Excessive Daytime Sleepiness and Sudden-Onset Sleep in Parkinson Disease

A Survey by the Canadian Movement Disorders Group

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Context Somnolence is a recognized adverse effect of dopamine agonists. Two new dopamine agonists, pramipexole and ropinirole, have been reported to cause sudden-onset sleep spells in patients with Parkinson disease (PD) while they were driving. The frequency of these spells and whether driving should be restricted has yet to be established.

Objective To determine the frequency of and predictors for sudden-onset sleep and, particularly, episodes of falling asleep while driving among patients with PD.

Design, Setting, and Participants Prospective survey conducted between January and April 2000 in 18 clinics directed by members of the Canadian Movement Disorders Group; 638 consecutive highly functional PD patients without dementia were enrolled, of whom 420 were currently drivers.

Main Outcome Measures Excessive daytime sleepiness and sudden-onset sleep as assessed by the Epworth Sleepiness Scale and the Inappropriate Sleep Composite Score. The latter score, designed for this study, addressed falling asleep in unusual circumstances. The 2 scales were combined in 3 separate formats: dozing off, sudden unexpected sleep, and sudden blank spells.

Results Excessive daytime sleepiness was present overall in 327 (51%) of the 638 patients and in 213 (51%) of the 420 drivers. Patients taking a variety of different dopamine agonists had no differences in Epworth sleepiness scores, in the composite score, or in the risk of falling asleep while driving. Sixteen patients (3.8%) had experienced at least 1 episode of sudden onset of sleep while driving (after the diagnosis of PD); in 3 (0.7%), it occurred without warning. The 2 risk factors associated with falling asleep at the wheel were the Epworth Sleepiness Scale score (odds ratio [OR], 1.14; 95% confidence interval [CI], 1.06-1.24) and the Inappropriate Sleep Composite Score (OR, 2.54; 95% CI, 1.76-3.66). A standard Epworth Sleepiness Scale score of 7 or higher predicted 75% of episodes of sleep behind the wheel at a specificity of 50% (exclusion of the question related to driving provided 70% sensitivity and 52% specificity), whereas a score of 1 on the Inappropriate Sleep Composite Score generated a sensitivity of 52% and specificity of 82%.

Conclusions Excessive daytime sleepiness is common even in patients with PD who are independent and do not have dementia. Sudden-onset sleep without warning is infrequent. The Epworth score has adequate sensitivity for predicting prior episodes of falling asleep while driving and its specificity can be increased by use of the Inappropriate Sleep Composite Score. It is unknown if routinely performing these assessments could be more effective in predicting future risk for these rare sleep attacks. Patients should be warned not to drive if they doze in unusual circumstances.

JAMA. 2002;287:455-463 www.jama.com

THE NEW NON-ERGOT DOPAMINE agonists ropinirole and pramipexole are effective options for treating Parkinson disease (PD).[1] Recently published data[2,3] supporting the potential of delaying the onset of dyskinesias have provided a strong incentive to use the medications as monotherapy early in this disease. Somnolence is a recognized adverse effect of dopamine agonists.[4] The safety of driving while taking these medications has become the subject of recent debate.

Frucht et al[5] made the observation that patients taking the new agonists may experience what they termed "sleep attacks" (sudden, irresistible, overwhelming sleepiness without awareness of falling asleep) leading to automobile collisions. Since this publication, there has been an explosion of reports of somnolence or sleep attacks with pramipexole,[6-8] ropinirole,[7-10] pergolide,[8,11,12] bromocriptine,[11,13,14] carbergoline,[8] apomorphine,[15] lisuride,[11,13] piribedil,[11] levodopa,[3,13,14] tolcapone,[8] and entacapone.[8,14] Ola-

For editorial comment see p 509.

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Table 1. Modified Epworth Sleepiness Scale

The modified score is the standard Epworth score plus 4 questions designed to detect falling asleep in inappropriate situations. Patients were asked to complete each of 3 versions of the questionnaire.

Version 1: Dozing off.
Patients were given the question, "How likely are you to doze or fall asleep in the following situations (in contrast to just feeling tired)? This refers to your usual present way of life. Even if you have not done some of these things recently, try to recall whether they may have occurred previously." Patients were instructed to use the following scale to choose the most appropriate number for each situation: 0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing.

Version 2: Sudden onset of sleep.
Patients were given the question, "If you were likely to doze or fall asleep in any of the following situations, was the episode ever sudden or unpredictable?" Patients were instructed to use the following scale to choose the most appropriate number for each situation: 0 = never; 1 = occasional but usually gradual or with warning; 2 = often unpredictable; 3 = always sudden and unpredictable.

Version 3: Blank spells.
Patients were given the question, "Have you ever had any episodes of sudden "blank spells," occurring without warning, during which you were unaware of your surroundings in any of the following situations? By sudden blank spells we mean sudden unexpected episodes during which you have had a loss of awareness of what was going on around you without being asleep." Patients were instructed to use the following scale to choose the most appropriate number for each situation: 0 = never; 1 = infrequently (once per month or less); 2 = occasionally (up to once per week); 3 = frequently (more than once per week).

Situation	Chance of Event at Present (Score, 0-3)
Epworth Sleepiness Scale	
1. Sitting and reading	
2. Watching television	
3. Sitting, inactive, in a public place (eg, theater or a meeting)	
4. As a passenger in a car for 1 hour without a break	
5. Lying down to rest in afternoon when circumstances permit	
6. Sitting and talking to someone	
7. Sitting quietly after lunch without alcohol	
8. In car, when stopped for a few minutes in traffic	
Modified Epworth Sleepiness Scale/additional situations	
9. While driving	
10. While eating a meal	
11. While attending to work	
12. While attending to routine household activities	

*Questions 1-8 of version 1 of the questionnaire comprise the full original Epworth Sleepiness Scale and were self-administered by the patient (as per the validation of the Epworth Scale[17]) while all other questions in version 1 and all questions in versions 2 and 3 of the questionnaire were administered by clinic staff.

now et al[16] presented their view that these events are not sudden, are usually predictable, and that a screening tool such as the Epworth Sleepiness Scale (ESS)[17] (a measure of the general level of sleepiness in adults) might be useful to detect preceding sedation in patients at risk. At present, the prevalence of excessive daytime sleepiness or sleep attacks in patients taking antiparkinson medications is unclear. In spite of this, many patients taking ropinirole or pramipexole are being prevented from driving, thereby possibly failing to achieve an appropriate "balance between protecting the public safety and the rights of the individual."[18] To determine the frequency of excessive daytime sleepiness and sleep attacks and their relationship to specific antiparkinson medication or other predisposing factors, the Canadian Movement Disorders Group initiated the present study. As suggested by Olanow et al,[16] we also evaluated whether the full ESS, certain subcomponents of this scale, or additional questions could be predictive of sudden-onset sleep while driving.

