

## A FIVE-YEAR STUDY OF THE INCIDENCE OF DYSKINESIA IN PATIENTS WITH EARLY PARKINSON'S DISEASE WHO WERE TREATED WITH ROPINIROLE OR LEVODOPA

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### ABSTRACT

**Background** There is debate about whether the initial treatment for patients with Parkinson's disease should be levodopa or a dopamine agonist.

**Methods** In this prospective, randomized, double-blind study, we compared the safety and efficacy of the dopamine D<sub>2</sub>-receptor agonist ropinirole with that of levodopa over a period of five years in 268 patients with early Parkinson's disease. If symptoms were not adequately controlled by the assigned study medication, patients could receive supplementary levodopa, administered in an open-label fashion. The primary outcome measure was the occurrence of dyskinesia.

**Results** Eighty-five of the 179 patients in the ropinirole group (47 percent) and 45 of the 89 patients in the levodopa group (51 percent) completed all five years of the study. In the ropinirole group, 29 of the 85 patients (34 percent) received no levodopa supplementation. The analysis of the time to dyskinesia showed a significant difference in favor of ropinirole (hazard ratio for remaining free of dyskinesia, 2.82; 95 percent confidence interval, 1.78 to 4.44;  $P < 0.001$ ). At five years, the cumulative incidence of dyskinesia (excluding the three patients who had dyskinesia at base line), regardless of levodopa supplementation, was 20 percent (36 of 177 patients) in the ropinirole group and 45 percent (40 of 88 patients) in the levodopa group. There was no significant difference between the two groups in the mean change in scores for activities of daily living among those who completed the study. Adverse events led to the early withdrawal from the study of 48 of 179 patients in the ropinirole group (27 percent) and 29 of 89 patients in the levodopa group (33 percent). The mean ( $\pm$ SD) daily doses given by the end of the study were  $16.5 \pm 6.6$  mg of ropinirole (plus  $427 \pm 221$  mg of levodopa in patients who received supplementation) and  $753 \pm 398$  mg of levodopa (including supplements).

**Conclusions** Early Parkinson's disease can be managed successfully for up to five years with a reduced risk of dyskinesia by initiating treatment with ropinirole alone and supplementing it with levodopa if necessary. (N Engl J Med 2000;342:1484-91.)

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**A**LTHOUGH the antiparkinsonian effect of the dopamine precursor levodopa was first demonstrated 30 years ago,<sup>1</sup> and that of dopamine D<sub>2</sub>-receptor agonists more than 25 years ago,<sup>2</sup> the most appropriate time to begin these two treatments in patients with Parkinson's disease remains controversial.<sup>3</sup> Some neurologists promote the early use of levodopa, emphasizing the rapid symptomatic benefit<sup>4</sup> and the possible reduction in mortality that the drug provides.<sup>5</sup> Others, more concerned about the potential neurotoxicity<sup>6</sup> and the long-term complications, such as dyskinesia, associated with the use of levodopa,<sup>7-11</sup> encourage the early use of dopamine agonists. This long-standing controversy remains largely unresolved,<sup>12</sup> although recent data suggest that initiating treatment with a dopamine agonist confers some advantage.<sup>13,14</sup> Data from studies of monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine have demonstrated that dopamine agonists are less likely than levodopa to induce dyskinesia in animals that have not been exposed to levodopa.<sup>15</sup> Because dyskinesia is one of the most debilitating effects of levodopa therapy, we studied the incidence of dyskinesia associated with the two treatments in a large, prospective, randomized, five-year study.

Ropinirole is a non-ergot-derived D<sub>2</sub>-like dopamine-receptor agonist that is effective in the treatment of early<sup>14,16,17</sup> and late<sup>18,19</sup> Parkinson's disease. The effectiveness of ropinirole in the treatment of early Parkinson's disease has already been demonstrated through a planned interim analysis of the data from the study described here, conducted six months after the study was begun, in which the primary end point was the score for motor function on the Unified Parkinson's Disease Rating Scale (UPDRS).<sup>17</sup> We present here the results of the final five-year analysis, in which

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the primary outcome measure was the incidence of dyskinesia.

