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Assessment of sleepiness and unintended sleep in Parkinson's disease patients taking dopamine agonists

Thomas Roth[a,*], David B. Rye[b], Leona D. Borchert[c], Cindy Bartlett[d], Donald L. Bliwise[b], Charles Cantor[e], Jay M. Gorell[a], Jean P. Hubble[f], Bruno Musch[c], C. Warren Olanow[g], Charles Pollak[f], Matt B. Stern[e], Ray L. Watts[b]

[a]*Henry Ford Hospital, Sleep Disorders and Research Center, Clara Ford Pavilion, 3rd Floor, 2799 West Grand Boulevard CFP-3, Detroit, MI 48202, USA*
[b]*Emory University School of Medicine, Department of Neurology, Atlanta, GA, USA*
[c]*Pharmacia Corporation, Bedminster, NJ, USA*
[d]*Pharmacia Canada,Markham, Ont., Canada*
[e]*University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[f]*The Ohio State University, Department of Neurology, Columbus, OH, USA*
[g]*Mount Sinai School of Medicine, New York, NY, USA*

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Abstract

Objective: We sought to determine if patients with Parkinson's disease (PD), taking dopamine agonists (DAs) and reporting unintended sleep episodes (SEs), exhibit physiologically defined daytime sleepiness and can thus be differentiated from those taking DAs but not reporting SEs.

Methods: Twenty-four patients with abnormal Epworth Sleepiness Scale scores of >10 who were taking DAs were enrolled into one of two groups: those with SEs (SE+, $n = 16$) and those without (SE−, $n = 8$). Three consecutive days of testing included two nights of polysomnography followed by the Multiple Sleep Latency Test (MSLT).

Results: Overall frequency of pathological sleepiness (MSLT <5 min) was 42% (10/24). Mean levels of sleepiness, frequencies of pathological sleepiness, and naps with stage 2 or REM-sleep were similar between SE+ and SE− groups. Sleep tendency was similar in patients prescribed pergolide, ropinirole, and pramipexole combined with levodopa. Polysomnography testing revealed no significant differences between the groups in total sleep time, sleep efficiency, sleep architecture, or presence of restless legs syndrome or periodic leg movements. There was no relation between degree of nocturnal sleep disturbance and level of daytime sleepiness.

Conclusions: The results of this study suggest SEs in PD patients occur upon a background of excessive daytime sleepiness and are unrelated to nocturnal sleep or use of a specific DA.

Keywords: Multiple Sleep Latency Test; Polysomnography; Excessive daytime sleepiness; Pramipexole

1. Introduction

Sleep disturbances are a common complaint among patients with idiopathic Parkinson's disease (PD) [1]. The nature of these disturbances ranges from difficulties initiating and maintaining sleep to decreases in time spent asleep. In addition, sleep studies show a decrease in REM and slow-wave sleep [2]. There are multiple potential causes for these sleep changes, including sleep fragmentation due to movements during sleep [3,4], an increased prevalence of periodic limb movements in sleep (PLMS) [5], sleep-related breathing disorders [6], an increased prevalence of depression and its associated sleep disturbance [7], and sleep disturbances secondary to medication [8].

Sleep fragmentation (i.e. difficulty with sleep maintenance), which represents a qualitative deficiency of nocturnal sleep, is the earliest and most frequent sleep disturbance recognized in PD patients [2]. One study found a relationship between nighttime awakenings and the presence of PD:

* Corresponding author. Tel.: +1-313-916-4417; fax: +1-313-916-5167.
E-mail address: troth1@hfhs.org (T. Roth).

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problematic sleep maintenance (reported as multiple awakenings) occurred in almost 89% of PD patients surveyed ($N = 78$) [9]. Another study found that the rate of patients with PD reporting symptoms indicative of sleep fragmentation was as high as 98% [1].

