Contributions of Dopaminergic Drugs and Disease Severity to Daytime Sleepiness in Parkinson Disease

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**Background:** Excessive daytime somnolence is a common report among patients who have Parkinson disease (PD). The relative contributions of disease severity and of the various dopaminergic drugs are unclear.

**Objective:** To separate and quantify the contributions of disease markers and drug doses.

**Methods:** Patients seen during a 7-month period at a center for movement disorders completed the Epworth Sleepiness Scale. Treatment subgroups were compared. The relationship to sedation of age; dopaminergic drug classes and doses; Hoehn and Yahr stage; duration of disease; total score on the motor subsection of the Unified Parkinson Disease Rating Scale; and the presence or absence of dementia, depression, or hallucinations was calculated using simple and multiple regression and t tests.

**Results:** The Epworth Sleepiness Scale scores were higher among patients with PD (mean [SD], 10.8 [5.3]; n=368) compared with patients with other neurological disorders (mean, 8.5 [5.1]; n=243; P<.001). A model containing the Hoehn and Yahr stage, levodopa dose, and use of a dopamine agonist was the best at predicting the total score of Epworth Sleepiness Scale in patients who have PD, but accounted for only 9% of the interindividual variance. The parameter estimates (SE) corresponded to a 1.02 (0.03)–point increase per Hoehn and Yahr stage, a 0.14 (0.06)–point increase per 100-mg increase in levodopa dose over 24 hours, and a 2.33 (0.57)–point increase with use of an agonist. There was no statistically significant dose response for agonists. No statistically significant difference in sedation among the commonly used dopamine agonists was found.

**Conclusions:** Somnolence in patients with PD, which is on average 25% higher than in other neurological diseases, is related to PD stage, levodopa dose, and the use of a dopamine agonist. However, most of the variability in sedation levels in patients with PD as well as in controls is the result of, as yet, unidentified factors.

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**RESULTS**

**PATIENTS WITH PD COMPARED WITH CONTROLS**

Seven hundred sixty-nine unique patients were seen in the clinic during the study period, and Epworth data were available for 611. The study cohort was composed of 368 patients with PD (94% of all patients with PD seen during the study period) and 243 controls (65% of the patients without PD seen during the study period).

The patients with PD had a mean (SD) age of 66.8 (10.3) years, and a mean (SD) disease duration of 7.9 (6.0) years. The numbers at each Hoehn and Yahr stage were as follows: 0, 1 patient; 1, 56 patients; 2, 144 patients; 2.5, 40 patients; 3,
PATIENTS AND METHODS

We attempted to study all patients presenting to the Clinical Center for Movement Disorders at the University of Texas Southwestern Medical School, Dallas, between January 4, 2001, and July 24, 2001. The Epworth Sleepiness Scale was distributed at check-in. The scale consists of 8 questions about the likelihood of sleep under various conditions in their daily life, and patients respond with scores of 0 (no chance of dozing) to 3 (high chance of dozing); the sum of the 8 responses is reported as the Epworth total. These data were entered into a database in which demographics, drug information, and clinical notes are linked. For those patients seen more than once during this period, the most recent visit was included in the study.

The equivalent dopamine agonist dose over 24 hours was calculated with conversion factors of 1 mg of ropinirole mesylate equals 1.5 mg of pramipexole equals 10 mg of bromocriptine mesylate equals 5 mg of ropinirole hydrochloride. The equivalent levodopa dose over 24 hours was calculated with conversion factors of 75 mg of immediate-release levodopa equals 100 mg of controlled-release levodopa. Tables generated using Microsoft Access queries were imported into SAS for analysis. The main outcome of interest was the Epworth total. The PD group and controls were compared using t tests. The PD treatment groups were analyzed using analysis of variance (ANOVA) with post hoc Scheffe tests. Regression analysis was performed for each of the continuous, interval, or ordinal independent variables of interest: equivalent agonist dose, equivalent levodopa dose, age, Hoehn and Yahr stage, disease duration, and Unified Parkinson Disease Rating Scale (UPDRS) total. The best multiple regression model was selected by stepwise adding variables in order of their significance in univariate tests.

80 patients; 4, 39 patients; and 5, 8 patients. The UPDRS motor function (part III) scores, typically in the “on state” (ie, when the individual is taking medication), were almost complete for 301 patients. By “almost complete,” we mean that either 24 or 25 of the 27 fields were filled: in our database the action tremor fields are always omitted when the tremor field is commonly unreported. The mean (SD) UPDRS motor score was 23 (15) points. Subjects were not systematically assessed for dementia, depression, or hallucinations as part of the study protocol, but participants’ notes were searched for references to these problems. Dementia was noted in 33 patients, active depression in 37, and hallucinations in 40.

The controls had other movement disorders (n=191; most of these were parkinsonian syndromes, essential tremor, or dystonia) or other neurological problems (n=52, of which the most common diagnoses in order were headaches, dementia, neuropathy, and pain).

Twenty-five of the controls were taking levodopa and 8 were taking a dopamine agonist.

Mean (SD) Epworth total in patients with PD was 10.8 (5.3) points while in the controls the mean was 8.5 (5.1) points (P<.001). If the 33 controls taking a dopaminergic drug were omitted from consideration, the control group mean was 8.0 (5) points.

SLEEPINESS IN PD AS A FUNCTION OF TREATMENT CLASS

Of the patients with PD, 18 were untreated and 350 were taking medications for PD. Treatment was with levodopa monotherapy (n=106), dopamine agonist monotherapy (n=57), or combined agonist-levodopa therapy (n=187).

