Sudden Uncontrollable Somnolence and Medication Use in Parkinson Disease

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Background: Episodes of sudden uncontrollable somnolence have been reported in patients with Parkinson disease (PD) receiving dopamine agonists, including pramipexole and ropinirole, but controversy persists concerning their nature, severity, and frequency.

Objectives: To quantify the risk of sudden uncontrollable somnolence in patients taking specific PD medications and to define its predictors.

Methods: We contacted 929 patients with PD and administered a 45- to 60-minute interview addressing medication use, adverse events, and the patient’s clinical status in the preceding 6 months. Their physicians completed record reviews detailing their clinical histories and drug regimens. The outcome of interest in this case-control study was an episode of somnolence that was uncontrollable, severe, and inappropriate, such as while driving or engaged in social activity. For multiple events, the first was chosen as the index event. For each case, we sampled control time from all respondents who had no event as of the index time for that case. Multiple logistic regression was used to adjust for potential confounders.

Results: Episodes of uncontrollable somnolence were reported by 22% of all respondents. After controlling for age, sex, PD duration and severity, frailty, and other medication use, we found that patients receiving a dopamine agonist (pramipexole, ropinirole, or pergolide) were nearly 3-fold as likely to have episodes of sudden uncontrollable somnolence (odds ratio, 2.8; 95% confidence interval, 1.8-4.2) compared with all other PD medication users. Similar risks were seen for the 3 agents, pramipexole, ropinirole, and pergolide, each compared with levodopa alone (odds ratio, 2.2, 1.8, and 2.1, respectively), with a clear dose-response relationship for each. No increase in risk was seen with any other drugs studied.

Conclusions: Dopamine agonists widely used for the management of PD significantly increase the risk of sudden uncontrollable somnolence in a dose-related manner. Greater attention to this potentially serious adverse effect will be necessary to improve the safety of use of this important category of PD drugs.

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The growing use of newer dopamine agonists (DAs) has had an important impact on the management of Parkinson disease (PD). Pramipexole (Mirapex; Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Conn), ropinirole (Requip; GlaxoSmithKline, Research Triangle Park, NC), and pergolide (Permax; Amarin Pharmaceuticals Inc, Warren, NJ) are synthetic D2-selective DAs often used as primary initial therapy for PD as well as in combination with levodopa. While these agents have been well received by patients with PD and their physicians, case reports of the sudden onset of somnolence have caused concern among physicians, patients, and regulators. Particular attention has focused on events in which patients fell asleep while driving.

Frucht et al first described 8 such events among patients with PD treated with pramipexole. One patient was switched to ropinirole and experienced similar effects. The events were described as “sudden irresistible attacks of sleep.” Additional case reports followed, raising the question of whether DAs, as a class, cause what came to be known as “sleep attacks.” The reported prevalence of the phenomenon has varied widely, from 4% to 23%, in survey studies. In one study of 2952 patients with PD, sudden unexpected and irresistible sleep episodes while engaged in some activity were reported in 6% of patients.

Subsequent studies raised the question of whether these events were sudden attacks of sleep, represented the known somnolence caused by these medications, or were disturbances of sleep-
wake regulation related to the disease itself.11 A prospective study12 of 47 patients with PD concluded that excessive daytime sleepiness is independent of dose and type of dopaminergic drug use but might be related to abnormal sleep-wake control. It was suggested that these episodes are narcolepsy-like rapid eye movement sleep disorders.13,14 Rye et al15 documented an abnormally short mean sleep latency in 27 patients with PD, independent of disease duration or medication use.

It remains unclear whether such events represent a newly described phenomenon or are simply a consequence of somnolence in patients with PD and whether they are related to a specific drug or drug class.16 Little is known about other risk factors, including age, sex, and PD duration or severity, for such adverse events. We sought to systematically define the nature and prevalence of these episodes of uncontrolled somnolence and to measure their relationship to specific PD medications, particularly the DAs.

METHODS

This was a case-control study of the occurrence of sudden uncontrolled somnolence in a large group of patients with PD. Participating neurologists in 6 movement disorder clinics were invited to refer pharmacologically managed patients with idiopathic PD for study. The only exclusion criteria were dementia or psychiatric illness severe enough to prevent participation in a telephone interview. A priori sample-size calculation estimated the number of needed participants to be 930. We recruited an additional 10%, for a total of 1041 patients. The patients were recruited from the following movement disorder centers: the Hospital of the University of Pennsylvania, Philadelphia; the Clinical Neuroscience Center, Southfield, Mich; Baylor College of Medicine, Houston, Tex; and the Massachusetts General Hospital, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center, Boston.

