Levodopa-Associated Dyskinesia Risk Among Parkinson Disease Patients in Olmsted County, Minnesota, 1976-1990

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Background: The threat of levodopa-induced dyskinesias often influences early treatment decisions in those with Parkinson disease.

Objective: To determine the long-term risks of levodopa-associated dyskinesias of any severity, dyskinesias sufficient to require medication adjustment, and dyskinesias failing medication adjustments.

Design: The medical records linkage system of the Rochester Epidemiology Project was used to identify all incident Parkinson disease patients treated with levodopa (1976-1990). All records were independently reviewed by 2 neurologists who recorded demographic and drug data, dates when dyskinesias were initially identified, and dates when dyskinesias were sufficient to require medication changes; dyskinesias not controlled by drug adjustments were also tabulated.

Results: We identified 126 incident Parkinson disease patients treated with levodopa for at least 2 months. By Kaplan-Meier analysis, the estimated rate of dyskinesias was 30% by 5 treatment years and 59% by 10 years. However, the rate of dyskinesias requiring medication adjustment was estimated to be only 17% by 5 years and 43% by 10 years. At 10 treatment years, the rate of dyskinesias that could not be controlled with medication adjustments was estimated at only 12%. An increased risk was associated with younger age and higher initial levodopa dose, but not with sex.

Conclusions: Levodopa-associated dyskinesias can be expected to develop in nearly 60% of patients in our community after 10 years, but these will be severe enough to require medication adjustments in only 43% of patients. At 10 treatment years, nearly 90% of these patients can expect to be spared dyskinesias that could not be controlled by drug adjustments. This population-based study suggests dyskinesia risk may not be a major concern for most Parkinson disease patients.

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DYSKINESIAS REPRESENT AN excessive levodopa response and can always be eliminated by levodopa reduction. In some patients, however, such dose reduction results in loss of parkinsonism control, and dyskinesias must then be accepted to experience the benefits of levodopa.

The threat of levodopa-induced dyskinesias often affects Parkinson disease (PD) treatment decisions. To reduce the risk, some experts advocate deferring levodopa treatment and initiating a dopamine (DA) agonist.1-3 Parkinsonism control, however, is less satisfactory with initial DA agonist treatment, compared with levodopa (even when levodopa can be added later).1,4,5 Because dyskinesias influence prescribing practices, it is important to know the risks associated with long-term levodopa therapy.

In clinical trials,6 a little less than 40% of PD patients will experience their first episode of dyskinesias after 4 to 6 years of levodopa therapy. Incident dyskinesia statistics, however, may not be directly relevant to clinical practice; dyskinesias are often mild and inconsequential or nonpersistent, or they may be easily controlled with medication adjustment. Furthermore, dyskinesia incidence in referral-based clinical trials may not exactly mirror the experience with patients treated in the community.

We wanted to look beyond incident levodopa-dyskinesia statistics reported in clinical trials to assess the risks of clinically important dyskinesias in a community-based setting. Thus, we were interested in assessing the risk of not only the first episode of dyskinesias but also whether these episodes persisted and interfered with activities sufficient to require medication adjustments; furthermore, we wanted to know how often they could not be controlled with medication changes. To address these issues, we retrospectively analyzed the medical re-
METHODS

We identified all residents of Olmsted County diagnosed as having incident PD between January 1976 and December 1990 and subsequently followed up, using the medical records linkage system of the Rochester Epidemiology Project. A description of the study population and of the criteria for identifying the incident PD cases in our cohort has previously been published.14 We included only those patients who had been treated with levodopa for at least 2 months. All records were independently reviewed by 2 of us (J.A.V.G. and N.K.), with data collection including sex; patient age at PD onset, age when levodopa was first administered, levodopa dose at each visit, other PD medications (including dose) at each visit, date of levodopa-dyskinesia onset, and dyskinesia severity at each physician visit. These data were collected retrospectively without a uniformly used prospective scheme for recording or grading dyskinesias. Therefore, we operationally graded dyskinesias as follows: (1) mild and insufficient to require medication adjustment (of no substantial concern to the patient or treating physician); (2) sufficient to require medication adjustment (levodopa or other PD medication), but this reduced dyskinesias to grade 1 or less without compromising symptomatic PD control; (3) required medication adjustment, but this either failed to reduce dyskinesias to grade 1 or less or undermined PD control; and (4) severe disabling dyskinesias that persisted despite maximal acceptable levodopa reduction.

Only peak-dose or biphasic levodopa-associated dyskinesias were tabulated; “off” dystonia was not tabulated. Dyskinesias did not have to be observed by a physician to be counted. Four of us (J.A.V.G., N.K., J.H.B., and J.E.A.) collectively adjudicated discrepancies in scoring between the 2 principal reviewers. The frequency of physician visits, noting separately all physician encounters and neurology follow-ups, was also recorded.

Kaplan-Meier estimates were calculated to evaluate duration of levodopa treatment to dyskinesias of each grade. From these Kaplan-Meier calculations, we also estimated the probability that a patient would be free of dyskinesias of each grade after 1, 5, and 10 years of levodopa therapy.

