and DKS and conventional clinical rating scales has been discussed elsewhere [24].

### 2.2. Identification of immobility by the PKG

Ten day PKG recordings provided BKS and DKS every 2 min and Fig. 1 provides examples of day long recordings from a control and 2 PD subjects. On inspection of Fig 1 A, B, C it was apparent that some BKS were very low ($\leq -80$, highlighted by beige band). According to the sensor in the PKG, the device was being worn at these times, but the output of the accelerometer indicated that the subject was completely motionless and so the episodes were called episodes of immobility (Fig. 1). Thus Episodes of Immobility were of 2 min or greater in duration and with BKS that were at or below the threshold of −80 BKS. These Episodes of Immobility were removed from all subsequent assessments of BKS and DKS used to represent bradykinesia and dyskinesia in these subjects.

### 2.3. Method for ambulatory daytime polysomnography (PSG)

Ambulatory PSG was performed using a Philips Respironics Alice PDx device for data acquisition, using a modified montage only acquiring a frontal EEG signal (references to A1/A2 depending on application point) and a single lead ECG. Recordings were made from 900 h to 1930 h on 3 PD subjects. The data was analyzed using Respironics SleepWare G3 version 3.3.3 software and 30 s epochs were scored for sleep presence, focusing mainly on stages N1–N3 (non REM sleep), according to the ASTA/ASA guidelines for the Scoring of Sleep issued in 2010 [26]. No REM sleep was observed. As the PKG provides a BKS every 2 min and the PSG provides a sleep score every 30 s, the PSG was reduced to single score over the 2 min to allow the PKG and PSG to be compared. If two or more 30 s PSG epochs in a 2 min PKG epoch were "positive" for sleep, then the PSG was taken as reporting "sleep" for that 2 min period.

## 3. Results

PKG recordings were obtained from 68 PD patients aged 40–80 years (median 65.9), with disease duration from 6 months to 25 years (mean 8.7 years), LED (median 895, interquartile range: 400–431) and UPDRS III scores ranging from 4 to 53 (mean 25.9). There were 30 controls, aged 50–84 years (mean 65.8), and 10 of these who were matched for age (range 56–82 years: mean 68) also had an ESS performed.

### 3.1. Periods of immobility as a measure of daytime sleep

Epochs of immobility (see Methods) last 2 min and would qualify as a period of sleep when measured by actigraphy [25] and appeared to coincide with sleep in our study. For example, examination of Fig. 1F suggests this subject awoke most days about 0630 h and retiring about 2000 h, and immobility (suggesting sleep) is almost continuous before and after these times respectively. It is unlikely that most epochs of immobility represents severe bradykinesia because in many cases (e.g. subject in Fig. 1F) these periods last for >10 min, occur immediately alongside periods of much lesser bradykinesia severity, occur in controls (albeit less frequently) and importantly the subject and/or their spouses reported that they are explained by somnolence or sleep. Because the time interval of interest will vary, the proportion of time immobile (PTI) will be used. For example, the period between 0900 and 1800 is 540 min, and so the case in Fig. 1B and E had 32 min of PTI, representing a PTI of 6%.

Daytime ambulatory PSG was performed on 7 PD subjects whose time immobile, measured on a previous PKG recording were greater than 30 min/day. PSG and PKG were recorded simultaneously from ~0900 h until 1930 h, with ~250 two minute epochs/patient and thus a total 1805 two min epochs for analyses. Fig. 1G is a graphical representation of the presence (+) or absence (−) of immobility (PKG score) and sleep (PSG score) for each subject. There was concordance between immobility and PSG scores in 85.6% of the 1805 two minute epochs: 1206 epochs were negative for sleep by both methods and 342 epochs were positive for sleep by both methods ($p < 0.0001$, Chi Squared test). The Kappa statistic for the concordance of the two methods was 0.63 and the Sensitivity was 0.83 and Selectivity was 0.89. Two thirds (167) of the discordant epochs occurred when immobility was detected by PKG but not by PSG. Discordant epochs (brown and green lines in Fig. 1G) tended to cluster around periods when both methods were also likely to detect immobility and sleep (red lines in Fig 1G).

The other widely accepted marker of EDS is the ESS. Those PD patients with an ESS of 10 or greater, which is considered "high" and consistent with EDS [6,7], had significantly higher PTI than subjects with a low ESS ($p = 0.01$ Mann–Whitney U, Fig 2A and C). Thus, in a manner similar to actigraphy, immobility detected by the PKG is a surrogate marker of sleep. We therefore exploited the advantages provided by the PKG of comparing bradykinesia, dyskinesia and the consumption of medication using immobility as a marker of daytime sleep.

### 3.2. Daytime sleepiness in PD

The median PTI of 30 controls was 2.0 (interquartile range 1.2–5.0, Fig. 2B). In the 10 controls who also had ESS performed, the