METHODS

Participants

Eighteen movement disorder clinics directed by members of the Canadian Movement Disorders Group participated in a prospective questionnaire survey of consecutive independent patients with PD. Experienced movement disorder personnel (neurologists, fellows, or nurse specialists) conducted the survey between January and April 2000. Training sessions were held with all participating centers to ensure uniformity of form completion. Although we did not test for interrater or intrarater variability for the entire questionnaire, the ESS score has been previously validated.[17] Eligibility criteria were: a clinical diagnosis of PD, a Mini-Mental Status Examination (MMSE) score of 24 or greater (maximum score = 30, indicating no cognitive impairment), and a Schwab and England[19] activities of daily living (ADL) "on" (ie, when medications were working) score of 70% or greater (100% = no functional impairment). Patients with dementia and those severely affected were not included, as we were interested in choosing highly functioning patients, including those still able to drive, who would be most impaired by excessive daytime sleepiness or sudden sleep "attacks" and would be able to recall the information required in the questionnaires. This group was considered well representative of similar patients not attending a movement disorder clinic, although the use of dopamine agonists may be more frequent in this specialty care setting. Patients with parkinsonism due to illnesses other than PD were excluded.

The study was approved by the ethics review board of the University Health Network (Toronto Western Hospital), and as required by the institutional review boards at other participating centers. All patients consented to participate in the study.

Data Collection

Patients were asked initially to complete a set of 12 questions (TABLE 1). The first 8 questions consisted of the standard ESS. This standard scale has been validated only when self-administered.[17] The 12-question set was completed in response to 3 scenarios (Table

1, versions 1-3). After completion of the 3 versions of the 12 questions, patients were asked about their likelihood of falling asleep while driving (question 9). Three additional questions (Table 1, questions 10-12) were devised by the authors to represent activities that one would expect individuals to be alert and stimulated by; therefore, sleepiness during these times would represent problematic and pathological excessive sleepiness (in contrast to some of the items of the ESS). These later questions together with the original 8 questions from the ESS made up the "modified" ESS referred to herein. After completion of the 3 versions of the 12 questions, patients were asked if they were currently driving. Eligibility inclusion criteria and the ESS were completed during clinic visits. The remainder of the questionnaire was completed in the clinic in 92% of cases, and by telephone in 8%.

Demographic data (age, sex, disease duration), the Hoehn and Yahr[20] score (an assessment of the stage of PD: range = 1-5; 1 = mild, 5 = wheelchair bound), and part 1 (mentation, behavior, and mood) of the Unified Parkinson's Disease Rating Scale were collected. A list of current medications, doses, and duration of use was obtained. A series of 10 additional questions to screen for symptoms suggestive of common sleep disorders was also included: 3 for narcolepsy, 4 for rapid eye movement (REM) sleep behavior disorder (the lack of expected muscle paralysis during REM sleep allowing motor actions to occur during dreaming), 1 for periodic leg movements in sleep, and 2 for sleep apnea.

Analysis

Statistical analyses were conducted using SPSS version 10.1 (SPSS Inc, Chicago, Ill). Data were analyzed to estimate the overall prevalence of falling asleep at the wheel (affirmative response to item 8 of the ESS or item 9 of the modified ESS) as well as sudden onset of sleep, and to determine if a high ESS score, use of specific medication, total medication dose, or other factors could predict these events. For purposes of this analysis, a standard ESS of 7 or greater is considered high (based on the modal score for Johns'[17] normative data in a younger population).

An "Inappropriate Sleep Composite Score" (ISCS) was calculated to examine the likelihood of falling asleep while driving, eating, working, conversing, and doing household chores. The ISCS was the total added score of responses to questions 6 and 8 through 12 of the modified ESS (Table 1). We performed univariate analyses in which the data were compared between drivers and nondrivers using 1-way analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables (or Fisher exact test, as appropriate). Differences in demographic characteristics between the ESS score and the ISCS were assessed using Spearman correlation coefficients (ρ). For all tests, statistically significant results using a 2-tailed distribution ($P<.05$) were further analyzed by Tukey post hoc paired comparisons.

To test for systematic differences by clinical center, medication type, and presence of sudden-onset sleep, we used a 1-way multiple analysis of variance (MANOVA) to control for multiple comparisons. Wilks lambda (λ) was the multivariable test of significance. This test ranges from 0 to 1, with lower values indicating differences between group means.

Medication effects were assessed by comparing patients receiving a specific drug with those taking an alternate drug, or comparing those receiving a specific drug with all others not taking that drug. If one drug was compared with another, patients taking both drugs simultaneously were excluded. When one drug was compared with others, the first group consisted of all patients taking the drug (regardless of the other medications taken) and the second group consisted of the remainder of the patients surveyed.

To directly compare different medications at doses of equivalent efficacy, it was necessary to convert the dosages to levodopa dosage equivalents. The following formula was derived from the collective experience of the authors treating PD. Total levodopa equivalents = regular levodopa dose × 1 + levodopa continuous release dose × 0.75 + pramipexole dose × 67 + ropinirole dose × 16.67 + pergolide dose × 100 + bromocriptine dose × 10 + [regular levodopa dose + (continuous release levodopa dose × 0.75)] × 0.25 if taking tolcapone.