## METHODS

### Study Population

A total of 268 patients were enrolled at 30 centers (in Europe, Israel, and Canada). All patients were 30 years of age or older, had a clinical diagnosis of Parkinson's disease<sup>20</sup> with a Hoehn-Yahr rating of stage 1 through 3 (with stage 1 indicating unilateral, early disease and stage 3 more advanced, bilateral disease),<sup>21</sup> and required dopaminergic therapy. Prior short-term treatment with levodopa or dopamine agonists was limited to a maximum of six weeks and had to be discontinued at least two weeks before entry into the study.

Patients were excluded if they had severe dizziness or fainting, severe systemic disease, major psychosis, severe dementia, alcoholism or drug dependence, or a contraindication to levodopa. In addition, treatment with a monoamine oxidase inhibitor within two weeks before entry (with the exception of selegiline) or previous treatment with ropinirole were reasons for exclusion.

### Study Design

This prospective, randomized, double-blind study was designed to compare the risk of dyskinesia in early Parkinson's disease among patients treated with ropinirole (Requip, SmithKline Beecham, Philadelphia) with that among patients treated with a combination of levodopa and benserazide (Madopa, Hoffmann-LaRoche, Nutley, N.J.; referred to hereafter as levodopa) over a period of five years. Random treatment assignment was performed with a ropinirole-to-levodopa ratio of 2:1. Benserazide has been shown previously to have properties that are similar to those of carbidopa (used with levodopa in Sinemet [Dupont Merck, Wilmington, Del.]) in blocking dopa decarboxylase in the periphery.<sup>22,23</sup> Blinding of the study was maintained with the use of a double-dummy technique. Sealed copies of the randomization code were held by the principal investigator at each site and by the study sponsor.

Patients underwent a single-blind placebo run-in period lasting seven days to demonstrate at least 80 percent compliance with taking study medication. Patients were then randomized (with stratification according to whether they were receiving concomitant selegiline therapy), and assessments were performed at weekly intervals for the first month, every two weeks for the next two months, every month up to six months, and every two months thereafter.

The study was conducted in accordance with Good Clinical Practices guidelines and the Declaration of Helsinki. The protocol was approved by an ethics committee at each center, and written informed consent was obtained from each patient.

### Treatment

Both ropinirole and levodopa were taken orally in tablet form. The dose of study medication was adjusted weekly as required, with 13 possible increasing dose levels. Ropinirole therapy was initiated (dose level 1) at 0.75 mg per day (0.25 mg three times daily) and levodopa therapy at 50 mg once daily plus placebo twice daily. The maximal daily doses of study medication allowed (dose level 13) were 24 mg of ropinirole per day (8 mg three times daily) and 1200 mg of levodopa per day (400 mg three times daily). Investigators were encouraged to treat patients only with the assigned study medication. Patients whose symptoms were not adequately controlled by the adjustment of study medication alone (i.e., those with recurrent, persistent, or functional disability), despite use of the highest tolerated dose, could be given supplementary levodopa in open-label fashion. No other antiparkinsonian therapies were permitted after the start of the study. Domperidone was permitted according to the normal practice at each individual study center, to control severe dizziness, nausea, or vomiting.

## Clinical Assessments

### Dyskinesia

Dyskinesia (the incidence of which was assessed in patients before withdrawal from the study or until completion of the study) was considered to be present if a patient had a score of 1 or more (on a scale from 0 to 4, where a score of 0 indicates no dyskinesia and a score of 4 indicates dyskinesia during most waking hours) on item 32 of the UPDRS<sup>24</sup> ("Duration: what proportion of the waking day are dyskinesias present?") or if dyskinesia was reported as an adverse event. In addition, all reports of adverse events consisting of abnormal movements considered to be dyskinesia were reviewed before the randomization code was broken.

### Additional Variables

"Disabling" dyskinesia was defined as a score of 1 or more on items 32 and 33 of the UPDRS ("How disabling are the dyskinesias?").

The scores for activities of daily living and motor function were measured with the use of parts II and III of the UPDRS (items 5 through 17 [range of possible scores, 0 to 52, where 0 indicates no disability and 52 indicates maximal impairment] and items 18 through 31 [range of possible scores, 0 to 108, where 0 indicates no disability and 108 indicates maximal impairment]), respectively, for the patients who completed the study.

"Wearing off" (defined as periods of increased severity of parkinsonian symptoms as medication wears off) was assessed by reviewing the data from patients who reported increases in the duration of time awake and in an "off" period on item 39 of the UPDRS. "Freezing when walking" was assessed by reviewing responses to item 14 of the UPDRS.

