Long-term Treatment of Restless Legs Syndrome With Dopamine Agonists

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Background: Controlled clinical trials robustly demonstrate the short-term efficacy of dopamine agonists (DA) for restless legs syndrome (RLS), but little is known about the long-term efficacy and long-term adverse events. Augmentation—an increase in the duration, intensity, and anatomy of RLS symptoms—is commonly associated with dopaminergic treatments; however, risk factors for this troubling scenario have not been formally evaluated.

Objectives: To evaluate the long-term efficacy and tolerability of DA for RLS and to evaluate factors that could predict the occurrence of augmentation.

Methods: We queried all subjects seen from 1996 to 2003 and followed up those initiated on any DA by the Baylor College of Medicine Movement Disorders Clinic, Houston, Tex. Patients with Parkinson disease, uremia, or medications that could affect RLS were excluded. Demographics, efficacy, dosing, adverse events, and augmentation were tracked across time. Statistical modeling was used to evaluate for factors that could predict augmentation.

Results: After eliminating all patients with RLS who had factors that could affect DA dosing or the accuracy of data, we observed 83 subjects with at least 6 months’ use of DA (mean ± SD, 39.2 ± 20.9 months). Efficacy was maintained across time but at the expense of moderate but significant increases in doses (P < .01). Adverse events were frequent but usually mild and seldom resulted in discontinuation. Augmentation was frequent (48% of subjects) but usually modest, and it was predicted by a positive family history for RLS and especially the lack of any neuropathy on electromyographic or nerve conduction velocity tests.

Conclusions: Dopamine agonists continued to effectively treat RLS without long-term adverse events but often required adjustments across time. The higher rate of augmentation in familial and nonneuropathic RLS should be considered when initiating therapy.

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RESTLESS LEGS SYNDROME (RLS), as defined by the International Restless Legs Syndrome Study Group criteria, may occur in more than 10% of predominately Caucasian populations. Historically, numerous treatments have been used with varying degrees of success, yet evidence-based medicine most consistently supports the efficacy of levodopa and dopamine agonists (DA). These studies, however, mostly involve short treatment periods.

Relatively few data address the long-term use of DA for RLS. Although studies of up to 1 year have shown that most patients taking DA continue to benefit from the medications, some reports have raised specific concerns about both the development of tolerance and dopaminergic-induced augmentation, a scenario associated with an earlier phase shift of symptom onset and increased intensity or anatomic involvement. This is most notable with levodopa, which has the shortest half-life of any dopaminergic treatment. Augmentation, however, is also reported with pergolide and pramipexole but, to date, not with cabergoline. No report has ever evaluated the longitudinal use of multiple dopaminergic medications concurrently to make efficacy and tolerability comparisons. Furthermore, factors that might predict problems with continued DA treatment for RLS have not been systematically evaluated.

METHODS

All patients with RLS seen at the Baylor College of Medicine Parkinson Disease Center and Movement Disorders Clinic between January 1996 and June 2003 were initially included in a medical record review. The study onset coincides with the date we began using DA as first-line therapy for RLS. Patients with concur-
rent Parkinson disease or other diseases that required dopaminergic therapy, patients previously given DA elsewhere, and patients with RLS associated with uremia were immediately excluded. We also subsequently eliminated subjects classified in the database as having RLS but who did not meet International Restless Legs Syndrome Study Group criteria. Usually, these patients had nocturnal leg pain but no urge to move. Patients with less than 6 months of DA treatment since the initiation of treatment were not included because we did not feel that they would facilitate our evaluation of long-term treatment.