Multivariable analyses were performed using a logistic regression model to estimate the odds ratio (along with the 95% confidence interval) of falling asleep behind the wheel (ie, affirmative response to either item 8 of the ESS or item 9 of the modified ESS). Variables significantly associated with falling asleep at the wheel in univariate analysis (defined as $P<.10$) were entered into the model and retained through backward elimination if $P<.05$. Calibration of the logistic model was assessed using the Hosmer-Lemeshow goodness-of-fit test to evaluate the importance of the discrepancy between observed and expected episodes of sleep. Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve to determine how well the model distinguished patients who fell asleep behind the wheel from those who did not. The points on the ROC curve are generated by calculating the sensitivity and specificity of the test or prediction at various criteria of positivity. The greater the area under the curve (on a scale of 0.5 to 1), the better the discrimination of the test or prediction.

Finally, one of the authors (D. E. H.) reviewed the individual histories of the patients reporting sudden onset of sleep or falling asleep while driving.

RESULTS

Patient Characteristics

Two hundred seventy-eight (30.3%) of 916 patients approached were excluded based on the eligibility criteria. Of these, 177 (63.7%) were excluded due to a low MMSE or Schwab and England ADL score. Additional reasons for exclusion were: 67 patients refusing to

Table 2. Demographic Characteristics

Variable	Mean (SD)	
	All Patients (N = 638)	Drivers (n = 420)
Age, y	65.7 (10.6)	63.6 (10.4)
Hoehn and Yahr score[20]*	2.2 (0.68)	2.0 (0.6)
Schwab and England score[19]†		
"On"	86.7 (8.15)	87.8 (7.7)
"Off"	75.0 (17.3)	78.0 (15.8)
Mini-Mental Status Examination score‡	28.5 (1.59)	28.7 (1.40)
Disease duration, y	8.1 (5.4)	7.2 (4.9)

*A measure of Parkinson disease stage: range = 1-5 (1 = mild, 5 = wheelchair bound).
†An activity of daily living scale: range = 0%-100% (100% = no functional impairment). "On" score indicates medications are working.
‡A cognitive score: maximum = 30.

Table 3. Medications Used by Drivers (n = 420)*

Medication	Patients, n/N (%)†	Dose, Median (Range), mg/d
Antiparkinson		
Levodopa	338/420 (80.5)	300 (100-400)
Pramipexole	93/413 (22.5)	3 (0.25-7.5)
Ropinirole	91/413 (22.0)	6 (0.25-36)
Pergolide	37/410 (9.0)	2.25 (0.15-7)
Bromocriptine	14/406 (3.4)	16.25 (2.5-45)
Selegeline	62/416 (14.9)	5 (5-15)
Amantadine	60/412 (14.6)	200 (100-300)
Tolcapone	19/415 (4.6)	300 (300-300)
Other		
Sleeping aid	75/395 (19.0)	NA
Antidepressant	86/408 (21.1)	NA
Other psychotropics	17/355 (4.8)	NA

*n indicates the number of patients receiving the medication; N, total sample size; and NA, not available.
†N varies because of missing data.

Table 4. Results of 3 Versions of the Epworth Sleepiness Scale*

Situations	Patients, n/N (%)†		
	With Dozing Off	With Sudden Onset of Sleep	With Blank Spells
Epworth Sleepiness Scale			
1. Sitting and reading	425/638 (67)	74/627 (12)	11/637 (2)
2. Watching television	494/637 (78)	87/626 (14)	17/637 (3)
3. Sitting, inactive, in public place (eg, theater or meeting)	251/638 (39)	54/627 (9)	15/637 (2)
4. As a passenger in a car for 1 hour without a break	2894/638 (46)	46/628 (7)	14/637 (2)
5. Lying down to rest in afternoon when circumstances permit	543/638 (85)	53/626 (8)	3/637 (<1)
6. Sitting and talking to someone	108/636 (17)	24/627 (4)	19/637 (3)
7. Sitting quietly after lunch without alcohol	358/637 (56)	45/625 (7)	11/637 (2)
8. In car, when stopped for a few minutes in traffic	65/637 (10)	20/627 (3)	7/637 (1)
Modified Epworth Sleepiness Scale			
9. While driving	49/638 (8)	19/628 (3)	2/637 (<1)
10. While eating a meal	23/637 (4)	15/628 (2)	4/637 (1)
11. While attending work	38/635 (6)	6/628 (1)	3/637 (<1)
12. While attending to routine household activities	18/637 (3)	5/628 (1)	9/637 (1)

*n indicates the number of positive responders; N, the total sample size.
†N varies because of missing data.

participate, 12 de novo (untreated) patients (1 center inappropriately excluded such patients), 9 patients lost to follow-up between the completion of the ESS in the office and the completion of the questionnaire by phone, and 4 with atypical parkinsonism. Nine were excluded for other miscellaneous reasons. Overall, 638 eligible patients completed the questionnaire. The 18 centers each enrolled an average of 35.4 patients (range, 17-85). The demographics of these patients are summarized in TABLE 2. Of these patients, 64% (420) were active drivers. The demographics of the drivers were statistically similar to the entire sample except they were more frequently men (307/420 [73%] of drivers vs 338/638 [53%] of subjects overall). The medication profile of the 420 drivers is displayed in TABLE 3.

Significant differences for dependent measures were found among the 18 clinical centers (Wilks $\lambda = 0.55$, $F_{204,5056} = 1.55$, $P < .001$). Specifically, age ($F_{17,532} = 2.60$; $P < .001$), Schwab and England "on" score ($F_{17,532} = 2.32$; $P = .002$) and ESS ($F_{17,532} = 1.74$; $P = .03$) differed between clinical centers. However, Tukey post hoc paired comparisons were not statistically significant except for Schwab and England "on" scores that differed between center 11 vs center 14 and center 12 vs centers 3, 8, and 14. No differences were detected between clinics in the proportion of people falling asleep at the wheel (ie, ESS item 8: $c^2_{17} = 10.80$ [n = 420], $P = .87$; or modified ESS item 9: $c^2_{17} = 19.50$ [n = 420], $P = .30$).

