Sudden Uncontrollable Somnolence and Medication Use in Parkinson Disease

Jerry Avorn, MD; Sebastian Schneeweiss, MD, ScD; Lewis R. Sudarsky, MD; Joshua Benner, PharmD, ScD; Yuka Kiyota, MD, MPH; Raisa Levin, MS; Robert J. Glynn, PhD, ScD

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.

Arch Neurol. 2005;62:1242-1248
wake regulation related to the disease itself. A prospective study 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. Rye et al 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. 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 uncontrollable 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 uncontrollable 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 (tri-hexyphenidyl, ethopropazine, and benztprine), 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 scale ranging from 0 (no sign of disease) to 5 (wheelchair bound). This scale has high interrater agreement and correlates well with striatal uptake of fluorodopa F18. Activities of daily living were reported using a modified Schwab and England scale 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. General somnolence was assessed at the time of the interview with an 8-item Epworth Sleepiness Scale with scores ranging from 1 to 24. The Epworth scale has a demonstrated correlation with the Respiratory Disturbance Index and overnight oxygen saturation and has been found to be reliable and to have high internal consistency.

**STUDY END POINT**

The primary outcome was a patient’s report of episodes of sudden and inappropriate somnolence, described as “untotally 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 literature 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 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 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 ropinirole alone or with another agent, and 18.5% used rolaptlire 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-
patients only receiving medications grouped into “other ant-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 (≥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, 1.78-5.30) 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;...
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 (OR=2.83; 95% CI, 1.38-5.83), levodopa plus DA (low or medium dose: OR=1.68, 95% CI; 0.94-3.00; high dose: OR=2.41; 95% CI, 1.59-4.89), ropinirole (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 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.

### Table 3. Antiparkinson Drug Therapy at Interview Date by Patient Characteristics

<table>
<thead>
<tr>
<th>Antiparkinson Drug Therapy Group</th>
<th>Patients, No. (%)</th>
<th>Patients With at Least 1 Event No. (%)</th>
<th>Patients Reporting Severe Episodes, No. (%)</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>186 (20.0)</td>
<td>25 (13.4)</td>
<td>0.1-0.2</td>
<td>70.9 (10.7)</td>
<td>3.6 (4.8)</td>
<td>4.6 (1.4)</td>
<td>2.5 (3.6)</td>
</tr>
<tr>
<td>DA only</td>
<td>59 (6.4)</td>
<td>13 (22.0)</td>
<td>0.1-0.3</td>
<td>59.4 (12.1)</td>
<td>1.2 (1.5)</td>
<td>3.6 (1.4)</td>
<td>0.5 (1.1)</td>
</tr>
<tr>
<td>DA plus DA</td>
<td>209 (22.5)</td>
<td>59 (28.2)</td>
<td>0.2-0.3</td>
<td>67.9 (10.1)</td>
<td>3.7 (4.6)</td>
<td>4.5 (1.6)</td>
<td>2.2 (3.1)</td>
</tr>
<tr>
<td>Levodopa plus DA plus other‡‡</td>
<td>262 (28.2)</td>
<td>83 (31.7)</td>
<td>0.3-0.4</td>
<td>65.0 (9.5)</td>
<td>4.0 (5.7)</td>
<td>4.7 (1.4)</td>
<td>2.0 (3.0)</td>
</tr>
<tr>
<td>Levodopa plus other‡‡</td>
<td>139 (15.0)</td>
<td>15 (10.8)</td>
<td>0.1-0.2</td>
<td>67.4 (9.3)</td>
<td>4.9 (6.9)</td>
<td>4.6 (1.5)</td>
<td>2.6 (3.7)</td>
</tr>
<tr>
<td>DA plus other‡</td>
<td>38 (4.1)</td>
<td>11 (28.9)</td>
<td>0.1-0.4</td>
<td>60.7 (9.8)</td>
<td>1.9 (2.3)</td>
<td>3.6 (1.2)</td>
<td>0.3 (0.6)</td>
</tr>
<tr>
<td>Other only‡</td>
<td>21 (2.3)</td>
<td>0 (0.0)</td>
<td>NA</td>
<td>65.0 (8.0)</td>
<td>2.3 (3.6)</td>
<td>3.7 (1.5)</td>
<td>0.7 (1.2)</td>
</tr>
</tbody>
</table>

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

### 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 (32)</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>

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 at the time of the episode, and a patient’s 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.

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-
gists were aware of the case reports of sleepiness in patients receiving DAs, so selection bias would have been more likely to operate in the opposite direction.