Sleep fragmentation, such as that observed in PD, is a major determinant of excessive daytime sleepiness (EDS) in normal individuals as well as in clinical populations [10]. There have been several clinical, epidemiological, and laboratory reports of EDS in idiopathic PD. A study conducted in Norway found that 15.5% ($N = 239$) of patients with PD experienced EDS compared with 4% ($N = 100$) of patients with diabetes mellitus and 1% ($N = 100$) of healthy elderly persons ($P < 0.01$) [11]. Stocchi et al. reported that spontaneous daytime dozing is much more common in PD patients than in controls [4]. Similarly, Factor et al. observed that EDS and dozing were reported more frequently by PD patients than by elderly controls [9]. In a recent objective study of EDS in PD patients, Rye et al. reported a high prevalence of pathological sleepiness on the Multiple Sleep Latency Test (MSLT) [12] that has been extended and confirmed by Arnulf and colleagues [13]. Mean and median sleep latencies of less than 5 min (i.e. pathological sleepiness) were reported in 19 and 37% of PD patients, respectively [12], and in as many as 50% of patients complaining of sleepiness [13]. Finally, in a recent study examining sudden-onset sleep in PD patients, 51% ($N = 638$) exhibited EDS, defined as an Epworth Sleepiness Scale score > 7 [14].

The consistent finding of EDS in PD patients raises questions about its etiology. Sleep duration and continuity, circadian rhythms, central nervous system (CNS) drugs, and CNS pathology are four key variables in EDS [10]. In patients with PD, the increased prevalence and severity of sleep disturbances, the pathophysiology of the disease, and use of CNS drugs all have the potential to produce EDS. The contribution of each of these factors, as well as their interactions, has not yet been comprehensively addressed.

Dopamine agonists (DAs) are currently used to treat PD, including the new non-ergot DAs such as pramipexole and ropinirole. In clinical trials, up to 27% and 13% of patients taking pramipexole and ropinirole, respectively, experienced somnolence [15,16]. Recently, EDS and unintended sleep episodes (SEs) have been reported in PD patients taking DAs. In one study, 'sleep attacks' were reported in eight patients with PD taking pramipexole and in one patient taking ropinirole [17]. The sleep attacks were described as having occurred acutely and without any perceptible warning – in other words, in the absence of EDS. It is unclear from this report if these sleep attacks were due solely to the presence of a DA rather than occurring on a background of EDS since no objective assessments of sleepiness were performed. Subsequent reports have indicated SEs are not unique to PD patients taking pramipexole or ropinirole [18,19] and might even occur in unmedicated patients [20,21]. Although it is widely thought that SEs are characteristics of most dopaminergic agents, medication effects may not be the only cause of EDS in patients with PD.

The present study was undertaken to determine if patients taking DAs, and reporting undesired SEs, are indeed sleepy during the day (i.e. experiencing EDS), and if their physiological sleep tendency is any different than that expressed by PD patients taking DAs but not reporting SEs. To enrich the sample of PD patients with some degree of daytime sleepiness, we recruited patients whose significant others had reported their dozing off during the day at undesired times.

2. Subjects and methods

2.1. Subjects

This study employed a selected population of patients with idiopathic PD and a modified Hoehn and Yahr scale score of I–III with at least two of the cardinal signs (bradykinesia, postural reflex impairment, resting tremor, rigidity). Other inclusion criteria included use of pergolide (1.5–8.75 mg/day), pramipexole (0.75–6.0 mg/day), or ropinirole (1.5–15.0 mg/day) alone or in combination with levodopa (150–1000 mg/day) without medication change for at least 2 weeks prior to the screening assessments. In addition, patients had to demonstrate sufficient cognitive ability (Mini-Mental Status Examination score ≥ 22) to provide detailed verbal history and complete the sleep assessment questionnaires and laboratory testing. Only patients whose significant others reported undesired sleep episodes were admitted into the study (38.6% of all screened patients). This was formalized by a Significant Other Epworth Sleepiness Scale (SOESS) score of ≥ 10 [22,23]. There were 35 patients who were screen failures due to scores < 10.