Cox proportional hazards models with these same dyskinesia grades as end points were used to estimate the hazard ratios associated with the variables: sex, age at PD symptom onset, and initial levodopa maintenance dose. This distribution of levodopa doses maintained during the first treatment year was skewed, so we used the natural logarithm of the levodopa doses. Analyses were performed using computer software (S-PLUS 6.1.2; Insightful Corp, Seattle, Wash). This investigation was approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center, Rochester, Minn.

Of the initial 154 incident PD patients, 26 were excluded because they had never been treated with levodopa or were taking it for less than 2 months. Two additional patients did not consent to having their records used for research, leaving 126 PD patients (78 males [61.9%] and 48 females [38.1%]) for study.

The demographic characteristics of our cohort are as follows. The median (interquartile range [IQR]) age of PD onset was 69 (61-76) years, with levodopa initiated at a median (IQR) age of 72 (65-78) years. The median (IQR) duration between symptom onset and the start of levodopa therapy was 2 (1-3) years. The median (IQR) levodopa dose during the first year was 450 (300-750) mg. Physicians saw the patients regularly. The median (IQR) number of visits to a physician per 5-year period was 26.5 (20-33); to primary care per 5-year period, 11 (6-17); and to a neurologist per 5-year period, 6 (2-10). The median (IQR) time from symptom onset to last follow-up was 10.9 (7.2-13.8) years.

None of the subjects in our study were treated initially with a DA agonist (5 received amantadine first and 3 received selegiline first). This reflects the PD prescribing tendencies before 1990, when DA agonists were typically used as adjunctive therapy after levodopa complications developed. The use of adjunctive drugs was too limited to include in the risk assessments. This included DA agonists taken for at least 2 months by 22 (17.5%) of the 126 patients; only 18 patients (14.3%) took an agonist for more than 1 year. Selegiline was taken for at least 2 months by 37 patients (29.4%) and amantadine by 19 patients (15.1%).

By Kaplan-Meier estimates, the probability of levodopa-associated dyskinesias of any severity was 30% by 5 treatment years and 59% by 10 years, as shown in Table 1. The risk of dyskinesias sufficient to require medication adjustment was 17% at 5 treatment years and 43% at 10 years. At 10 years, there was only a 12% risk of developing dyskinesias that failed to adequately respond to medication adjustment (ie, dyskinesias still greater than grade 1 or parkinsonism control compromised); this risk was 1% at 5 years.

Severe, disabling, and uncontrollable dyskinesias of the type that become a primary treatment focus were docu-
ment in only 1 patient during the first 10 treatment years. Therefore, these grade 4 dyskinesias were not further assessed in the Kaplan-Meier or Cox proportional hazards models.

The Kaplan-Meier curves are shown in the Figure. The median time to the first episode of dyskinesias of any severity was estimated to be 8.0 years (lower bound of the 95% confidence interval, 7.0 years; and upper bound, undefined).

As documented in Table 2, higher ages by 10-year age increments reduced the risk of dyskinesias of any grade (through grade 3), even after controlling for sex and initial levodopa dose. Higher doses of levodopa at the start of treatment were also associated with increased dyskinesia risk, after controlling for age and sex. As an example, we estimate the increased risk of any dyskinesias for a patient at the 75th percentile of dose level compared with a patient at the 25th dose percentile is 68% for a patient at the 75th percentile of dose level compared with a patient at the 25th dose percentile for any dyskinesia at any given time, after adjusting for age and sex. Initial levodopa dose did not reach statistical significance for grade 3 dyskinesias, perhaps because of insufficient power due to fewer grade 3 events. We found no evidence that sex influenced the risk of dyskinesias.

In this population-based cohort, only a minority of patients can expect to experience dyskinesias sufficient to require medication changes: 17% after 5 years and 43% after 10 years of levodopa treatment. Moreover, medication adjustments were successful in most patients. By 10 treatment years, only 12% of patients can expect to experience dyskinesias that could not be adequately controlled with drug changes.

These data suggest that troublesome dyskinesias are not a high risk among PD patients in the community, and many may be completely spared. Approximately 40% of patients in this study had not experienced dyskinesias (of any severity) by 10 years of levodopa treatment. This figure is similar to data from 2 referral center series, although less than recorded in the early levodopa era, in which 96% of patients developed dyskinesias by 9 to 14 treatment years. The 5-year 30% dyskinesia incidence risk (of any severity) is only slightly less than tabulated in a meta-analysis of all modern-era levodopa trials through the 20th century: 36% to 39% dyskinesia frequency after 4 to 6 treatment years.

Figure. Kaplan-Meier estimates and 95% confidence intervals of the probability that a patient with Parkinson disease who is taking levodopa will be free of dyskinesias of any severity (A), will be free of dyskinesias requiring medication adjustment (B), and will be free of dyskinesias that are unresponsive to medication adjustment (C).