The distribution of Epworth totals for each PD treatment group is shown in the Figure. Combination therapy, levodopa monotherapy, agonist monotherapy, and the nontreated groups had mean (SD) scores of 11.8 (5.2) points, 9.9 (5.4) points, 10.1 (5.3) points, and 8.2 (4.3) points, respectively (F3,364=5.27, P<.001). Post hoc comparisons showed that the combination group had higher scores than the levodopa or untreated groups. The mean (SD) ages of the 4 treatment groups were different: 67 (9.7), 72 (8.6), 58 (9.3), and 63 (8.7) years, respectively (F3,364=29, P<.001) as were UPDRS motor scores: 21 (13) points, 30 (16) points, 15 (11) points, and 22 (19) points, respectively (F3,364=12.3, P<.001). When these 2 variables were included with the treatment group as independent variables, the ANOVA model was again significant (F3,364=3, P=.01), with the UPDRS motor score (P=.01) and treatment group (P=.01) as significant predictors.

Analysis of covariance comparing Epworth totals between the dopamine agonists when controlling for levodopa dose did not reveal a difference among the agonists. There was a trend toward a higher Epworth total for those using pergolide (least squares method mean estimate, 12.8, n=71) and pramipexole (12.2, n=107) compared with ropinirole (10.6, n=62) or bromocriptine (8.0, n=4). If the least commonly used agonist was omitted, the agonist drugs again failed to show a significant difference.
Patients with PD were sleepier than our control patients, supporting the perception that there are additional sedating factors in PD above and beyond those in other neurological disease. However, with mean scores about only 25% higher, the patients with PD were not that much sleepier than the controls, and there was a broad area of overlap of their distributions. Untreated patients with (early-stage) PD had Epworth scores similar to controls. Based on their parameter estimates, 3 factors (levodopa dose, use of an agonist, and PD severity) could account for most of the extra 2.3 points of sedation experienced by the average patient with PD compared with the average neurological control.

These 3 factors also predict to some degree sedation levels within the PD cohort. While the predictors are correlated, combined models and subset analyses suggest that drugs and disease each contribute to somnolence. In agreement with our data, a statistically significant association between sedation and increasing doses of levodopa was recently reported. We quantified this effect and found it to be small. An increment of 7 tablets of immediate-release 25 mg of carbidopa/100 mg of levodopa per day worsened the Epworth total by approximately 1 point. This may be an underestimation owing to probable bias against those subjects with particular sensitivity to sedation from levodopa therapy, as they are likely to remain at lower doses to avoid this adverse effect.

A dose effect was not identifiable for dopamine agonists, but use of an agonist at any dose was associated with an increase of more than 2 points in the Epworth total. We do not know whether the discrepancy between the graded effect of levodopa and the all-or-nothing effect of dopamine agonists reflects a biological difference in their mode of action or is merely a statistical fluke. An association between nocturnal sleep disruption and disease severity has also been previously reported. In our study, an association between daytime somnolence and parkinsonism was more striking when the Hoehn and Yahr stage was used as the measure of disease severity, arguably because the Hoehn and Yahr stage better represents disease burden than the on-state UPDRS total. How disease burden might contribute to sedation is unclear. The relationship may be indirect, for example, from nocturnal rigidity or nocturia disrupting sleep.
sleep, or perhaps could be due to progressive degeneration of brainstem arousal neurons.

Notwithstanding the contributions of dopaminergic drugs and disease severity to somnolence in PD, the important point remains that these factors account for only 9% of the interindividual variability in the Epworth total. As yet unidentified factors are needed to explain most of the variability. The unidentified factors may be similar in PD to those in other neurological diseases, as the variability in our PD and control groups was about the same. The Epworth Sleepiness Scale was developed as a measure of the tendency to doze off.20 We believe this scale has face validity as a measure of drowsiness. It is our impression that this drowsiness is a common chronic problem in PD for which there is no validated measure. Not to be confused with this problem, a public health concern has also been raised about the uncommon phenomenon of sudden-onset sleep in PD. Others have used the Epworth Sleepiness Scale to categorize patients as higher risk vs lower risk of sudden onset of sleep. In a study focused on this problem, Hobson et al12 recently reported that just over half of their patients with PD suffered excessive daytime sleepiness using a cutoff point Epworth total of 7. If we use the same standard, an even larger fraction of our patients would be classified as excessively sleepy. However, it might be argued that this threshold is too low to be meaningful, as most neurological patients with PD and controls have elevated scores by this standard. For those clinicians who use an Epworth score in deciding whether to advise against driving, we would caution against using too low a threshold and against using this standard more restrictively in patients with PD compared with other clinic patients, as no more than anecdotal evidence exists that patients with PD above that threshold are at a sufficiently higher risk of sudden-onset sleep than neurological patients in whom driving is not restricted. In addition, we suggest there is, as yet, insufficient rationale for dichotomizing patients with PD into normal vs sedated using any particular cutoff point, as Epworth totals have a reasonably bell-shaped distribution (Figure). Instead, a clinician recording an Epworth score can locate that patient’s sedation along a spread, based on a mean and SD derived either locally or from a published cohort such as ours.

How has this elevated awareness of sedation, and the results of our analysis, affected our practice? We now ask all our patients about daytime somnolence. In the few patients with a clear temporal relationship between drug dosing and sedation, we reduce or change the offending drug. We compromise motor control by reducing dopaminergic drugs only among the subset of patients with intolerance to all agents as demonstrated by sedation on challenge and rechallenge. However, because levodopa therapy contributes modestly to the problem for the average patient with PD, we pay more attention to other drugs that may have sedative adverse effects, and to nocturnal sleep patterns. If sleep is poor because of reemergent immobility or stiffness, or because of rapid eye movement sleep behavioral disorder, we try to address these matters of treatment with nocturnal levodopa and clonazepam, respectively. We consider off-label use of modafinil for those patients without another solution to dis-}

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### REFERENCES