### Safety and Tolerability of the Drugs

Adverse events were assessed in a standard manner by the investigator. Neuropsychiatric adverse events (i.e., hallucinations, confusion, delirium, psychosis, illusion, delusion, depersonalization, personality disorder, abnormal thinking, amnesia, dementia, impaired concentration, and other related events, as defined by the World Health Organization) were the only predetermined measures of safety in the statistical analyses.

### Statistical Analysis

We planned to enroll 240 patients into the study (160 randomly assigned to ropinirole and 80 to levodopa); this number was calculated on the assumption of an underlying rate of response to treatment of 85 percent. Samples of 110 patients in the ropinirole group and 55 in the levodopa group who could be evaluated at the six-month interim analysis<sup>17</sup> provided the study with an 80 percent chance of demonstrating equivalent efficacy in the two groups (with a 90 percent confidence interval), on the assumption that the response rate in the levodopa group would not be more than 15 percent higher than that in the ropinirole group. It was anticipated that 30 patients in the ropinirole group and 50 in the levodopa group would complete all five years (predicted withdrawal rates, 30 percent and 10 percent per year, respectively). These numbers of patients provided the study with 88 percent power to detect a difference ( $P < 0.05$ ) in the incidence of dyskinesia between the two groups, assuming an incidence of 5 percent in the ropinirole group and an incidence of 30 percent in the levodopa group.

All analyses (except those based on the scores for activities of daily living and motor function) were performed on an intention-to-treat basis and include all randomized patients who had at least one assessment after receiving study medication. Patients were not followed up for assessment of dyskinesia after withdrawal from the study.

The rates of dyskinesia and disabling dyskinesia in the two groups were compared with the use of the Cox proportional-hazards model<sup>25</sup> in an analysis of failure time (time to an episode of dyskinesia or disabling dyskinesia). Kaplan-Meier curves,<sup>26</sup> haz-

ard ratios with 95 percent confidence intervals, and P values were calculated. Data on patients were censored at the time they withdrew from the study without having dyskinesia.

Statistical analyses of variance of the mean changes in the scores for activities of daily living and motor function between base line and the end of the study were based on data from the patients who completed the study. The results of these analyses are presented as adjusted treatment differences, with 95 percent confidence intervals and P values. It was not possible to analyze these scores over the duration of the study without bias because the number of patients at each time point varied and because of the problems with performing multiple tests.

The proportions of patients with neuropsychiatric adverse events in the two groups were compared with the exact chi-square test.

Statistical tests were performed using two-tailed tests at the 5 percent level of significance.