Epworth Sleepiness Scale and Inappropriate Sleep Composite Score

The results of the 3 versions of the modified ESS for all patients are provided in TABLE 4. Overall, the median ESS score was 7.00 (range, 0-23) and the median ISCS was 0 (range, 0-11). Both ESS total and ISCS correlated positively with disease duration (ESS: $\rho_{627} = 0.18$, $P < .001$; ISCS: $\rho_{625} = 0.13$, $P = .002$) and Hoehn and Yahr staging (ESS: $\rho_{626} = 0.17$, $P < .001$; ISCS: $\rho_{624} = 0.19$, $P < .001$) and correlated negatively with Schwab and England "on" score (lower numbers

indicate greater disability) (ESS: $\rho_{568}=0.16$, $P<.001$; ISCS: $\rho_{566}=0.15$, $P<.001$). The mean (SD) standard ESS score for all patients was 7.38 (4.60). The mean score for drivers vs nondrivers was 7.30 (4.42) vs 7.56 (4.93), respectively. This latter difference was not statistically significant ($F_{1,630}=0.45$, $P=.50$). Excessive daytime sleepiness (ESS score >7) was present in 327 (51%) of 638 patients and in 213 (51%) of the 420 drivers.

TABLE 5 lists predictive factors associated with falling asleep at the wheel (affirmative response on items 8 or 9 of the modified ESS) ($P<.10$). Of these 9 predictive factors, 2 were independently associated with falling asleep at the wheel in multivariable analysis (TABLE 6): the ESS and the ISCS. The Hosmer-Lemeshow goodness-of-fit test showed that the model was well calibrated with $P=.65$.

Using an affirmative response to item 8 of the ESS or item 9 of the modified ESS yielded comparable ROC areas of 0.65 for the ESS (excluding item 8 of the ESS) and 0.67 for ISCS (excluding items 8 and 9 of the modified ESS), showing that the model adequately discriminated between patients who fell asleep and those who did not (FIGURE).

The standard ESS total (including item 8) had an ROC area of 0.71, with a cutoff score of 7 generating a sensitivity of 75% and specificity of 50% for falling asleep at the wheel ("yes" on item 9 of the modified ESS). Specificity was increased to 72% with a cutoff of 10 and 93% with a cutoff of 15 on the standard ESS but with the cost of decreased sensitivity to 52% and 29%, respectively. A cutoff of 1 on the ISCS provided 52% sensitivity and 82% specificity.

Medication Effects

The 2 outcome measures (ESS and ISCS) were analyzed relative to the antiparkinson medication patients were taking. A 1-way MANOVA detected differences between patients treated with no medication or with specific dopaminergic agents (ie, regular levodopa preparations, controlled-release levodopa/carbidopa, pramipexole, ropinirole, pergolide, or bromocriptine) with respect to the 2 outcome measures (Wilks $\lambda=0.96$; $F_{12,1244}=1.99$; $P=.02$). However, follow-up ANOVAs failed to show any differences between antiparkinson medication type and the ESS score ($F_{6,623}=1.78$, $P=.10$) or the ISCS ($F_{6,623}=1.35$, $P=.23$). Although levodopa dosage equivalents correlated positively with the ESS ($\rho_{630}=.16$, $P<.001$) and the ISCS ($\rho_{628}=.13$, $P=.001$), there was no systematic relationship between levodopa dosage equivalents and affirmative response to question 8 of the ESS or question 9 of the modified ESS (ie, falling asleep at the wheel, $F_{1,406}=2.30$, $P=.13$).

Forty-nine (12%) of the 420 drivers experienced dozing while driving whereas 78 (19%) documented dozing while driving or while stopped in traffic (ie, affirmative response to item 8 of the ESS or item 9 of the modified ESS). The medication profile of the 49 patients varied considerably: 1 was taking no medication, 43 were taking levodopa (5 taking levodopa alone and 11 with pramipexole, 18 with ropinirole, 3 with pergolide, 6 with 2 or more additional medications), 24 were taking ropinirole (1 taking ropinirole alone and 18 with levodopa, 4 with amantadine or selegeline, 1 with 3 additional medications), 13 were taking pramipexole (1 taking pramipexole alone and 11 with levodopa, 1 with pergolide), and 5 were taking pergolide (1 taking pergolide alone, 3 with levodopa, 1 with pramipexole). The fact that most individuals were taking multiple drugs reduced our power to separate clearly the effects of individual medications.

Table 5. Univariate Associations of Predictive Factors for Falling Asleep While Driving (n = 420)*

Predictive Variable	Fell Asleep Driving?† Yes	Fell Asleep Driving?† No	OR (95% CI)
Epworth Sleepiness Scale, mean (SD)	10.4 (4.8)	6.5 (3.6)	1.3 (1.2-1.4)
Inappropriate Sleep Composite Score, mean (SD)	1.2 (1.3)	0.19 (0.53)	3.5 (2.5-4.9)
Hoehn and Yahr score,[20] mean (SD)	2.2 (0.68)	2.0 (0.61)	1.6 (1.1-2.4)
Mini-Mental Status Examination, mean (SD)	29.0 (1.3)	28.7 (1.4)	1.2 (1.0-1.5)
Periodic leg movements in sleep, n/N (%)‡			
Yes	35/141 (24.8)	106/141 (75.2)	1.7 (0.96-3.0)
No	27/165 (16.4)	138/165 (83.6)	
Antiparkinson medication, n/N (%)‡			
Ropinirole			
Yes	27/90 (30.0)	63/90 (70.0)	2.3 (1.3-3.9)
No	50/313 (16.0)	263/313 (84.0)	
Pergolide			
Yes	11/35 (31.4)	24/35 (68.6)	2.2 (1.0-4.6)
No	64/365 (17.5)	301/365 (82.5)	
Selegeline			
Yes	18/67 (26.9)	49/67 (73.1)	1.8 (0.97-3.3)
No	58/339 (17.1)	281/339 (82.9)	
Sleeping aid			
Yes	6/70 (8.6)	64/70 (91.4)	2.8 (1.2-6.7)
No	65/315 (20.6)	250/315 (79.4)	

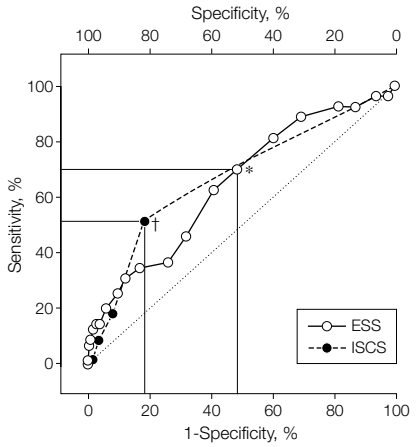
*n indicates the number of positive or negative responders to items 8 or 9 of the modified Epworth Sleepiness Scale; N, the total sample of patients categorized with the predictive variable; OR, odds ratio; and CI, confidence interval.
†Affirmative response on items 8 or 9 of the modified Epworth Sleepiness Scale.
‡N varies because of missing data.