Participating neurologists were asked to recruit all eligible patients at the time of scheduled visits. Patients signed a consent form agreeing to be contacted by researchers at the study center (Division of Pharmacoepidemiology, Brigham and Women's Hospital) and to have their medical records abstracted by their neurologists and sent to the study center. Each participant's consent was reconfirmed at the beginning of a 45- to 60-minute telephone interview. The referring neurologists completed detailed medical record abstractions covering the period under study. The study was approved by the institutional review boards of the Brigham and Women's Hospital and each of the other study sites.

ASSESSMENT OF DRUG USE AND PATIENT CHARACTERISTICS

During a standardized telephone interview, we asked respondents to focus on the 6 months immediately preceding the interview date. Research assistants asked each patient to identify the dose and frequency of use of all antiparkinsonian medications during this period, including the start or discontinuation of each drug as well as the date of any changes in strength or dosing. For analysis, the drugs were grouped into the following categories: levodopa/carbidopa, pramipexole, ropinirole, older DAs (bromocriptine and pergolide), anticholinergic agents (trihexyphenidyl, ethopropazine, and benztropine), amantadine, monoamine oxidase inhibitors (selegiline and rasagiline), and catechol-O-methyltransferase inhibitors (tolcapone and entacapone). We also assessed the use of all non-PD-related drugs and grouped them as having central nervous system–sedating activity, central nervous system–activating activity, and all others (Figure). Time-varying drug exposure was transformed into a 180-day drug use calendar for each study subject.

The severity of PD for each patient was assessed by the referring neurologist for the interval of the study period using the Hoehn and Yahr scale17 ranging from 0 (no sign of disease) to 5 (wheelchair bound). This scale has high interrater agreement18 and correlates well with striatal uptake of fluorodopa F18.19 Activities of daily living were reported using a modified Schwab and England scale18 ranging from 0% to 100% of independence in activities of daily living. Patients provided self-reports of functional status using a standard index of activities of daily living.20 General somnolence was assessed at the time of the interview with an 8-item Epworth Sleepiness Scale21 with scores ranging from 1 to 24. The Epworth scale has demonstrated correlation with the Respiratory Disturbance Index and overnight oxygen saturation22 and has been found to be reliable and to have high internal consistency.22

STUDY END POINT

The primary outcome was a patient's report of episodes of sudden and inappropriate somnolence, described as “uncontrollably falling asleep,” during the 6-month period immediately preceding the interview. Our experience in a pilot study and the highly variable descriptions of such episodes in the literature20,21,24 indicated that it would be necessary to clarify the definition of these episodes for study subjects. Therefore, we presented 2 examples of such episodes to each participant: (1) “You fall asleep while sitting and talking with friends, although you did not want to fall asleep. Your friends might later tell you that you fell asleep.” (2) “You are driving a car along the road and suddenly find that, without knowing it, you dozed off.” The reported dates of all such events were recorded.

It is generally not appropriate to adjust for a variable, such as the score on the Epworth Sleepiness Scale, that may lie on the causal pathway of the outcome being studied (episodes of uncontrollable somnolence). However, we were interested in
learning how much of the association between D2 agonists and uncontrollable somnolence could be explained by the capacity of these drugs to cause less extreme manifestations of sleepiness. If adding the Epworth score to the multivariate model eliminated the association, it would indicate that the relationship could be completely explained by (ie, was mediated through) an exacerbation of everyday sleepiness. If, on the other hand, the association between drug use and uncontrollable somnolence persisted despite controlling for more conventional sleepiness symptoms, it would suggest that the drugs may precipitate episodes of uncontrollable somnolence somewhat independently from their capacity to cause sleepiness.

To improve the specificity of end point definition, we also defined a secondary study outcome, severe episodes of uncontrollable somnolence, as a subset of all reported episodes. This determination was based on patients’ free text descriptions of the event(s) and their reports of the presence or absence of 9 specific characteristics of their episodes. Examples included patients whose episodes occurred while driving, speaking, or engaging in an activity in which falling asleep was particularly inappropriate (such as in the final minutes of a sporting event they were following closely) and/or hazardous.