Collected data included patient demographics and disease-specific features (age at onset, severity, family history, ferritin, neuropathy based on electromyography and nerve conduction velocity studies, and previous treatments). Family history data were gathered on each visit and, when possible, were confirmed by phone calls to first-degree relatives. We only called second-degree relatives if the patient reported that he or she was the only family member with RLS. During every visit and every phone call that resulted in a medication change, we recorded the medication(s) dose(s), treatment response, and the presence and severity of augmentation symptoms. Responses were rated by the investigator but were entirely based on the subjective report of the patient. Efficacy was rated with the following scale: 0, no change in onset of RLS symptoms; 1, mild, earlier onset of RLS not requiring any intervention; 2, earlier onset of symptoms that require the earlier use but not an additional dose of a DA and are not worse in severity than the original nocturnal RLS; 3, earlier onset of symptoms that require an additional dose of a DA but are not worse in intensity than the original nocturnal symptoms; and 4, earlier onset of symptoms that require additional medication changes with symptoms that are worse than the original nocturnal symptoms. We calculated a DA equivalent dose (dose = pramipexole/1 + pergolide/1 + ropinirole/3.5 + bromocriptine/10 + cabergoline/0.5).

Patients were contacted to complete any missing demographic or disease-specific data. We did not try to fill in missing response data if the time of that data point was more than 6 months in the past because we did not trust the reliability of that information. We also attempted to contact by phone all patients whom we had not seen within the last year. Therefore, if a patient started taking mediation first prescribed by us and was then followed up elsewhere, we may only have the initial data and data from our phone call or second visit (2 points in time), whereas some patients seen regularly by us had more than 20 data points.

We used logistic regression to assess the relationship between the probability of augmentation of a grade of 2 or higher. The possible risk factors used in the analysis were duration of follow-up, number of visits, sex, the specific DA (pergolide, pramipexole, or ropinirole), age at initiation of DA, the initial daily dose of DA, family history of RLS (n=80, with acceptable history), ferritin levels (greater or less than 50, n=70), and electromyographic findings (presence or absence of any neuropathy, n=61). Family history, sex, electromyography, ferritin, and selection of DA were categorical variables. Initially, we used the simple logistic regression with the logit of the probability of nonaugmentation as the dependent variable and the individual possible risk factor as the independent variable. For further analysis, we used multiple logistic regression to adjust the possible confounder of total duration of follow-up and the number of visits in observing the augmentation of the patients. We performed a log-rank test to compare the survival curves of predictors of augmentation. Finally, we performed the same analysis for the first augmentation of 3. The logistic regression was carried out using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC). P<.05 was used to indicate significance for the risk factor on augmentation.

**RESULTS**

We initially identified 270 patients with RLS. Seventeen patients did not meet strict criteria for RLS and were eliminated from further analysis. We excluded 59 for the concurrent diagnosis of a parkinsonian condition and 14 for having RLS associated with uremia. Fifty-eight never started taking a DA, mostly early in the cohort. Thirty-four were previously given a DA elsewhere and were thus eliminated from analysis. Two were identified as having RLS, but they required a medication (tetrabenazine) that potentially interfered with treatment responses and were thus eliminated. Some of these patients were eliminated for more than 1 of these reasons. This left 103 subjects with nonuremic RLS who were initially given a DA by us. Twenty of these lacked 6 months of data predominately because they stopped taking DA because their RLS symptoms improved such that they no longer required therapy (5); stopped taking DA because of a lack of efficacy (4); stopped taking DA because of logistical, financial, or compliance issues (3); stopped taking DA because of adverse events (3); began taking a DA within the 6 months prior to manuscript preparation (3); or were lost to follow-up (2). Therefore, 83 patients who began taking a DA that we prescribed were followed up for at least 6 months of DA treatment and met all a priori inclusion criteria. Demographics of the group are summarized in Table 1 and were similar to those of the patients with idiopathic RLS who were excluded because they either did not start taking a DA or had already started taking a DA (n=74).

At the time that we prescribed the initial DA, 43 (51.8%) of 83 subjects were currently taking other medications for RLS: benzodiazepines (23), levodopa (22), opioids (6), gabapentin (3), and other medications (5). Sixteen of these patients were taking more than 1 medication. Previously, these 83 subjects had also tried and discontinued benzodiazepines (17), levodopa (9), opioids (9), and other medications (10). By the second follow-up visit after starting a DA, levodopa was discontinued in 19 (86.4%) of 22 subjects, opioids in 5 (83.3%) of 6, benzodiazepines in 11 (47.8%) of 23, and gabapentin in 2 (66.7%) of 3 subjects.