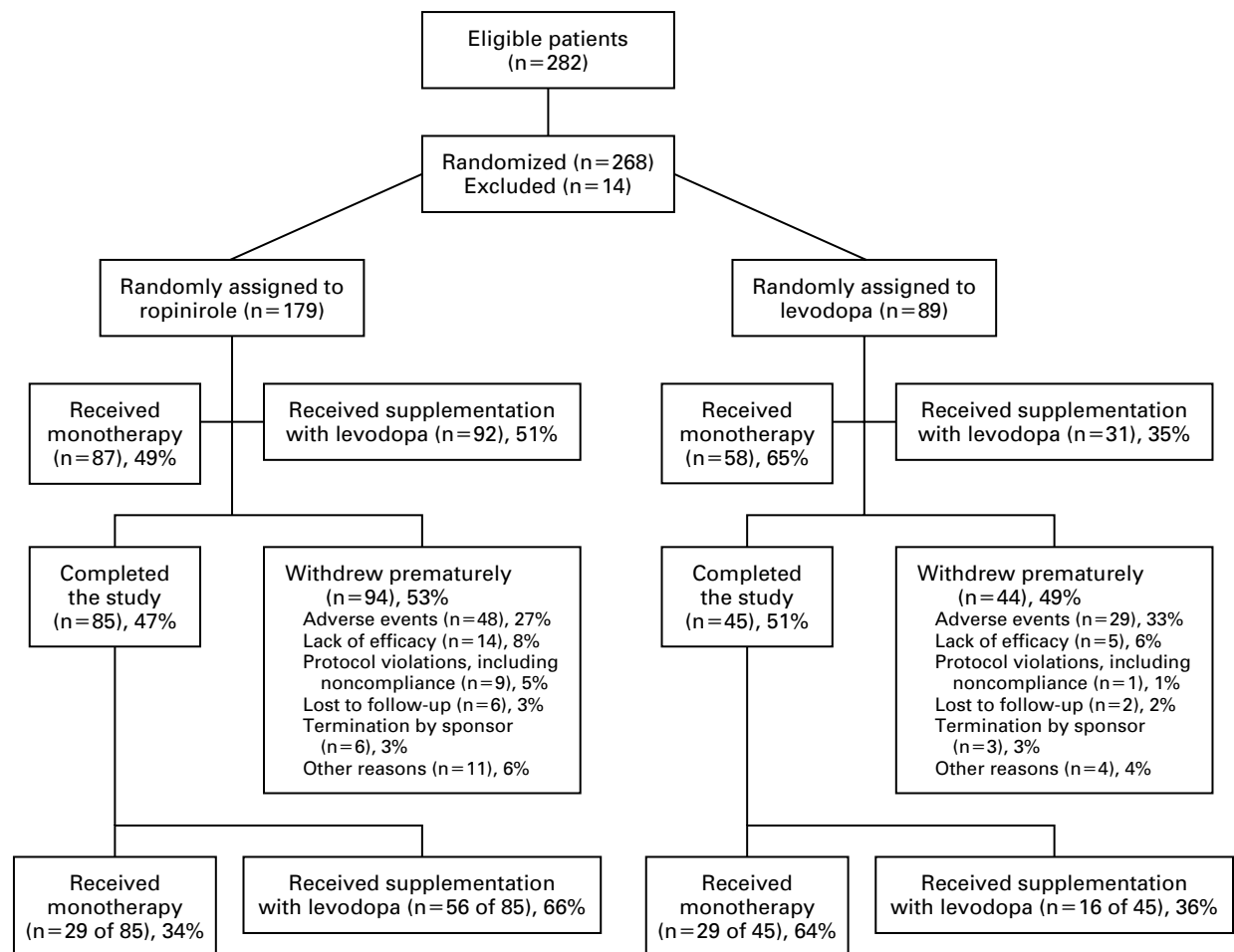
## RESULTS

### Patients and Treatment

Of the 268 patients who entered the trial, 179 were randomly assigned to ropinirole and 89 to levodopa (Fig. 1). The demographic characteristics of

the two groups were similar (Table 1). Two patients in the ropinirole group and one in the levodopa group had dyskinesia at base line and were excluded from the analyses of the incidence of dyskinesia. Eighty-five of the patients in the ropinirole group (47 percent) and 45 of those in the levodopa group (51 percent) completed the study. Of these patients, 29 in the ropinirole group (34 percent) and 29 in the levodopa group (64 percent) did so without open-label levodopa supplementation. The reasons for withdrawal from the study are presented in Figure 1.

Mean ( $\pm$ SD) daily doses at the completion of the study were  $16.5 \pm 6.6$  mg of ropinirole (plus  $427 \pm 221$  mg of open-label levodopa in patients requiring supplementation) and  $753 \pm 398$  mg of levodopa (including open-label supplements). Fifty-two patients in the ropinirole group (29 percent) and 24 in the levodopa group (27 percent) received domperidone at some time during the five-year study.



**Figure 1.** Enrollment and Treatment of the Study Patients.

"Termination by sponsor" refers to one center that was closed early by agreement with the investigator because of noncompliance with the protocol.

**TABLE 1.** CHARACTERISTICS OF THE INTENTION-TO-TREAT POPULATION.\*

CHARACTERISTIC	ROPINIROLE (N=179)	LEVODOPA (N=89)
Age — yr	63±9	63±9
Sex — no. (%)		
Male	113 (63.1)	52 (58.4)
Female	66 (36.9)	37 (41.6)
Selegiline treatment at start of study — no. (%)	81 (45.3)	39 (43.8)
Prior levodopa treatment for ≤6 wk — no. (%)	26 (14.5)	7 (7.9)
Duration of disease — mo	30±34	29±27
Hoehn-Yahr stage — no. (%)†		
1	23 (12.8)	20 (22.5)
1.5	27 (15.1)	8 (9.0)
2	66 (36.9)	33 (37.1)
2.5	46 (25.7)	19 (21.3)
3	17 (9.5)	9 (10.1)
UPDRS Score‡		
Base-line score for ADL	8.0±5.0	8.0±4.6
Base-line for motor function score	21.5±10.5	21.7±11.3

\*Plus-minus values are means ±SD.