Exclusion criteria included medically relevant clinical abnormalities (e.g. unstable angina) or significant findings at physical examination that would interfere with the testing procedures, use of investigational drugs within 30 days of screening assessment, and absence of daily interaction with a person who could reliably give information regarding the patient's sleepiness.

Twenty-four patients (five women, 19 men) whose significant other reported undesired SEs were divided into two groups based on the patient's self-report: those reporting SEs (SE+, $n = 16$) and those denying them (SE−, $n = 8$). SEs were defined as falling asleep in inappropriate situations or at unwanted times and included both patient self-described episodes and those described by significant others. Demographic and treatment data are presented in Table 1.

In summary, 59 subjects were recruited for participation. Of these 59, 35 subjects were excluded because of spouses' reports of sleepiness (i.e. they did not have a SOESS score ≥ 10). There were no other exclusions.

Table 1
Demographic and clinical characteristics of Parkinson's disease patients with reported excessive daytime sleep[a]

	SE+ ($n = 16$)	SE− ($n = 8$)	Total ($N = 24$)
Mean age (range), year	62.4 (51–71)	59.6 (39–73)	61.5 (39–73)
Male, no (%)	11 (68.8)	8 (100)	19 (79.2)
Hoehn and Yahr score (1–5)	2.19 ± 0.70	2.00 ± 0.53	2.13 ± 0.65
Mean UPDRS II (0–52)	12.6 ± 5.6	9.9 ± 3.8	11.7 ± 5.1
Mean UPDRS III (0–56)	20.6 ± 8.3	19.0 ± 6.5	20.0 ± 7.6
Pergolide alone	0	1	1
MMSE	27.9 ± 2.7	28.4 ± 1.6	28.0 ± 2.4
Pramipexole alone	1	0	1
Levodopa + pergolide	6	2	8
Levodopa + pramipexole	5	3	8
Levodopa + ropinirole	3	2	5
Levodopa + pergolide + pramipexole	1	0	1

[a] SE+ = patients with unintended sleep episodes; SE− = patients without unintended sleep episodes; UPDRS = Unified Parkinson's Disease Rating Scale; and MMSE = Minimental Status Exam.

2.2. Polysomnography (PSG)

Patients underwent two consecutive nights of PSG. Nine channels were recorded including the following: two Electroencephalogram (EEG) leads (central and occipital), two eye movement leads, one Electromyogram (EMG) lead, one lead to the tibialis muscle (to determine limb movement), one Electrocardiogram (EKG) lead, and two separate leads to detect respiratory efficiency, respiratory flow, and oximetry. The PSG is used to measure many parameters including (but not limited to) total sleep time, sleep efficiency (i.e. total sleep times, time in bed), the amount of time spent in each stage of sleep, breathing-related pathology during sleep, and movement-related pathology during sleep including restless legs syndrome (RLS) and PLMS.

2.3. Multiple Sleep Latency Test (MSLT)

Daytime sleepiness testing with the MSLT was done following each of the two consecutive nights of PSG. The test was administered approximately 2 h after each patient's customary wake-up time and followed the standard procedures outlined by Carskadon and colleagues [24]. All patients were given four nap opportunities, at 10:00, 12:00, 14:00, and 16:00 h. Two days of MSLT testing were used because of the previous report of high variability in PD patients.

Sleep latency on any given nap on the MSLT was defined as the time from lights-out to the first 30-s epoch scored as sleep. A sleep-onset REM period (SOREMP) episode was defined as one or more epochs of REM sleep occurring within 15 min of the first epoch scored as sleep. Each nap was terminated after 20 min of wakefulness or after a maximum of 15 min of sleep. Fifteen percent of the MSLTs (one from each of eight subjects) were randomly selected to check inter-rater reliability of the scoring to time of sleep onset. Across the eight MSLTs, the mean change between original and reliability scoring was 0.5 min. The greatest difference in scoring was 2.5 min.