Our initial DA was pramipexole (for 52 patients), ropinirole (19), or pergolide (12). A single nightly dose was taken by 46 patients, whereas 16 took 2 doses and 21 initially took 3 or more doses. When we used our conversion formula, the initial mean ± SD dose averaged 0.79±0.055 mg (Figure 1). Patients were subsequently followed up for a mean ± SD duration of 39.2±20.9 months (range, 7-101 months). During that time, we collected data at a mean ± SD rate of 6.9±3.5 time points per patient (range, 2-26 time points). Twenty subjects...
(24.1%) changed from one DA to another DA at some point.

Some adverse event of DA was reported by 47 subjects (56.7%). These subjects were queried, and adverse events included daytime sleepiness (26), nausea (13), peripheral edema (13), dizziness/light-headedness (5), gastrointestinal upset (4), constipation (3), headache (3), itchiness (2), and rash (2). Ten subjects stopped taking DA altogether after 6 months because of adverse events (2), lack of efficacy (2), natural improvement in symptoms (2), logistical reasons (2), augmentation (1), and concurrent medical condition (1). At some point during the period after subjects began taking DA, 16 (19.3%) subjects required additional non-DA medications: opioids (6), benzodiazepines (5), levodopa (3), and gabapentin (3).

The efficacy of DA was maintained across time but at the cost of a modest but significant dose increase (initial dose to final dose; \( t = -2.7; P < .01 \)) (Figure 1). Rebound (onset of symptoms late at night or early in the morning) was not reported. Mild augmentation (requiring an earlier onset of treatment) was seen in 40 (48.2%) of 83 subjects, but more severe augmentation requiring additional doses occurred in only 18 subjects (21.7%), and actual increased symptom intensity was rare, occurring in only 1 subject (1.2%) (Figure 2). The \( P \) values based on the log-rank test of comparing the 2 survival curves were .04 and .05 for Figure 2A and Figure 2B, respectively.

From the simple and multiple logistic regressions, we obtained the odds ratios, the associated \( P \) values, and the 95% confidence intervals of the odds ratios. The results are shown in Table 2. The simple logistic regression revealed that a positive family history of RLS, the lack of any neuropathy, and fewer clinic visits increased the probability of augmentation. Because it was expected that longer duration of follow-up would predict augmentation, we used multiple logistic regression with the follow-up time, the number of visits, and the other risk factors in the model. After we controlled for both covariates, the lack of neuropathy still significantly predicted augmentation, without significant change in the odds ratios (Table 2).

It is worth noting that the follow-up time was measured with the unit of month. Although 1 unit (month) change did not result in a significant change in the probability of augmentation, the coefficient associated with follow-up time in the models was negative. Hence, the follow-up time did have a positive impact on the probability of augmentation, which was consistent with the expectation. We also measured follow-up time assessed by years; however, the direction of impact and the \( P \) value did not change.

In the final model of the multiple logistics regression based on the independent variables showing individual significance, only the lack of neuropathy provided significant impact on the likelihood of developing augmentation (\( P = .002 \)). However, because of missing values, 29 patients were excluded from the modeling, mostly from lack of electromyographic data. Therefore, caution should

| Table 1: Age and Demographic Data From the Point of Dopamine Agonist Initiation |
|-----------------------------------|---------|---------|---------|---------|
| Study Group | No. of Patients | Mean ± SD | No. of Patients | Mean ± SD |
| Sex | 83 | NA | 74 | NA |
| Men | 32 | NA | 28 | NA |
| Women | 51 | NA | 46 | NA |
| Age | 83 | 56.8 ± 11.5 y | 74 | 57.8 ± 14.8 y |
| Family history of restless legs syndrome (RLS)* | 80 | NA | 73 | NA |
| Yes | 57 | NA | 42 | NA |
| No | 22 | NA | 31 | NA |
| Evidence of neuropathy | 61 | NA | 33 | NA |
| Yes | 22 | NA | 14 | NA |
| No | 39 | NA | 19 | NA |
| Arm involvement | 83 | NA | 74 | NA |
| Yes | 23 | NA | 21 | NA |
| No | 60 | NA | 53 | NA |
| Age at onset | 83 | 34.8 ± 16.1 y | 70 | 35.2 ± 18.3 y |
| Ferritin level | 70 | 76.1 ± 51.5 ng/mL | 39 | 84.1 ± 98.2 ng/mL |