STATISTICAL ANALYSIS

Event dates were identified for all of the episodes that met study criteria. For each subject who reported more than 1 event, the first was used as the index event. Control index dates were frequency matched to the case-defining index dates at a ratio of 4:1; these were drawn from all person-time preceding a case-defining event for each subject. Thus, controls at 1 point in the study could become cases later, but not vice versa. Exposure was determined on the basis of PD drug use at the time of the first event or on the randomly assigned index date for controls. To adjust for potential confounding by clinical and demographic characteristics, disease severity, and use of other prescription drugs, we fitted multivariate logistic regression models to the data.

Exposure was defined in 3 ways: (1) use of any DA as compared with all regimens that did not include a DA; (2) any use of 4 broad groups of antiparkinsonian medications and their combinations (levodopa, DAs, anticholinergic agents, and all others), with the use of levodopa alone serving as the reference group; and (3) use of specific drugs or drug categories (to allow for a more detailed analysis of specific agents independent of their use with one another), again using exposure to levodopa alone as the reference exposure. All of the drug exposures were determined as of the day of the event. We also analyzed potential dose-response relationships by dividing the use of pramipexole, pergolide, and ropinirole into 3 equipotent dosage groups2,12,16,27; nisoxetine; low-to-medium dosage (pramipexole and pergolide, 0.03 mg/d; ropinirole, 0.12 mg/d), and high dosage (pramipexole and pergolide, >3 mg/d; ropinirole, >12 mg/d).

To explore the sensitivity of results to the outcome definition itself, we repeated all of the regression analyses using only the subset of patients with severe episodes of uncontrollable somnolence as the case definition. We also repeated the analyses based on the number of events during 180 days (patients with 1-10 events vs patients with >10 events) to determine whether frequent events might have different predictors than rare events. Finally, in an exploratory analysis, we included the Epworth Sleepiness Scale score in the model to assess how controlling for the level of daytime sleepiness affected any associations between the drugs and the outcome of uncontrollable somnolence.

The sensitivity of the results to potential misclassification of event dates was estimated using the simulation-extrapolation approach. Each event index date was randomly changed to a simulated index date before and after the recorded index date, with 1 of these randomly assigned as the “simulated index date.” This was repeated 1000 times and the average association, including the 5th and 95th percentiles, was calculated. We repeated this simulation by incrementing the range of simulated index dates from 1 to 30 days before or after the recorded date and then plotted the misclassified index dates. If increasing random measurement error leads to increasingly attenuated effect estimates, a backward extrapolation of the simulation effects beyond the observed effect would assess the effect of random misclassification.

In all analyses, we calculated proportions and 95% confidence intervals by standard methods. Proportions were compared using the χ² test with 2-sided P values. All of the analyses were performed using SAS version 8.3 software (SAS Institute Inc, Cary, NC).

RESULTS

Of 1041 referred patients, 4 were excluded because of predefined exclusion criteria, 44 refused to participate, 22 could not be contacted because of incorrect or disconnected telephone numbers, 14 could not be reached after 10 attempts, 5 were not able to communicate on the telephone, and 3 died before the interview. Twenty patients were excluded because they did not use any antiparkinsonian drugs during the study period. A total of 929 patients, or 89% of all those originally referred, completed the telephone interview and constituted the final study population.

Study subjects were, on average, 66.7 years old and were predominantly white and male (Table 1). Most reported that they operated a car and described their overall health as good or excellent. Their average duration of PD was 3.6 years. Of the patients, 91.3% used levodopa either alone or in combination with another agent, 38.8% used pramipexole alone or with another agent, and 18.5% used ropinirole alone or with another agent.

(Table 2) Amantadine, monoamine oxidase inhibitors, and catechol-O-methyltransferase inhibitors were also commonly used. The most frequent regimen was levodopa plus a DA plus a third class of antiparkinsonian medication (28.2% of patients), followed by levodopa plus a DA (22.5%) and levodopa alone (20.0%) (Table 3).

Patients who were prescribed a DA alone were the youngest group (mean age, 59.4 years), had the shortest duration of disease (mean duration, 1.2 years), had the least severe PD (mean Hoehn and Yahr Scale score, 3.6), and had the least impaired activities of daily living. By contrast, those taking levodopa alone were the oldest (mean age, 70.9 years), had a longer duration of disease (mean duration, 3.6 years), and had Hoehn and Yahr Scale scores indicating greater PD severity (mean score, 4.6). However, in crude analyses, the proportion of patients receiving a DA alone who reported episodes of uncontrollable somnolence (22.0%) was substantially greater than that of those who received levodopa alone (13.4%). Those receiving levodopa in combination with a DA were quite similar to the patients receiving levodopa alone in terms of their mean age, PD duration, and Hoehn and Yahr Scale scores. Yet, more than twice as many patients in the levodopa-DA group (28.2%) reported episodes of uncontrollable somnolence as compared with those in the levodopa-only group (13.4%). The 21 pa-
tients only receiving medications grouped into “other anti-PD drugs” (Table 2) reported no study outcome events. Fifty-seven percent of patients did not change their antiparkinsonian drugs, including the dosage, during the 6-month study period.