Interestingly, for several of the D_{2} 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 that 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.\footnote{2} 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\footnote{2} 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 nonreferral 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. However, we attempted to standardize this as much as possible by providing each patient with a benchmark definition of what was meant by “inappropriate.”

To our knowledge, this is the largest published study of the increased risk of uncontrollable somnolence with DA therapy; its findings are consistent with earlier case reports and smaller studies. In addition, we found a class effect for all selective DAs, with the use of any of these agents producing an almost 3-fold increase in risk. Pramipexole, pergolide, and ropinirole all showed a dose-response relationship, suggesting that using these drugs at lower doses might help reduce the risk of the outcome studied. The absence of statistical significance for

---

### Table 5. Uncontrollable Somnolence and Drug Use in 929 Patients With Parkinson Disease (Multiple Logistic Regression Analysis by Drug Class)

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>OR (95% CI)</th>
<th>All Episodes (n = 206)</th>
<th>Severe Episodes (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levodopa only</strong></td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>DAs only</strong></td>
<td>1.91 (0.89-4.09)</td>
<td>2.05 (0.80-5.27)</td>
<td></td>
</tr>
<tr>
<td><strong>DAs plus levodopa</strong></td>
<td>2.26 (1.27-4.01)</td>
<td>3.17 (1.52-6.59)</td>
<td></td>
</tr>
<tr>
<td><strong>Pramipexole</strong></td>
<td>2.22 (1.43-3.43)</td>
<td>3.07 (1.78-5.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Pergolide or bromocriptine</strong></td>
<td>2.11 (1.24-3.81)</td>
<td>2.16 (1.11-4.21)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CNS, central nervous system; DAs, dopamine agonists; OR, odds ratio; PD, Parkinson disease.

**Table 6. Uncontrollable Somnolence and Use of Individual Antiparkinsonian Medications (Drug-Specific Multiple Logistic Regression Analysis)**

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>OR (95% CI)</th>
<th>All Episodes (n = 206)</th>
<th>Severe Episodes (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levodopa only</strong></td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Pramipexole</strong></td>
<td>2.22 (1.43-3.43)</td>
<td>3.07 (1.78-5.30)</td>
<td></td>
</tr>
<tr>
<td><strong>Pergolide or bromocriptine</strong></td>
<td>2.11 (1.24-3.81)</td>
<td>2.16 (1.11-4.21)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CNS, central nervous system; COMT, catechol-o-methyltransferase; MAO, monoamine oxidase; OR, odds ratio; PD, Parkinson disease.

**Significant at P<.05.**
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 treatment, 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.

Accepted for Publication: January 4, 2005.

Correspondence: Jerry Avorn, MD, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont St, Suite 3030, Boston, MA 02120 (javorn@partners.org).

Author Contributions: Study concept and design: Avorn, Schneeweiss, Sudarsky, Benner, and Kiyota. Acquisition of data: Avorn, Schneeweiss, Sudarsky, Benner, Kiyota, and Levin. Analysis and interpretation of data: Avorn, Schneeweiss, Sudarsky, Levin, and Glynn. Drafting of the manuscript: Avorn, Schneeweiss, and Kiyota. Critical revision of the manuscript for important intellectual content: Avorn, Schneeweiss, Sudarsky, Benner, Kiyota, Levin, and Glynn. Statistical analysis: Schneeweiss, Kiyota, Levin, and Glynn. Obtained funding: Avorn and Benner. Administrative, technical, and material support: Avorn, Schneeweiss, Benner, and Kiyota. Study supervision: Avorn, Schneeweiss, Sudarsky, and Benner.

Funding/Support: This study was funded by an unrestricted research grant from Pharmacia Corp, Peapack, NJ.

Role of the Sponsors: The study was designed by the authors, and the sponsor had no control over the methods, data analysis, interpretation of results, or publication of findings.

Acknowledgment: We are grateful to the referring physicians who helped make this study possible. In particular, we wish to acknowledge the invaluable assistance of Dr Matthew Stern of the University of Pennsylvania, Dr Peter Lewitt of the Clinical Neuroscience Center, Dr Joseph Jancovic of Baylor College of Medicine, Dr John Growden of the Massachusetts General Hospital, and Dr Daniel Tarsy of the Beth Israel Deaconess Medical Center. We appreciate the contribution of the research assistants who performed the extensive patient interviews: Alison LaTourette, Michele Burgener, Amitha Jangamnath, Hailu Cheng, Danielle Cabral, Andrea Licari, Ashley Logan, Rita Bloom, Sharon Hawley, and Kathleen McCarty. The perceptive methodological contributions of Professor Kenneth Rothman, Brigham and Women's Hospital, are gratefully acknowledged.

REFERENCES