Abbreviation: NA, not applicable.
*In 3 cases, a family history was indeterminate.
be used in interpreting the results of this model. An augmentation of 3 was experienced by only 18 subjects. When we used the same final model for that end point, a lack of neuropathy tended to predict augmentation ($P = .05$).

Our results demonstrate that DA effectively treat RLS for more than 6 months. Efficacy is generally maintained across time but at the cost of a moderate but significant dose augmentation. The medications are very well tolerated, and adverse events are uncommon after the dose initiation. Modest augmentation, as defined by an earlier onset of symptoms, occurs frequently, but severe augmentation that increases symptom intensity is uncommon and usually managed by dose adjustments. Patients with a family history and patients with normal electromyographic examination results had significantly more augmentation, although normal electromyographic examination results were the strongest predictor for augmentation. Overall, our results support the long-term use of DA for RLS.

The pathophysiology of RLS augmentation is not known. Empirical evidence suggests that dopaminergics with shorter half-lives, especially levodopa, increase the risk of augmentation, whereas longer-acting DA protect against augmentation. This could result from the simple fact that more continuous dopaminergic stimulation will cover up the RLS symptoms or, more intriguingly, that some biological advantage of continuous dopaminergic stimulation may prevent augmentation. Our data, which suggest that the lack of a family history of RLS and the presence of neuropathy protect against augmentation, also suggest some intrinsic biological difference between genetic and nongenetic RLS. We have previously reported that neuropathy is associated with nonfamilial RLS, although in this cohort there was only a trend toward this association ($\chi^2$ based on the Goodman and Kruskal statistic; $P = .10$).

We set up very formalized criteria for data collection in an attempt to minimize features such as recall bias.
Nevertheless, some data were collected from medical records and are therefore retrospective, and they suffer from all the intrinsic weaknesses of retrospective data. The majority of the data was prospective and collected during the past 24 months. Also, we are affiliated with a tertiary referral center and are thus subject to potential referral biases toward more severe or refractory RLS cases. To assure accurate and detailed results, we initially eliminated 69% of all subjects seen by us. Although this is a potential weakness, we do not feel that this group as a whole intrinsically differed from those nonparkinsonian, nonuremic patients with RLS. The large number of subjects with RLS and Parkinson disease who were eliminated from evaluation likely results from our clinic’s status as a movement disorder center. Furthermore, we suspect that RLS can be a nonmotor symptom in Parkinson disease and that RLS in Parkinson disease is intrinsically different than RLS as a whole. It is difficult to control for the initial dosing of DA because patients who received multiple and earlier dosing throughout the day may be less likely to report an earlier onset of symptoms but also probably had more severe RLS. Nevertheless, total DA dose did not predict augmentation. We used a nonvalidated and simplified efficacy scale because it correlated with medical record documentation, and no validated scale existed at the onset of the study. We also produced a large number of P values in our modeling process. Hence, interpretation of the P values without formal corrections of multiple comparisons should be done with caution. Finally, RLS intensity and duration of symptoms generally increase across time, so the earlier onset may in part represent natural progression of the disease.

Despite these potential weaknesses, we feel that nonfamilial and neuropathic RLS is less likely to develop augmentation and therefore may warrant treatment with DA at a lower symptom intensity compared with treatment for patients with familial RLS. Future research in RLS augmentation will need to prospectively compare continuous dosing with dosing only during RLS (nocturnal) symptoms, develop validated scales for augmentation, prospectively evaluate the effects of drug withdrawal and reinstitution, and evaluate the strategy of rotating different DA.

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