Among the 206 patients who reported at least 1 episode of uncontrollable somnolence, most reported either a small number of events (1-4 events; 34% of patients) or many frequent events (8-26 episodes; 37% of patients) during the 180 days preceding the interview, with 24 (12%) of the patients reporting daily episodes (Table 4). Of all 206 patients who reported events, 124 (62%) were classified as having severe episodes. The total number of events was similarly distributed among the 124 patients with severe events compared with the 82 patients who reported only nonsevere events (Table 4).

Following these unadjusted analyses, we then performed a multivariate adjusted regression analysis to assess the association of each antiparkinsonian drug class with episodes of uncontrollable somnolence. After adjusting for a wide variety of patient characteristics, this analysis continued to demonstrate a pattern of significantly increased risk associated with DAs alone or in combination as compared with the use of levodopa alone; adjusted odds ratios (ORs) indicated a doubling or tripling of such risk. This association was also seen for specific DA regimens as well as specific DA agents (Table 5 and Table 6). It could not be explained by patient age, PD duration or severity, the use of other central nervous system-sedating medications, the number of PD medications received, or any other potential confounder studied.

We then performed an aggregated analysis in which we studied the effect of receiving any DA compared with that of receiving any other antiparkinsonian drugs without DAs. After controlling for all available patient characteristics, this analysis yielded an adjusted OR of 2.75 (95% confidence interval [CI], 1.79-4.24) for the use of any DA (pramipexole, ropinirole, pergolide, or bromocriptine). A multivariate analysis of specific individual drugs compared with levodopa only (Table 6) showed significant associations for pramipexole (OR=2.22; 95% CI, 1.43-3.43), ropinirole (OR=1.76; 95% CI, 1.03-3.00), and the older DAs (primarily pergolide [OR=2.11; 95% CI, 1.24-3.61]). Additional control for Hoehn and Yahr staging changed these results by less than 5%. When we considered only severe events as the study outcome, there were slightly stronger effects for pramipexole (OR=3.07; 95% CI, 1.79-4.95) and ropinirole (OR=2.00; 95% CI, 1.01-3.97). The multiple regression models also suggested dose-response relationships for pramipexole (low or medium dose: OR=2.08; 95% CI, 1.29-3.35; high dose: OR=2.79;
In a nested case-control study of 929 patients with PD receiving antiparkinsonian drugs, we found that the risk of an episode of uncontrollable somnolence was higher than commonly appreciated, occurring at least once in 22% of the patients. The risk of this adverse event was 2.8-fold higher in patients who received a DA than in patients with PD receiving other medications, even after controlling for a wide variety of clinical and demographic variables. The data demonstrated a dose-response relationship for pramipexole, pergolide, and ropinirole. In view of the flattening of the therapeutic dose-response relationship seen with some of these agents, there may be important therapeutic implications.

The effects were independent of several indicators of PD severity, including its duration, the number of antiparkinsonian medication classes that a patient was receiving, the functional status of patients, and the score for activities of daily living, which characterized the comorbidity and functional status of patients.

Compared with patients receiving levodopa, the patients who received DAs as monotherapy were younger, had less severe disease as measured by the Hoehn and Yahr scale, and had more episodes of uncontrollable somnolence that were more severe. During the study period, all recruiting neurologists assessed Hoehn and Yahr staging as determined by the neurologist. Further, the reported effects were also adjusted for age, sex, number of non-PD medications, and the score for activities of daily living, which characterized the comorbidity and functional status of patients.