2.4. Data analyzes

The mean sleep latency (MSL) across the two nights of testing was used as the primary outcome measure. Individual patients with a mean MSL of <5 min across the two nights of testing were defined as having EDS. Comparisons between patients showing SOREMPs on the MSLT and those not showing SOREMPs were made with *t*-tests. For each patient, the PSG end points were based on the results of both nights of PSG, and statistics were calculated on the means of the values from the two nights. Differences between the two groups (i.e. with and without SEs) were determined using *t*-tests.

3. Results

Twenty-six patients (five women, 21 men) were recruited into the study and 24 completed the sleep-wake evaluation. Of the 24 patients, 16 (67%) reported experiencing unintentional or undesired SEs and eight (33%) did not (see Table 1). Evaluation with PSG revealed no statistically significant differences between the two groups in total sleep time, time spent in each stage of sleep, sleep efficiency, or in rates of RLS and/or PLMS (Table 2). These PSG variables were also compared between patients with pathological sleepiness (MSLT <5) and those without (see Table 3), and no significant differences were found except for latency to PS ($P = 0.048$). When these PSG variables were examined in relation to medication regimen, all were similar except for percent of time spent in REM sleep: patients taking levodopa plus ropinirole spent significantly more time in REM sleep than patients taking levodopa plus pergolide or levodopa plus pramipexole ($P = 0.03$).

Out of the 24 patients tested, 18 showed identical results

Table 2
Polysomnography results for SE+ and SE− patients[a]

		SE+ ($n = 16$)	SE− ($n = 8$)	P value*
Total sleep time (min)	Mean ± SD	309.8 ± 56.6	294.0 ± 40.8	0.489
Sleep efficiency (%)	Mean ± SD	66.0 ± 11.6	69.0 ± 8.8	0.523
Stage 1 time (%)	Mean ± SD	21.7 ± 11.6	19.4 ± 4.5	0.488
Stage 2 time (%)	Mean ± SD	59.0 ± 14.6	67.7 ± 6.0	0.052
Stage 3–4 time (%)	Mean ± SD	5.8 ± 9.1	1.9 ± 3.6	0.149
Stage REM (%)	Mean ± SD	13.5 ± 7.9	11.1 ± 3.4	0.299
Restless leg syndrome	Present ≥1 night *N* (%)	1 (6.3)	1 (12.5)	1.000
	Absent *n* (%)	15 (93.8)	7 (87.5)	
Periodic limb movements/hour of sleep	<5 *n* (%)	11 (68.8)	2 (25.0)	0.082
	≥5 *n* (%)	5 (31.3)	6 (75.0)	

[a] P value for continuous variables is from the t-test of SE+ versus SE− . P value for categorical variables is from Fisher's Exact Test. SE+ = patients with unintended sleep episodes; and SE− = patients without unintended sleep episodes.

on both days with 6 having pathological sleepiness and 12 having normal levels of sleepiness on both days. Of the ten patients with pathological sleepiness, six exhibited pathological sleepiness on both days and four on only 1 of the 2 days. Mean sleep latency across the 2 days of MSLT testing was 7.2 in the SE+ group and 8.7 in the SE− group (Table 4). This difference was not statistically significant ($P < 0.10$). In addition to mean latency, the frequency of pathological sleepiness (i.e. mean MSL <5), frequency of naps with stage 2 sleep, and frequency of patients showing at least one REM onset were evaluated. All but one of the patients exhibited stage 2 sleep in at least one of the naps. Thus, we analyzed frequency of stage 2 sleep on a nap rather than a patient basis. Overall, 143 of 192 nap opportunities (74%) exhibited stage 2 sleep. The frequency of stage 2 naps was not significantly different between the two groups ($P > 0.10$). Twenty-nine percent of patients exhibited REM-onset sleep at least once in their 2 days of MSLT testing. There was no significant difference between the two groups in frequency of patients showing REM-onset naps ($P > 0.10$). However, a comparison of level of sleepiness between patients showing REM onset in their naps and those not having any REM-onset naps revealed a significant difference ($P < 0.05$): mean MSL scores were 4.5 ± 2.7 in patients having REM-onset naps and 9.1 ± 5.1 in patients with no REM-onset naps.