†The stages range from 1, indicating unilateral, early disease, to 3, indicating more advanced, bilateral disease.

‡UPDRS denotes Unified Parkinson's Disease Rating Scale, and ADL activities of daily living. The range of possible scores for activities of daily living is 0 to 52, with a higher score indicating more severe dysfunction. The range of possible scores for motor function is 0 to 108, with a higher score indicating more severe dysfunction.

**Incidence of Dyskinesia**

The reduced risk of dyskinesia among the patients in the ropinirole group, regardless of levodopa supplementation, is evident in Figure 2 (hazard ratio for remaining free of dyskinesia in the ropinirole group, as compared with the levodopa group, 2.82; 95 percent confidence interval, 1.78 to 4.44; P<0.001). There were too few patients with dyskinesia in the ropinirole group to calculate the length of time until dyskinesia developed in 50 percent of the patients remaining in the study. However, the length of time until dyskinesia developed in 25 percent of the patients remaining in the study was 214 weeks among the patients in the ropinirole group and 104 weeks among the patients in the levodopa group. Overall, dyskinesia developed in 36 of the 177 patients in the ropinirole group (20 percent) and in 40 of the 88 in the levodopa group (45 percent), as assessed by item 32 of the UPDRS and by reports of adverse events. Before the addition of supplementary levodopa, 9 of 177 patients in the ropinirole group (5 percent) and 32 of 88 in the levodopa group (36 percent) had dyskinesia.

**Other Variables**

The risk of disabling dyskinesia was significantly lower in the ropinirole group, regardless of whether

the patient received supplementary levodopa (hazard ratio for remaining free of disabling dyskinesia in the ropinirole group as compared with the levodopa group, 3.02; 95 percent confidence interval, 1.52 to 6.02; P=0.002). Fourteen of the 179 patients in the ropinirole group (8 percent) had disabling dyskinesia, as compared with 20 of the 89 in the levodopa group (23 percent).

Figure 3 shows the mean scores for activities of daily living throughout the study. Among the patients who completed the study, the mean (±SD) change from base line in the score for activities of daily living was an increase of 1.6±5.4 points (a slight worsening) among the patients in the ropinirole group and 0.0±4.7 points among those in the levodopa group. This difference was not significant (adjusted difference, 1.53 points; 95 percent confidence interval, -0.14 to 3.22; P=0.08).

Figure 3 also shows the mean scores for motor function during the study. For the patients who completed the study, there were mean decreases from base line in motor-function scores of 0.8±10.1 point (a slight improvement) among the patients in the ropinirole group and 4.8±8.3 points among those in the levodopa group. The difference in mean scores was significant in favor of levodopa (adjusted treatment difference, 4.48 points; 95 percent confidence interval, 1.25 to 7.72; P=0.008).

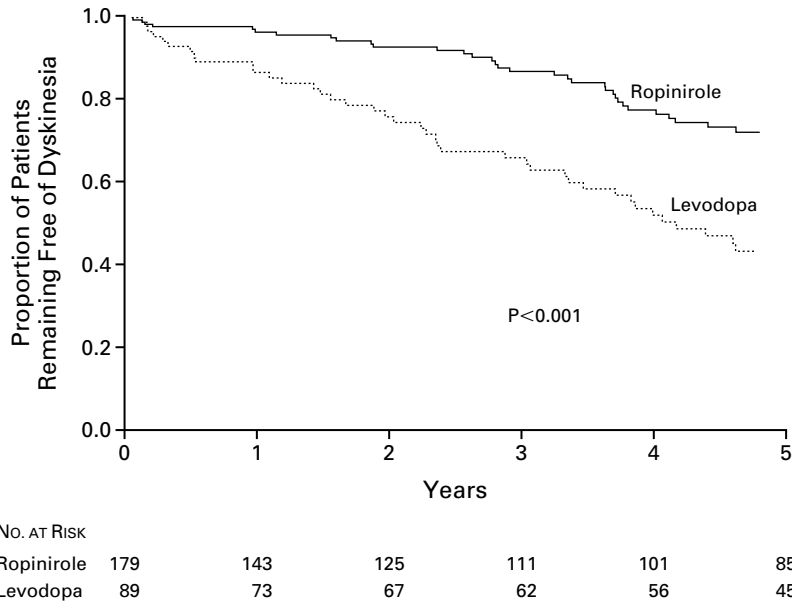
The length of time until 25 percent of the patients remaining in the study first had an increase in the wearing-off effect was 199 weeks in the ropinirole group and 145 weeks in the levodopa group. Of the patients for whom data were available, 39 of 172 patients in the ropinirole group (23 percent) and 29 of 85 in the levodopa group (34 percent) had an increase in symptoms due to the wearing off of the drugs during the study.