**Table 2. The HRs for Time-to-Event (Dyskinesia) Models**

<table>
<thead>
<tr>
<th>Time-to-Event Model and Risk Factors</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis†</th>
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<tbody>
<tr>
<td>Dyskinesias of any severity (grade ≥1)</td>
<td></td>
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<tr>
<td>Age at first symptoms, 10-y increase‡</td>
<td>0.72 (0.55-0.94)§</td>
<td>0.74 (0.56-0.97)§</td>
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<tr>
<td>Sex, male vs female</td>
<td>1.23 (0.70-2.15)</td>
<td>0.94 (0.53-1.68)</td>
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<tr>
<td>Log of initial levodopa dose, increase equivalent to IQR</td>
<td></td>
<td>1.76 (1.08-2.85)§</td>
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<tr>
<td>Dyskinesias sufficient to require medication adjustment (grade ≥2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first symptoms, 10-y increase‡</td>
<td>0.66 (0.47-0.91)§</td>
<td>0.67 (0.48-0.94)§</td>
</tr>
<tr>
<td>Sex, male vs female</td>
<td>1.06 (0.55-2.03)</td>
<td>0.76 (0.40-1.49)</td>
</tr>
<tr>
<td>Log of initial levodopa dose, increase equivalent to IQR</td>
<td></td>
<td>2.38 (1.30-4.38)¶</td>
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<tr>
<td>Dyskinesias failing to respond to medication adjustment (grade ≥3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first symptoms, 10-y increase‡</td>
<td>0.70 (0.38-1.29)</td>
<td>0.73 (0.39-1.40)</td>
</tr>
<tr>
<td>Sex, male vs female</td>
<td>1.06 (0.33-3.34)</td>
<td>0.87 (0.27-2.79)</td>
</tr>
<tr>
<td>Log of initial levodopa dose, increase equivalent to IQR</td>
<td></td>
<td>2.47 (0.81-7.54)¶</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; log, logarithm.

*There were too few events to model time to severe and uncontrollable dyskinesias (grade 4).
†Includes sex and linear terms for age at first symptoms and natural log of initial levodopa dose.
‡Comparison of patients differing by 10 years of age at Parkinson disease symptom onset.
§P<.05.
¶The IQR (75th vs 25th percentile) of the natural log of the initial levodopa dose was 0.9 log (milligrams).
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Although these data may be extrapolated to other community settings, there is one caveat for treating clinicians to consider: age at PD onset. Dyskinesia risk decreased with older age, reducing the risk by 20% to 30% for 10 years’ age differences. It was previously reported that the 5-year levodopa-dyskinesia incidence declines by decades of age: 50% frequency between the ages of 40 and 59 years, 26% frequency between the ages of 60 and 69 years, and 16% frequency at 70 years or older. Others, however, have shown that with PD onset before the age of 40 years, the incidence of dyskinesias by 5 levodopa treatment years is more than 90%. Our cohort reflected PD found in the community: the median age of PD onset was 69 years, and only 4% experienced PD onset before the age of 50 years. Thus, these figures do not apply to the occasional young-onset PD patients seen at referral centers.

Dyskinesias risk significantly increased with higher initial levodopa maintenance doses. This could reflect more severe PD, which requires higher initial doses. Alternatively, liberal dosing might simply translate into a greater likelihood of unmasking latent dyskinesias; there is a levodopa dose threshold for dyskinesias, and higher doses are more likely to exceed that threshold. Whether initially aggressive dosing results in any long-term adverse consequences is unknown.

Previous referral center studies identified a significantly greater risk of levodopa-associated dyskinesias among females. We did not find this in our population-based investigation.

Limitations of this study include the retrospective study design and the absence of physician focus on dyskinesias. Although median physician visits were frequent (5.3 yearly), most were visits to nonneurologists (median, 1.2 neurology visits per year). Consequently, mild dyskinesias were probably overlooked or recorded months after first developing. However, we were interested in dyskinesias that were clinically important and, therefore, chose operational definitions that had practical implications. We reasoned that dyskinesias that are intrusive or interfere with activities should provoke medication changes; conversely, if the dyskinesias are clinically unimportant, no dose changes would be expected. Thus, our grade 2 dyskinesias should mark dyskinesias of more than trivial significance. Beyond that, medication changes that prove insufficient to control both parkinsonism and dyskinesias signal a level of greater clinical relevance (grade 3), and it is especially the threat of this grade that influences early medication decisions. Finally, it is noteworthy that physician-requested neurology consultations are easily obtained on relatively short notice in Olmsted County; therefore, expertise in the management of PD is readily available.

This study might be criticized because of small patient numbers. However, this reflects the relatively low incidence of PD in the general population. The cases used were the product of a large population-based analysis, with 1 424 474 person-years assessed overall. Our cohort reflected PD found in the community: the median age of PD onset was 69 years, and only 4% experienced PD onset before the age of 50 years. Thus, these figures do not apply to the occasional, young-onset PD patients seen at referral centers.

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