Table 6. Multivariable Logistic Regression Analysis*

Variable	Regression Coefficient (β)	SE	OR (95% CI)	*P* Value
Intercept	–3.05	.35	NA	<.001
Epworth Sleepiness Scale	.13	.04	1.14 (1.06-1.24)	<.001
Inappropriate Sleep Composite Score	.93	.19	2.54 (1.76-3.66)	<.001

**df* = 1 for all variables listed. OR indicates odds ratio; CI, confidence interval; and NA, not applicable.

Figure. Receiver Operating Characteristic Curves for the Prediction of Falling Asleep While Driving



By the Epworth Sleepiness Scale (ESS) and the Inappropriate Sleep Composite Score (ISCS). Receiver operating characteristic curves are generated by plotting the sensitivity against 1 minus the specificity for each value of the ESS and ISCS. The reference (dotted) line represents chance prediction of falling asleep while driving (ie, affirmative response to item 8 or 9 of the modified ESS). A cutoff of 7 (*) on the ESS (excluding item 8) provides 70% sensitivity and 52% specificity. Conversely, a cutoff of 1 (†) on the ISCS (excluding items 8 or 9 of the modified ESS) demonstrates 52% sensitivity and 82% specificity.

Overall, 292 patients were treated with levodopa preparations alone, 56 were treated with a dopamine agonist as monotherapy, and 290 received levodopa with a dopamine agonist. Of the drivers, 152 were treated with levodopa alone, 48 received a dopamine agonist as monotherapy, and 180 took levodopa in addition to a dopamine agonist. Forty-six patients were not taking any dopaminergic agents at the time of study.

Only 7 of the patients attributed the spells directly to a change in medication: 1 secondary to insomnia due to the addition of selegeline, 1 secondary to pramipexole, and 5 secondary to ropinirole. One patient experienced the spells subsequent to bilateral subthalamic nucleus deep brain stimulation.

Sudden-Onset Sleep While Driving

Nineteen patients (12 [63%] men) reported sudden onset of sleep while driving on version 2 of the questionnaire (Table 3) and this was recorded in the case report forms in 2 of the remaining 30 patients who reported dozing off while driving (total of 21/420 [5%]). Demographic characteristics of these patients, such as mean (SD) age (62.1 [10.4] years), Hoehn and Yahr score (2.2 [0.7]), Schwab and England "on" score (86.9 [9.5]), MMSE (29.2 [0.8]), and disease duration (8.6 [6.4] years), did not differ significantly from the other drivers (Wilks $\lambda = 0.95$; $F_{10,346} = 1.73$; $P = .07$) (see Table 1 for data on all patients and drivers). These events occurred prior to the diagnosis of PD in 5 of the patients, leaving 16 of 420 drivers (3.8%) with sudden onset of sleep while driving since the onset of PD. Eighteen of the 21 also experienced spells of dozing that were not sudden. Only 3 of the 21 with sudden onset of sleep claimed not to have experienced associated preceding drowsiness or other warning signs. These 3 patients' questionnaires are reviewed in detail below. All attributed the events to an alteration in their medication. Only 2 patients recalled any blank spells while driving (version 3 of the questionnaire).

Case 1 was a 66-year-old woman with a 2-year history of PD and an ESS score of 14. At the time of the questionnaire she was taking pramipexole (3 mg/d) and pergolide (1.5 mg/d). The sudden onset of sleep episodes had occurred in the past and not while she was taking her current medication. Previously, while taking ropinirole (unknown dose) for 12 months, she had 2 spells of sudden onset of sleep. She provided a history of frequently talking in her sleep and acting out her dreams, but denied any other symptoms of a sleep disorder at the time of the questionnaire.

Case 2 was a 49-year-old man with a 4-year history of PD and an ESS score of 10. The patient was taking levodopa (1000 mg/d) and pergolide (3 mg/d) at the time of the questionnaire. He admitted to a history of 72 episodes over a 6-month period of suddenly falling asleep at the wheel (an average of 2-3 episodes per week). The spells were attributed to daytime fatigue secondary to insomnia induced by selegiline, which he had been taking previously. The problem resolved when selegiline was discontinued. His other PD medication was unchanged. He snored at night and had occasional nocturnal leg twitching but denied any other symptoms of sleep disorders screened for. Although he initially stated that the sudden onset of sleep occurred without warning, he stated later in the questionnaire that the spells were preceded by his "eyes falling down." Therefore these probably were not truly sudden or without warning.

Case 3 was a 62-year-old man with a 6-year history of PD and an ESS score of 2 at the time of the survey. The patient had previously taken ropinirole (0.75 mg/d) for 3 months and had experienced a single spell of sudden onset of sleep while driving. There was no information to suggest forewarning symptoms of any kind. The patient was told to discontinue the ropinirole and at the time of the questionnaire was taking only levodopa (600 mg/d). He answered positively to questions suggesting symptoms of sleep apnea, periodic leg movement during sleep, and REM sleep behavior disorder.

Of the entire number of sudden onset of sleep spells (including those in the 5 patients occurring prior to the onset of PD), only 2 resulted in significant events. No personal injury occurred. In one episode, the car went into a ditch (this event occurred 20 years prior to the diagnosis of PD); in the other, the driver went through an intersection.