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### Table 3. Antiparkinson Drug Therapy at Interview Date byPatient Characteristics

<table>
<thead>
<tr>
<th>Antiparkinson Drug Therapy Group</th>
<th>Patients With at Least 1 Event No. (%)</th>
<th>Patients Reporting at Least 1 Event</th>
<th>PD Duration, y</th>
<th>Hoehn and Yahr Score*</th>
<th>Activities of Daily Living Score*</th>
<th>Epworth Sleepiness Scale Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa only</td>
<td>25 (13.4)</td>
<td>25 (13.4)</td>
<td>3.6 (4.8)</td>
<td>4.6 (1.4)</td>
<td>2.5 (3.6)</td>
<td>7.8 (5.0)</td>
</tr>
<tr>
<td>DA only</td>
<td>13 (11)</td>
<td>13 (11)</td>
<td>1.2 (1.5)</td>
<td>3.6 (1.4)</td>
<td>0.5 (1.1)</td>
<td>8.4 (5.0)</td>
</tr>
<tr>
<td>Levodopa plus DA</td>
<td>59 (12.1)</td>
<td>59 (12.1)</td>
<td>3.7 (4.6)</td>
<td>4.5 (1.6)</td>
<td>2.2 (3.1)</td>
<td>9.7 (5.2)</td>
</tr>
<tr>
<td>Levodopa plus DA plus other‡</td>
<td>63 (9.5)</td>
<td>63 (9.5)</td>
<td>4.0 (5.7)</td>
<td>4.7 (1.4)</td>
<td>2.0 (3.0)</td>
<td>10.2 (5.3)</td>
</tr>
<tr>
<td>Levodopa plus other†‡</td>
<td>38 (4.1)</td>
<td>38 (4.1)</td>
<td>1.9 (2.3)</td>
<td>3.6 (1.2)</td>
<td>0.3 (0.6)</td>
<td>9.3 (3.9)</td>
</tr>
<tr>
<td>DA only</td>
<td>13 (11)</td>
<td>13 (11)</td>
<td>2.3 (3.6)</td>
<td>3.7 (1.5)</td>
<td>0.7 (1.2)</td>
<td>6.3 (3.5)</td>
</tr>
</tbody>
</table>

### Table 4. Frequency of Episodes of Uncontrollable Somnolence During Preceding 6 Months

<table>
<thead>
<tr>
<th>Episodes, No.</th>
<th>Patients With Only Nonsevere Episodes, No. (%)</th>
<th>Patients Reporting Severe Episodes, No. (%)</th>
<th>P Value</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>30 (37)</td>
<td>40 (52)</td>
<td>.52</td>
<td>70 (34)</td>
</tr>
<tr>
<td>5-10</td>
<td>13 (16)</td>
<td>22 (18)</td>
<td>.72</td>
<td>35 (17)</td>
</tr>
<tr>
<td>11-25</td>
<td>12 (15)</td>
<td>13 (11)</td>
<td>.37</td>
<td>25 (12)</td>
</tr>
<tr>
<td>≥26</td>
<td>27 (33)</td>
<td>49 (40)</td>
<td>.34</td>
<td>76 (37)</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD).
†Hoehn and Yahr staging was assessed by referring neurologists.
‡Other antiparkinsonian drugs: trihexyphenidyl, ethopropazine, benztropine, amantadine, selegiline, rasagiline, tolcapone, and entacapone.

Abbreviations: CI, confidence interval; DA, dopamine agonist; NA, not applicable; PD, Parkinson disease.

95% CI, 1.59-4.89, ropinirole (low or medium dose: OR=1.68, 95% CI, 0.94-3.00; high dose: OR=2.41; 95% CI, 1.00-5.80), and pergolide (low or medium dose: OR=1.72; 95% CI, 0.90-3.28; high dose: OR=2.83; 95% CI, 1.38-5.83). In a separate analysis, we compared high-dose levodopa (≥550 mg/d) with low-dose levodopa (<550 mg/d) and found that while larger doses of levodopa were associated with higher rates of somnolence than lower doses of levodopa, this effect was smaller than that seen with the DAs.

When the Epworth Sleepiness Scale score was introduced as a dichotomous variable into the main multivariate model (score of ≤6 vs score of ≥7), Epworth scores higher than the median had a very strong association with the outcome of uncontrollable somnolence (OR=6.86; 95% CI, 3.98-11.82). In this model, the adjusted ORs for pramipexole and for the older DAs (pergolide and bromocriptine) were slightly attenuated but remained significantly elevated (OR=2.02; 95% CI, 1.28-3.20 and OR=1.74; 95% CI, 0.99-3.04, respectively).

The simulation-extrapolation analysis to explore the sensitivity of the findings to event date misclassification revealed that the results were attenuated by less than 5%, suggesting that it is unlikely that the findings were influenced by such misclassification. Irrespective of medication use, men had more than a 2-fold increased risk of reported episodes of uncontrollable somnolence.