The length of time until 25 percent of the patients remaining in the study first had an increase in freezing while walking was 166 weeks in the ropinirole group and 207 weeks in the levodopa group. Of the patients for whom data were available, 57 of 178 patients in the ropinirole group (32 percent) and 22 of 88 in the levodopa group (25 percent) had an increase in freezing while walking.

Fourteen of the 179 patients in the ropinirole group (8 percent) withdrew from the study early because of a lack of efficacy, as compared with 5 of 89 in the levodopa group (6 percent). Aggravated parkinsonism was responsible for the withdrawal of 6 of the 179 patients in the ropinirole group (3 percent) and 3 of the 89 in the levodopa group (3 percent).

**Adverse Events**

Relevant adverse events that occurred in more than 10 percent of the study population over the course of the study are listed in Table 2. There was no significant difference in the incidence of neuropsychiat-



**Figure 2.** Proportions of Patients Remaining Free of Dyskinesia in the Ropinirole and Levodopa Groups. The hazard ratio for remaining free of dyskinesia in the ropinirole group as compared with the levodopa group was 2.82 (95 percent confidence interval, 1.78 to 4.44).

ric adverse events between the two groups (43 of 179 patients in the ropinirole group [24 percent] and 15 of 89 patients in the levodopa group [17 percent];  $P=0.18$  by the chi-square test), although the incidence of hallucinations was higher in the ropinirole group (31 of 179 patients [17 percent]) than in the levodopa group (5 of 89 patients [6 percent]).

Adverse events caused the early withdrawal from the study of 48 of the 179 patients in the ropinirole group (27 percent) and 29 of the 89 patients in the levodopa group (33 percent). The two most common reasons for early withdrawal due to adverse events were nausea (ropinirole group, 5 of 179 patients [3 percent]; levodopa group, 5 of 89 patients [6 percent]) and hallucinations (ropinirole group, 8 of 179 patients [4 percent]; levodopa group, 2 of 89 patients [2 percent]). No other individual adverse event caused the early withdrawal of 4 percent or more of the patients in either group. No more than 3 percent of the patients in either treatment group died during the study (ropinirole group, 5 of 179 patients [3 percent]; levodopa group, 2 of 89 patients [2 percent]). No deaths were directly attributed to the study medications.

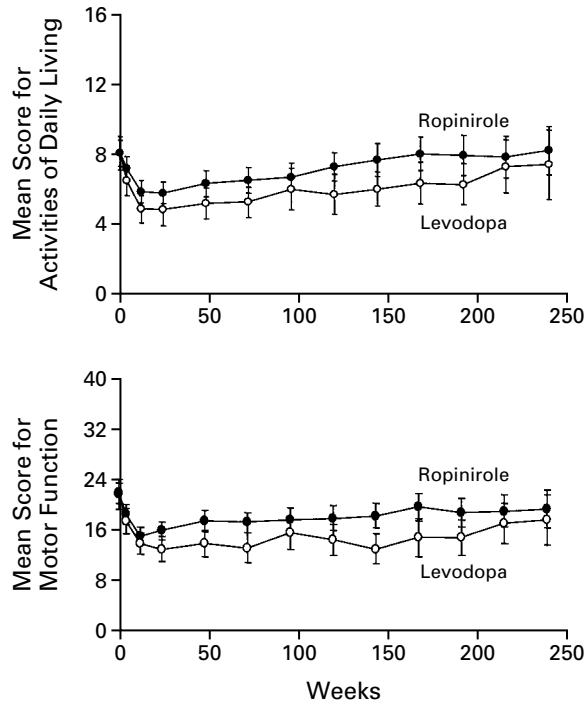
## DISCUSSION

This study shows that the early use of the dopamine agonist ropinirole significantly reduces the risk of dyskinesia in patients with Parkinson's disease. When all the patients randomly assigned to ropinirole were compared with those randomly assigned to