COMMENT

Excessive Daytime Sleepiness and Falling Asleep at the Wheel

One of the responsibilities of physicians caring for patients who drive is to identify medical conditions that place their patients and other members of society at risk. Excessive daytime sleepiness leading to falling asleep at the wheel is a common cause of motor vehicle collisions.[21] In sleepy drivers the risk of a collision is increased by the associated loss of awareness and slowed reaction time.[22] Although older age correlates with higher ESS scores, collision risk declines with age.[23] In the United States, 1% to 3% of all motor vehicle collisions are caused by driver sleepiness.[22] In Britain, 30% of 4621 male drivers felt close

to falling asleep during a 12-month period.[23] Over a 1-year period, 4% of women and 10% of men admitted to falling asleep at the wheel.[24] Sleep-related collisions in the general population peak around 2 AM, 4 AM, and 4 PM.[25] They are more likely to occur on dry roads, at high speeds, while driving one's own car,[24] and in monotonous driving conditions (straight roads, low traffic, and familiar roads).[26] Both the probability of "feeling close to" falling asleep at the wheel and collision liability have been shown to correlate with the ESS.[23] Although we did not have a control group of nonparkinsonian patients, the average ESS score in the latter study[23] involving 1755 drivers older than 55 years was 6.3. This was lower than the average of 7.3 in our parkinsonian drivers.

Excessive Daytime Sleepiness and "Sleep Attacks" in PD

Reports suggest a prevalence of excessive daytime sleepiness in PD of 15% to 32%.[15,27] Spontaneous daytime dozing is twice as common in patients with PD than in age-matched controls (49% vs 26%) despite an equal frequency of napping.[28] This excessive daytime sleepiness is evident in PD prior to medication treatment and increases with treatment duration.[29] Parkinson patients commonly have sleep fragmentation and sleep maintenance difficulty. Sleep fragmentation in PD is caused by disordered breathing,[30] nighttime motor disability, dysuria, depression,[31] periodic leg movements during sleep, and REM sleep behavior disorder. Depression has been identified as an independent risk factor for daytime fatigue in PD.[32]

The original description of "sleep attacks" by Frucht et al[5] emphasized their occurrence without warning. Olanow et al[16] have criticized this term by suggesting that "there is no evidence to suggest that drugs or medical conditions induce sleep episodes without a prodrome of sedation or sleepiness." They accept that some patients may be amnestic for the prodrome. Several reviews[21,26,33,34] have supported the latter concept, demonstrating that people often don't recollect actually falling asleep yet almost invariably recall the precursory state of feeling sleepy. It seems that the perception of falling asleep can lag behind electroencephalographic and other evidence that the process has actually started.[34] Most of the cases reported in the reviewed literature, when specifically asked, had clear indicators that would have predicted the spells. While the majority had associated excessive daytime sleepiness, many of the others had a prodrome of tearing, yawning, and/or eye blinking.[6,15,35] Some have become aware of a timing of sudden onset of sleep in relation to when they took their medication.[13] Even in Frucht's 8 cases, 4 had experienced excessive daytime sleepiness and 4 had nondriving sleep attacks to serve as "red flags" for the potential of sleep attacks while driving. Despite admitting to a prodrome of sleepiness, people generally fail to recognize the likelihood of imminent falling asleep at the wheel, the associated collision risk, and the resultant potential for injury or death.[21] Even when patients have experienced these episodes previously, some episodes occur so quickly that patients don't have enough time to recognize them and pull off the road.[36] In addition, a recent case report with polysomnographic correlation has shown that a patient can progress rapidly from a state of stable alertness to stage 2 sleep without a period of intervening drowsiness.[37]

Subjective Reports of Sleepiness

The ESS has been suggested as an approach to predicting excessive daytime sleepiness and sudden onset of sleep in patients with PD.[16,38] Episodes of sudden-onset sleep while driving were very uncommon and not temporally related to the timing of completion of the ESS by our patients. The cutoff values with the optimal combination of sensitivity and specificity in this study were an ESS score of 7 and an ISCS score of 1. Using cutoff values for the ESS scores higher than 7 resulted in the sensitivity of these values dropping steadily. Although the ESS has adequate sensitivity for predicting falling asleep at the wheel, its specificity was low. The ISCS improved this situation by raising specificity to clinically relevant values. Using the ESS in tandem with the ISCS (ie, our "modified" ESS) is recommended when probing the excessive daytime sleepiness in patients with PD. We did not combine these 2 scales because some questions overlap.

Evidence of excessive daytime sleepiness (ESS score >7) was present in 51% of drivers. Only 8.2% of these admitted to falling asleep at the wheel. These dozing spells were frequently solitary and occurred even without medications. Although in isolation these frequencies seem high enough to restrict driving, the vast majority were associated with a clear history of drowsiness prior to falling asleep. Only 0.5% of our whole patient group and 0.7% of drivers gave a history of sudden onset of sleep at the wheel without any previous warning. Our observations suggest that sudden onset of sleep is not related to any specific antiparkinson drug. Sudden onset of sleep during any activity was found to occur with all medications and combinations thereof. The frequency of sudden onset of sleep in drivers was 10.5% (43/407) in levodopa users, 26% (24/90) in ropinirole users, 9% (13/143) in pramipexole users, and 13.5% (5/37) in pergolide users. The latter statistics include patients taking combinations of medications, particularly the agonists plus levodopa. Our data did not identify any correlation between levodopa dose equivalent and the likelihood of falling asleep at the wheel or sudden onset of sleep. There was no statistically significant difference between the new dopamine agonists and the older agonists. There was no significant difference comparing ropinirole with pramipexole, or non-ergot agonists with ergot agonists. The presence of sleep disorders, as determined by our screening questions, was not useful in predicting those at risk of falling asleep at the wheel. None of the patients with sudden onset of sleep at the wheel without warning had any other symptoms suggestive of narcolepsy.