To determine if there was a difference between the three DAs, we compared mean MSLs for each of the three DAs plus levodopa. The MSLs were 8.0 ± 5.9 for pramipexole plus levodopa, 7.9 ± 5.5 for ropinirole plus levodopa, and 7.1 ± 4.5 for pergolide plus levodopa. Because of the small sample sizes in the three groups, a Kruskal–Wallis non-parametric test was used for the comparison; there were no significant differences ($P > 0.10$) between the three DAs on any of the MSLT-related variables measured (i.e. mean MSL), number of naps with stage 2 sleep, number of patients with pathological sleepiness (MSLT <5), and number of patients with REM-onset.

4. Discussion

The MSLT is the gold standard for the evaluation of daytime sleepiness [25]. Compared to all other measures of daytime sleepiness, the MSLT has been shown to be the most sensitive to the effects of sleep deprivation, sleep

Table 3
Polysomnography results for MSLT <5 and MSLT ≥5 patients[a]

		MSLT <5 ($n = 10$)	MSLT ≥5 ($n = 14$)	P value*
Total sleep time (min)	Mean ± SD	302.6 ± 55.6	305.9 ± 50.5	0.881
Sleep efficiency (%)	Mean ± SD	65.8 ± 10.1	67.8 ± 11.3	0.670
Stage 1 time (%)	Mean ± SD	23.9 ± 12.1	18.8 ± 7.4	0.222
Stage 2 time (%)	Mean ± SD	56.6 ± 14.5	65.6 ± 10.7	0.092
Stage 3–4 time (%)	Mean ± SD	4.6 ± 8.8	4.4 ± 7.4	0.934
Stage REM (%)	Mean ± SD	14.9 ± 6.7	11.1 ± 6.7	0.187
Latency to PS (min)	Mean ± SD	19.1 ± 17.3	52.4 ± 54.6	0.048
Restless leg syndrome	Present ≥1 night *N* (%)	0 (0.0)	2 (14.3)	0.493
	Absent *n* (%)	10 (100.0)	12 (85.7)	
Periodic limb movements/hour of sleep	<5 *n* (%)	6 (60.0)	7 (50.0)	0.697
	≥5 *n* (%)	4 (40.0)	7 (50.0)	

[a] *P value for continuous variables is from the t-test of MSLT <5 versus MSLT ≥5. P value for categorical variables is from Fisher's Exact Test.

Table 4
Multiple Sleep Latency Test results for SE+ and SE− patients[a]

		SE+ ($n = 16$)	SE− ($n = 8$)	P value*
MSL (min)	Mean ± SD	7.2 ± 5.1	8.7 ± 4.8	0.489
Patients with pathological sleepiness (MSLT <5)	*n* (%)	8 (50)	2 (25)	0.388
Naps with Stage 2 sleep	*n*/*N*, (%)	95/128 (74)	48/64 (75)	N/A
Patients with ≥1 nap having REM sleep	*n* (%)	4 (25)	3 (38)	0.647

[a] *P value for continuous variables is from the t-test of SE+ versus SE− . P value for categorical variables is from Fisher's Exact Test. SE+ = patients with unintended sleep episodes; SE− = patients without unintended sleep episodes; and N/A = not applicable.

fragmentation, and circadian time. Pathological sleepiness, operationalized as an MSLT score <5 [26], is present in patients with severe obstructive sleep apnea, narcolepsy, and normal volunteers undergoing sleep deprivation [27,28]. A novel aspect of the present study was the requirement that a patient have a mean MSLT score <5 min across the 2 days of testing in order to be defined as having EDS. Even applying this more stringent criterion, we found that EDS occurred in 42% of the patients in this study cohort, with no significant difference in the degree of sleepiness between SE+ and SE− patients. Although an EDS rate of 42% of the population seems high, it is not surprising in view of the inclusion requirement of observed dozing that was found in 38.6% of the screened patients. One potential confound to this analysis is the difficulty in distinguishing sleep onset REM-sleep in the parkinsonian condition, which is no trivial matter even for scorers familiar with assessing parkinsonian wake/sleep states [29]. Our internal reliability at a central scoring site was nonetheless reasonable and the results were completely in line with previously published patient series.