**COMMENT**

In a nested case-control study of 929 patients with PD receiving antiparkinsonian drugs, we found that the risk of an episode of uncontrollable somnolence was higher than commonly appreciated, occurring at least once in 22% of the patients. The risk of this adverse event was 2.8-fold higher in patients who received a DA than in patients with PD receiving other medications, even after controlling for a wide variety of clinical and demographic variables. The data demonstrated a dose-response relationship for pramipexole, pergolide, and ropinirole. In view of the flattening of the therapeutic dose-response relationship seen with some of these agents, there may be important therapeutic implications.

The effects were independent of several indicators of PD severity, including its duration, the number of antiparkinsonian medication classes that a patient was receiving, the functional status of patients, and the score for activities of daily living, which characterized the comorbidity and functional status of patients.

Compared with patients receiving levodopa, the patients who received DAs as monotherapy were younger, had PD for fewer years, and had less severe disease as measured by the Hoehn and Yahr scale, which might have made them less likely to develop episodes of uncontrollable somnolence independent of their drug use. These findings make it very unlikely that the higher risk of uncontrollable somnolence in these patients was the result of selection bias. In fact, any residual confounding owing to the preferential use of DAs in healthier patients would bias results toward a null finding and the true effect would be even stronger. During the study period, all recruiting neurolo-
The risks associated with each drug and drug class were assessed by performing logistic regression analyses. One examined whether these predictors were likely to operate in the opposite direction. Interestingly, for several of the D2 agonists, the association with episodes of uncontrollable somnolence persisted even after controlling for the level of overall sleepiness reported by patients at the time of the interview. This suggests that these drugs may increase the risk of these sudden events independent of the degree to which the drugs produce daytime sleepiness. A limitation here is the Epworth Sleepiness Scale score used in these analyses was reported at the time of the interview and not at the time of the event itself. Nevertheless, most patients did not change their drug regimens between the reported event(s) and the interview date. The initial reports of sleep episodes described patients falling asleep at especially inappropriate times, such as while driving a car. We therefore performed 2 additional analyses. One examined whether these predictors varied for patients with very frequent vs occasional episodes; the other restricted the case definition to patients with more severe episodes of uncontrollable somnolence. The risks associated with each drug and drug class were substantially the same in both secondary analyses.

Our use of drug exposure information on the event date to estimate these associations might have misclassified exposure status if a patient had changed drugs just before an episode (as a potential cause of the event) or after it (as a potential consequence of the event). We assessed the potential for underestimating the true effect owing to random exposure misclassification by simulating scenarios with increasing misclassification. The estimates were strikingly insensitive to this source of bias. Our patient population was drawn from neurology practices that cared for large numbers of patients with movement disorders, so the characteristics and treatment of the patients differ somewhat from patients with PD who are cared for in nonferral centers. It is not likely, however, that this would result in a selection bias that would limit the generalizability of these findings to patients with PD in other settings. The classification of inappropriate somnolence may vary with the normal level of activity of a given patient; that is, a more active patient may experience more situations in which severe somnolence is inappropriate than would a patient whose daily activities are limited. How-
some of the ropinirole estimates was likely the result of the much smaller number of subjects who used this particular medication as compared with pramipexole rather than a significant difference in risk.

The newer D₂-selective DAs have been shown to reduce the occurrence of dopaminergic motor complications as compared with levodopa when used as an initial treatment²,³ and may pose a significant advantage in this respect. However, these findings indicate that their increased capacity to cause clinically important episodes of uncontrollable somnolence will also need to be considered in the assessment of therapy for any given patient.

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REFERENCES

ing these more accurate and lower scores. All other relationships among these scores for the various groups studied remain unchanged.

It is important to note that as first reported, our main analyses of the relationship between PD drugs and the somnolence outcome of interest did not make use of the H&Y scale because it did not influence the drug effect estimates (this is still the case) and the scores were not available for all patients. In addition, even as initially analyzed, the data still preserved the natural order of the H&Y scale. Thus, the main findings of the article remain as first presented.

We are grateful to the sharp-eyed correspondents for bringing this coding problem to our attention and relieved that its correction does not change the main findings of our article.

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Correction Error in Table. In the Original Contribution by Avorn et al titled “Sudden Uncontrollable Somnolence and Medication Use in Parkinson Disease,” published in the August issue of the ARCHIVES (2005;62:1242-1248), the column “Hoehn and Yahr Score” in Table 3 contains incorrect values. The corrected Table 3 appears in a letter from Avorn et al on page 467.