This questionnaire survey has several limitations. We lacked an age-matched control population, and as there were very few untreated patients, we cannot comment on the frequency of excessive daytime sleepiness or sudden onset of sleep in patients with PD taking no medication. Also, the ESS scores were not collected at the time of the events. This may have caused less accurate reporting by the patients. It also prevents us from drawing any conclusions about predictive factors existing before or at the time of sudden onset of sleep events. Some patients may have underreported their spells for fear of losing the privilege of driving. When trying to draw comparisons between the effects of different PD medications on ESS scores, the unequal numbers of patients taking the different drugs and the very few patients receiving agonist monotherapy limited our ability to make more definitive conclusions. It is likely that, compared with patients with PD attending a nonspecialty clinic, the patients questioned for this study would be more frequently treated with dopamine agonists. If agonists make sleep attacks more likely, the reported risk of excessive daytime sleepiness in this group would likely be greater than in patients followed up in a nonspecialty setting.

Conclusions

Excessive daytime sleepiness is not uncommon in PD. Excluding questions directly asking about falling asleep while driving, we have found that 1 validated measure (the ESS) of this problem can satisfactorily predict the risk of dozing off while driving if supplemented with questions about sleepiness in uncommon situations (ie, the modified ESS questions that largely constituted the ISCS). Although a cutoff of 7 on the ESS provides a sensitivity of about 70% in predicting falling asleep at the wheel, its specificity for the underlying problem is low at about 50%. A cutoff of 1 on the ISCS has a specificity greater than 80%. Supplementing the traditional ESS with the ISCS could potentially increase the specificity of predicting which patients are likely to fall asleep while driving.

Falling asleep at the wheel is typically preceded by a warning of sleepiness rather than occurring suddenly and unpredictably. Patients should be warned about the nature of excessive daytime sleepiness. They should be educated to recognize the warning symptoms and the associated risks of these episodes occurring while driving, and about the importance of never driving when sleepy. Finally, patients should be asked regularly during follow-up visits about symptoms that suggest daytime sleepiness[39] or sudden onset of sleep. Episodes suggesting sudden "sleep attacks" were very uncommon in our study. At present it seems that the best predictor of future sleep attacks at the wheel is an initial sleep attack at the wheel.

The ESS in tandem with the ISCS is a useful tool to identify patients who are abnormally sleepy and may play a role in increasing patient and physician awareness of this significant clinical problem. Further research should be directed toward establishing whether this and other methods of assessment will predict future risk of falling asleep at the wheel.

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Author Contributions: Drs Hobson and Lang were co-first authors of this study. Drs Hobson and Lang, as principal investigators of this study, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.
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Acquisition of data: Hobson, Lang, Martin, Razmy, Rivest.
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Drafting of the manuscript: Hobson, Lang.
Critical revision of the manuscript for important intellectual content: Hobson, Lang, Martin, Razmy, Rivest, Fleming.
Statistical expertise: Lang, Razmy.
Obtained funding: Lang.
Study supervision: Hobson, Lang, Martin, Rivest.
Funding/Support: Boehringer-Ingelheim (Canada) Ltd provided an unrestricted educational grant for the conduct of this study.
Role of the Sponsor: Support for this survey was provided through Boehringer-Ingelheim (Canada) Ltd. This sponsor was approached by one of the authors (A. E. L.) to provide an unrestricted grant to carry out the study. The sponsor assisted in the logistics of developing the study (conference calls between investigators), development of the questionnaire forms, teaching sessions for the study centers (by the authors), and provision of funding (on a per subject basis) to the sites. Data were submitted by the sites to an independent third party where they were keyed into the database and checked. The third party communicated directly with the investigators (not the sponsor) about the data. The sponsor did not have access to the data and did not assist in data analysis.
Acknowledgment: We appreciate the cooperation of the following members of the Canadian Movement Disorders Group and their staff for conducting the questionnaires: A Goodridge, D Murphy (Memorial University, St John, Newfoundland); D King, P Gaudet (Dalhousie University, Halifax, Nova Scotia); C Melmed, L Beaudet (Jewish General Hospital, Montreal, Quebec); J Rivest, D Soucy (University of Sherbrooke, Sherbrooke, Quebec); E Pourcher, P Chabot (Polyclinique Sainte-Anne, Quebec City, Quebec); M Panisset, MJ Fortin, J Hall (McGill Centre for Studies in Aging, Montreal); V Soland, C Beauvais (Andre-Barbeau Movement Disorders Unit, Montreal); L Barclay, D Grimes, T Mendis, P Gray, BA Schwarz (Ottawa Civic Hospital, Ottawa, Ontario); A Lang, A Nieves, F Kahn, T Sanger, E Sime, J So, L DelRizzo (University of Toronto, Toronto, Ontario); M Guttman, J Burkholder (Markham Regional Hospital, Markham, Ontario); R Riopelle, S Weatherby (Queens University, Kingston, Ontario); D Stewart (Kitchener, Ontario); D Hobson, S Hobson (University of Manitoba, Winnipeg); O Suchowersky, R Ranawaya, AL Lafontaine, J Warner, N Labelle C Pantella (University of Calgary, Alberta); R Hsiung (Calgary); W Martin, P King, G McInnes (University of Alberta, Edmonton); and T Curran, S Balley (Vernon, British Columbia). We thank Shaun Hobson for her assistance with editing the manuscript, Corinne Buchanan of Boehringer-Ingelheim (Canada) Ltd for assistance in developing the questionnaire and conducting the study, and PharmIdeas Research & Consulting, Inc for assisting us in the initial statistical analysis.