The observed frequency of sleepiness was much higher than that seen in the general population, even among the elderly [9]. It appears consistent with the SOESS scores (≥10) required for study entry. Of particular interest is the high frequency of REM onset observed during naps (seven of 24 patients, 29%). Patients who exhibited REM during at least one nap were significantly sleepier than those without REM naps (mean MSLT 4.5 versus 9.1, $P < 0.05$). These observations are consistent with the results of Rye et al., who reported 13 REM periods during 134 nap opportunities (10%) among patients with PD [12]. Mean Sleep Latency Test scores reported in the Rye study were 6.3 for patients with REM naps and 12.4 for patients without REM naps. A recent study comparing EEG measurements of PD patients to healthy controls during REM sleep found frequency- and temporal-related changes in the PD patients that are suggestive of a dysregulation of REM-sleep [30].

The precise etiology of pathological sleepiness in patients with idiopathic PD is difficult to ascertain because of the various potential contributing factors. Sleep disorders such as PLMS are more common in PD patients than in the general population [9], suggesting that EDS in PD patients may be associated with a primary sleep disorder. The high rate of stage 2 sleep observed in the naps of this study cohort is consistent with chronic insufficient sleep [31]. However, there was no difference in nocturnal sleep between SE+ and SE− patients. It is also possible that the EDS seen in PD is primary to the disorder itself: a recent report indicates that patients with PD may develop EDS at a rate of approximately 6% a year, and that the development of EDS is correlated with more advanced disease and dementia [32]. Commonalities exist between our observations in PD patients and the phenomena observed in narcolepsy. In both narcoleptics and PD patients, EDS occurs independently of nocturnal sleep [20]. As in the Rye study [20], we found no correlation between any nocturnal PSG variable and degree of daytime sleepiness in the MSLT scores. Moreover, narcolepsy is characterized by an increased frequency of REM-onset sleep [33]. This relationship is consistent with our results, which show that 29% of PD patients have a SOREMP, and that those with REM-onset sleep are sleepier as measured by MSLT.

Drug effects may also contribute to sleepiness in PD patients [8]. A recent study has suggested that SEs (or 'sleep attacks' as they are described by the authors) are specifically associated with the non-ergot DAs, pramipexole and ropinirole [17]. A retrospective chart review of 40 patients with PD who were participating in clinical trials with pramipexole found that moderate to severe somnolence was frequently reported [34]. However, a recent case report described a patient with PD who experienced sudden, irresistible onsets of sleep that were documented by PSG and video recordings and occurred without non-ergot DA treatment, suggesting it is not that particular class of drugs responsible for the sleep events per se [35]. Additional reports have also indicated that SEs are not specific to PD patients taking pramipexole or ropinirole [18,36]. In the present study, a high frequency of EDS was observed that was similar among all DAs. We also found no significant differences in MSLT scores between the DAs. Additionally, we found that various PSG measures were similar across all DAs taken by the patients in this study with the exception of an increased time spent in REM sleep in patients taking a combination of levodopa and ropinirole. However, a recent study found no association between ropinirole and daytime episodes of REM sleep [36]. Further investigation carefully comparing DAs with placebo as well as other drugs is needed to more fully examine the relative weight of pharmacologic agents in SEs in PD.

We conclude that SE in PD patients occurs on a background of EDS and is not simply the result of insufficient sleep or the effects of any specific drug. This conclusion is based on our study of a population that was pre-selected by spousal reports of sleepiness and use of dopamine agonists. This result cannot therefore be generalized to a population-based sample of PD patients without SEs. Further studies are warranted in non-selected populations. Further studies are also needed to assess the contribution of specific DAs, other medications, disease progression, and other as yet unidentified factors in the etiology of SE among PD patients.

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