levodopa, the risk of dyskinesia was lower by a factor of almost three in the ropinirole group (Fig. 2). The overall incidence of dyskinesia at five years was 20 percent in the ropinirole group, as compared with 45 percent in the levodopa group. This difference was even more striking among the patients who did not require supplementary levodopa (rates of dyskinesia: ropinirole group, 5 percent; levodopa group, 36 percent). The clinical relevance of these differences between treatment groups is emphasized by the significant difference in favor of ropinirole in the incidence of dyskinesia considered to be disabling.

These results confirm the findings of several previous open-label studies<sup>7,9,10</sup> and shorter blinded studies,<sup>13,27</sup> in which fewer motor complications were reported among patients who initially received dopamine agonists. The incidence of dyskinesia in the patients assigned to levodopa in our study differed from that reported in a five-year trial comparing immediate-release and sustained-release levodopa, in which less than 25 percent of patients had dyskinesia.<sup>28</sup> This difference may be related to the different doses of levodopa used and different methods of assessment of the occurrence of dyskinesia. Generally, most authors report an incidence of dyskinesia similar to that found in our study.<sup>29</sup>

The reason why the early use of ropinirole reduced the risk of dyskinesia remains unclear. Factors implicated as contributing to the development of dyskinesia include a higher dose of levodopa, greater severity of underlying disease,<sup>29</sup> and abnormal pulsatile



No. AT RISK						
Ropinirole	179	143	125	111	101	85
Levodopa	89	73	67	62	56	45

**Figure 3.** Mean Scores for Activities of Daily Living and Motor Function.

The scores are for part II (activities of daily living) and part III (motor function) of the Unified Parkinson's Disease Rating Scale. The range of possible scores for part II is 0 to 52; the range for part III is 0 to 108. Higher scores indicate more severe disability and more severe dysfunction. I bars indicate ±2 SE.

stimulation of dopamine receptors as a result of the short elimination half-life of levodopa.<sup>30</sup> Ropinirole has a longer elimination half-life than levodopa (6 to 8 hours vs. 1.5 to 2 hours), thus providing more continuous stimulation of dopamine receptors. Patients treated with ropinirole also had reduced cumulative exposure to levodopa, since levodopa was used only later and at a lower dose, if necessary. The design of this study did not permit us to determine whether there was an additional neuroprotective effect of ropinirole.

The early use of ropinirole did not reduce the occurrence of wearing-off and freezing during walking to the same extent as it did the occurrence of dyskinesia. This finding suggests that these complications of motor function may not have the same pathophysiologic mechanisms as dyskinesia.

Delaying treatment with levodopa to prevent dyskinesia can be justified only if the underlying symptoms of Parkinson's disease are sufficiently controlled. The mean scores for activities of daily living remained

**TABLE 2.** REPORTS OF ADVERSE EVENTS OCCURRING IN 10 PERCENT OR MORE OF EITHER GROUP IN THE INTENTION-TO-TREAT ANALYSIS.

ADVERSE EVENT*	ROPINIROLE (N=179)	LEVODOPA (N=89)
	no. (%)	
Nausea	87 (48.6)	44 (49.4)
Somnolence	49 (27.4)	17 (19.1)
Insomnia	45 (25.1)	21 (23.6)
Aggravated Parkinson's disease	40 (22.3)	18 (20.2)
Dyspepsia	37 (20.7)	15 (16.9)
Dizziness	36 (20.1)	17 (19.1)
Hallucinations	31 (17.3)	5 (5.6)
Vomiting	29 (16.2)	10 (11.2)
Tremor	29 (16.2)	11 (12.4)
Abdominal pain	27 (15.1)	13 (14.6)
Depression	26 (14.5)	20 (22.5)
Headache	25 (14.0)	16 (18.0)
Edema of the legs	25 (14.0)	5 (5.6)
Ataxia	25 (14.0)	8 (9.0)
Anxiety	21 (11.7)	8 (9.0)
Postural hypotension	21 (11.7)	11 (12.4)
Constipation	17 (9.5)	11 (12.4)
Dyskinesia†	16 (8.9)	23 (25.8)
Dystonia	12 (6.7)	11 (12.4)
Increased sweating	11 (6.1)	9 (10.1)

\*Patients often had more than one adverse event.