REFERENCES

1. Hobson DE, Pourcher E, Martin WR. Ropinirole and pramipexole, the new agonists. *Can J Neurol Sci*. 1999; 26(suppl 2):S27-S33.
2. Rascol O, Brooks DJ, Korczyn AD, De-Deyn PP, Clarke CE, Lang AE, for the 056 Study Group. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med*. 2000;342:1484-1491.
3. Parkinson Study Group. Pramipexole vs levodopa in early Parkinson disease: a randomized controlled trial. *JAMA*. 2000;284:1931-1938.
4. Gottwald MD, Brainbridge JL, Dowling GA, Aminoff MJ, Alldredge BK. New pharmacotherapy for Parkinson's disease. *Ann Pharmacother*. 1997;21:1205-1217.
5. Frucht S, Rogers JD, Greene PE, Gordon MD, Fahn S. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology*. 1999;58:1908-1910.
6. Hauser RA, Gauaer L, Anderson WM, Zesiewicz TA. Pramipexole-induced somnolence and episodes of daytime sleep. *Mov Disord*. 2000;15:658-663.
7. Ryan M, Slevin JT, Wells A. Non-ergot dopamine agonist-induced sleep attacks. *Pharmacotherapy*. 2000; 20:724-726.
8. Ferreira JJ, Pona N, Costa J, et al. Somnolence as an adverse drug reaction of antiparkinson drugs: a

meta-analysis of published randomized placebo-controlled trials. *Mov Disord*. 2000;15(suppl 3):128.
9. Montastruc JL, Brefel-Courbon C, Senard JM, Desboeuf K, Rascol O, Lapeyre-Mestre M. Sudden sleep attacks and antiparkinsonian drugs: a pilot prospective pharmacoepidemiological study. *Mov Disord*. 2000;15(suppl 3):130.
10. Paladini D. Sleep attacks in two Parkinson's disease patients taking ropinirole. *Mov Disord*. 2000;15 (suppl 3):130-131.
11. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O. Sleep attacks in Parkinson's disease. *Lancet*. 2000; 355:1333-1334.
12. Schapira AH. Sleep attacks (sleep episodes) with pergolide. *Lancet*. 2000;355:1332-1333.
13. Ferreira JJ, Galitzky M, Brefel-Courbon C, et al. "Sleep attacks" as an adverse drug reaction of levodopa monotherapy. *Mov Disord*. 2000;15(suppl 3):129.
14. Ferreira JJ, Thalamas C, Galitzky M, et al. "Sleep attacks" and Parkinson's disease: results of a questionnaire survey in a movement disorders outpatient clinic. *Mov Disord*. 2000;15(suppl 3):187.
15. Homan CN, Wenzyl K, Suppan M, Feichtinger G, Ivanic N, Kriechbaum E. Sleep attacks after acute administration of apomorphine. *Mov Disord*. 2000;15 (suppl 3):108.
16. Olanow CW, Schapira AH, Roth T. Waking up to sleep episodes in Parkinson's disease. *Mov Disord*. 2000;15:212-215.
17. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*. 1992;15:376-381.
18. Drachman DA. Who may drive? who may not? who shall decide? *Ann Neurol*. 1988;24:787-788.
19. Schwab RS, England AC. Protection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML, eds. *Third Symposium on Parkinson's Disease*. Edinburgh, Scotland: Livingstone; 1969:152-157.
20. Hoehn MM, Yahr MD. Parkinsonism: onset progression and mortality. *Neurology*. 1967;17:427-442.
21. Reyner LA, Horne JA. Falling asleep while driving: are drivers aware of prior sleepiness? *Int J Legal Med*. 1998;111:20-31.
22. Lyznicki JM, Doege TC, Davis RM, Williams MA, for the Council on Scientific Affairs, American Medical Association. Sleepiness, driving, and motor vehicle crashes. *JAMA*. 1998;279:1908-1913.
23. Maycock G. Sleepiness and driving: the experience of U.K. car drivers. *Accid Anal Prev*. 1997;29: 453-462.
24. Sagberg F. Road accidents caused by drivers falling asleep. *Accid Anal Prev*. 1999;31:639-649.
25. Horne JA, Reyner LA. Sleep related vehicle accidents. *BMJ*. 1995;310:565-567.
26. Horne JA, Reyner LA. Driver sleepiness. *J Sleep Res*. 1995;4(suppl 2):23-29.
27. Arnulf I, Bonnet AM, Damier P, et al. Hallucinations, REM sleep, and Parkinson's disease. *Neurology*. 2000;55:281-288.
28. Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ. Sleep disorders and sleep effect in Parkinson's disease. *Mov Disord*. 1990;5:280-285.
29. Nausieda PA. Sleep disorders. In: Koller WC, ed. *Handbook of Parkinson's Disease*. New York, NY: Marcel Dekker Inc; 1987:371-380.
30. Stocchi F, Barbato L, Nordera G, Berardelli A, Ruggieri S. Sleep disorders in Parkinson's disease. *J Neurol*. 1998;245(suppl 1):S15-S18.
31. Partinen M. Sleep disorders related to Parkinson's disease. *J Neurol*. 1997;244:S3-S6.
32. Karlsen K, Larsen JP, Tandberg E, Jorgensen K. Fatigue in patients with Parkinson's disease. *Mov Disord*. 1999;14:237-241.
33. Ebersbach G, Norden J, Tracik F. Sleep attacks in Parkinson's disease: polysomnographic recordings. *Mov Disord*. 2000;15(suppl 3):89.
34. Itoi A, Cilveti R, Voth M, et al. *Can Drivers Avoid Falling Asleep at the Wheel? Relationship Between Awareness of Sleepiness and Ability to Predict Sleep Onset*. Washington, DC: American Automobile Association Foundation for Traffic Safety; 1993.
35. Reyner LA, Horne JA. Falling asleep whilst driving: are drivers aware of prior sleepiness? *Int J Legal Med*. 1998;111:120-123.
36. Frucht S, Rogers JD, Greene PE, Fahn S, Gordon MF. Falling asleep at the wheel: motor vehicle mishaps in people taking pramipexole and ropinirole [author reply]. *Neurology*. 2000;54:276.
37. Tracik F, Ebersbach G. Sudden daytime sleep onset in Parkinson's disease: polysomnographic recordings. *Mov Disord*. 2001;16:500-506.
38. Stiasny K, Oertel WH. Safety of pramipexole in patients with restless leg syndrome (RLS). *Mov Disord*. 2000;15(suppl 3):114.
39. National Center on Sleep Disorders Research Working Group. Recognizing problem sleepiness in your patients. *Am Fam Physician*. 1999;59:937-944.

Great geniuses have the shortest biographies.
—Ralph Waldo Emerson (1803-1882)