†Dyskinesia, the primary outcome measure, was assessed on the basis of both the Unified Parkinson's Disease Rating Scale and reports of adverse events.

similar in the two groups at each time point during the study (a difference of less than 1.5 points), and the changes between base line and completion of the study in the two groups were not significantly different. For the UPDRS motor score, although there was no significant difference between the two groups in the absolute value at the completion of the study, there was a significant difference in the change from base line in favor of levodopa. This difference, however, may not be clinically relevant, since it was not reflected in the measurements of activities of daily living. Moreover, the rates of early withdrawal from the study as a result of insufficient efficacy and aggravated parkinsonism were similar in the two treatment groups.

The fact that 85 of the 179 patients in the ropinirole group (47 percent) and 45 of the 89 in the levodopa group (51 percent) completed the study serves to confirm that the safety and efficacy profiles of the two treatment strategies are similar. A further measure of efficacy with respect to antiparkinson effect, sometimes used as a surrogate end point in clinical trials, is whether patients require supplementary levodopa. Although a higher percentage of ropinirole-

treated patients received supplementary levodopa than of those treated initially with levodopa in our study, this difference cannot be regarded as a reliable indicator of efficacy. The reason is that the investigators, aware of the association between levodopa and dyskinesia, appeared to be less willing to give patients with dyskinesia supplementary levodopa: of the patients in whom dyskinesia developed, only 17 percent (13 of 76) received supplementary levodopa after the onset of dyskinesia, whereas 58 percent of the patients without dyskinesia (110 of 189) received supplementary levodopa. Since dyskinesia was much more common in the levodopa group (45 percent) than in the ropinirole group (20 percent), a lower rate of supplementation in the levodopa group may have resulted.

Some physicians are cautious about using dopamine agonists, because they believe that such agents induce more adverse events (including nausea, hypotension, and hallucinations) than levodopa. This belief is based on experience gained in treating advanced Parkinson's disease, in which patients are generally older, are often receiving multiple medications, and may have a number of coexisting conditions. The doses of ropinirole administered in this study (mean,  $16.5 \pm 6.6$  mg per day at five years) were higher than those currently used in clinical practice in Europe and the United States. These higher doses, however, were well tolerated, with rates and profiles of adverse events that were similar for the two drugs and typical for any effective dopaminergic agent.

Neuropsychiatric adverse events are a major concern when dopamine agonists are used in the treatment of Parkinson's disease. In this study, there was no significant difference in the overall incidence of these complications, including the occurrence of somnolence, between the two treatment groups. There were no reports of falling asleep suddenly in either treatment group.<sup>31</sup> Although hallucinations were more frequent in the ropinirole group than in the levodopa group, they were mild and easily managed in most patients. No risk factors were identified that would predispose patients to have such adverse events with either treatment.

Our study, therefore, demonstrates that Parkinson's disease can be successfully managed for up to five years with ropinirole, with supplemental levodopa given as a second step if necessary. Such treatment significantly lowers the risk of dyskinesia as compared with treatment with levodopa alone.

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*script; to Mary Oldham and Jacqui Warner for performing all statistical analyses; and to all the coinvestigators and nurses who participated in the study.*

## APPENDIX

The following investigators participated in the 056 Study: Belgium — P.P. De Deyn, J. Harmant, J. Jacquy; Canada — D. King, A.E. Lang, W. Martin; France — A. Destee, F. Durif, O. Rascol; Israel — J. Aharon-Peretz, A. Korczyn, A. Reches; Italy — B. Bergamasco, F. Bracco, L. Fratola, P. Nordera, G. Pezzoli, G. Scarlato, F. Stocchi; the Netherlands — A. Hovestadt; and United Kingdom — R. Abbott, M. Bakheit, G. Boddie, D.J. Brooks, C.E. Clarke, R. Corston, C. Hawkes, C. Kennard, L. Loizou, L. McLellan, D. Park, H. Sagar, E. Spokes, C. Ward, S.V. Wroe.

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