ORIGINAL CONTRIBUTION

Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease

A 4-Year Randomized Controlled Trial

*The Parkinson Study Group**

Background: The best way to initiate dopaminergic therapy for early Parkinson disease remains unclear.

Objective: To compare initial treatment with pramipexole vs levodopa in early Parkinson disease, followed by levodopa supplementation, with respect to the development of dopaminergic motor complications, other adverse events, and functional and quality-of-life outcomes.

Design: Multicenter, parallel-group, double-blind, randomized controlled trial.

Setting: Academic movement disorders clinics at 22 sites in the United States and Canada.

Patients: Patients with early Parkinson disease (N=301) who required dopaminergic therapy to treat emerging disability, enrolled between October 1996 and August 1997 and observed until August 2001.

Intervention: Subjects were randomly assigned to receive 0.5 mg of pramipexole 3 times per day with levodopa placebo (n=151) or 25/100 mg of carbidopa/levodopa 3 times per day with pramipexole placebo (n=150). Dosage was escalated during the first 10 weeks for patients with ongoing disability. Thereafter, investigators were permitted to add open-label levodopa or other antiparkinsonian medications to treat ongoing or emerging disability.

Main Outcome Measures: Time to the first occurrence of dopaminergic complications: wearing off, dyskinesias, on-off fluctuations, and freezing; changes in the Unified Parkinson's Disease Rating Scale and quality-of-life scales; and adverse events.

Results: Initial pramipexole treatment resulted in a significant reduction in the risk of developing dyskinesias (24.5% vs 54%; hazard ratio, 0.37; 95% confidence interval [CI], 0.25-0.56; $P<.001$) and wearing off (47% vs 62.7%; hazard ratio, 0.68; 95% CI, 0.49-0.63; $P=.02$). Initial levodopa treatment resulted in a significant reduction in the risk of freezing (25.3% vs 37.1%; hazard ratio, 1.7; 95% CI, 1.11-2.59; $P=.01$). By 48 months, the occurrence of disabling dyskinesias was uncommon and did not significantly differ between the 2 groups. The mean improvement in the total Unified Parkinson's Disease Rating Scale score from baseline to 48 months was greater in the levodopa group than in the pramipexole group (2±15.4 points vs −3.2±17.3 points, $P=.003$). Somnolence (36% vs 21%, $P=.005$) and edema (42% vs 15%, $P<.001$) were more common in pramipexole-treated subjects than in levodopa-treated subjects. Mean changes in quality-of-life scores did not differ between the groups.

Conclusions: Initial treatment with pramipexole resulted in lower incidences of dyskinesias and wearing off compared with initial treatment with levodopa. Initial treatment with levodopa resulted in lower incidences of freezing, somnolence, and edema and provided for better symptomatic control, as measured by the Unified Parkinson's Disease Rating Scale, compared with initial treatment with pramipexole. Both options resulted in similar quality of life. Levodopa and pramipexole both appear to be reasonable options as initial dopaminergic therapy for Parkinson disease, but they are associated with different efficacy and adverse-effect profiles.

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The Writing Group members for the Parkinson Study Group who had complete access to the raw data needed for this report and who bear authorship responsibility for this report are given in the "Author Contributions" on page 1051. A complete list of the affiliations for the Writing Group appears along with a complete list of the members of the Parkinson Study Group on page 1052.

In 1996, the Parkinson Study Group initiated a multicenter randomized clinical trial comparing initial treatment of early Parkinson disease with pramipexole, a nonergot dopaminergic agonist,[1] with initial treatment of early Parkinson disease with levodopa. A report detailing the methods and results of the first 2 years of this clinical trial has been previously published.[2,3] After 2 years, initial pramipexole resulted in the significantly reduced risk of the development of wearing off, dyskinesias, or on-off motor fluctuations compared with levodopa (28% vs 51%). However, initial treatment with levodopa resulted in an early, and sustained, superior improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) total score compared with pramipexole (9.2 vs

4.5 points at 23.5 months). The clinical trial was extended to a minimum of 4 years to compare initial treatment with pramipexole with initial treatment with levodopa, with respect to the development and severity of dopaminergic complications, other adverse events, functional outcomes, and quality of life.

We recently published the effects of initiating pramipexole vs levodopa in early Parkinson disease on a subset of the clinical trial cohort with respect to imaging of striatal dopamine transporter density, a marker of the dopaminergic neuron terminal, during the course of 4 years.[4] Using single-photon emission computed tomography and iodine I 123–labeled 2 β-carboxymethoxy-3 β-(4-iodophenyl) tropane (β-CIT), we found that the percent loss in striatal ^{123}I–β-CIT uptake from baseline was reduced by approximately 40% at 22 months (P=.004), 34 months (P=.009), and 46 months (P=.01) in the group initially treated with pramipexole, as compared with the group initially treated with levodopa. These results demonstrate a reduction in the loss of striatal dopamine transporter density in the pramipexole group compared with the levodopa group. Here we present the entirety of the 4-year data to extend our 2-year clinical observations and to complement our recently published 4-year imaging observations.

METHODS

ORGANIZATION

This multicenter study was organized by the Parkinson Study Group in conjunction with the sponsor, Pharmacia Corporation, Peapack, NJ (formerly Pharmacia & Upjohn Inc, Kalamazoo, Mich). Eligible subjects were enrolled between October 1996 and August 1997 at 22 sites in the United States (17) and Canada (5), and were observed through August 2001, when the last subject enrolled completed a minimum of 4 years of follow-up. The study was reviewed and approved by the institutional review board at each of the participating sites. Subjects gave written consent to participate in the 2-year clinical trial and again provided consent to participate in the extended follow-up for at least an additional 2 years. An independent safety monitoring committee was responsible for unblinded monitoring of patient safety data. There were no prespecified formal guidelines for the safety monitoring committee to recommend modification or termination of the trial.

RECRUITMENT, RANDOMIZATION, AND ENROLLMENT

Details about eligibility criteria and randomization and enrollment procedures have been reported.[2] Eligible subjects had idiopathic Parkinson disease for fewer than 7 years and required dopaminergic antiparkinsonian therapy at the time of enrollment. Patients who had taken levodopa or a dopaminergic agonist in the 2 months prior to enrollment were excluded. Subjects were required to be in Hoehn and Yahr stage I, II, or III.[5] Eligible patients were randomized in a 1:1 ratio to pramipexole or levodopa, in combination with carbidopa, using a computer-generated randomization plan that included stratification by investigator and blocking. When a patient was judged eligible and consented to be enrolled, a telephone call was made to the Parkinson Study Group Coordination Center (Rochester, NY), which provided a unique subject identification number from the randomization module. Access to the randomization code was restricted to 2 programmers, 1 at the Parkinson Study Group Biostatistical Center and 1 at the Pharmacia Corporation.

Study subjects, steering committee members, site investigators and coordinators, and project and data management staff were blinded to treatment assignment. After the baseline visit, subjects were evaluated at 4 weeks, 10 weeks, and every 3 months until the last enrolled subject completed a 48-month visit in August 2001. Between June 2001 and August 2001, treatment assignments were disclosed to the subjects, and neither subjects nor investigators were asked to guess the subjects' original treatment assignments.

STUDY INTERVENTION

Study Drugs and 10-Week Dosage Escalation Phase

Subjects were randomly assigned to the intervention groups at the baseline visit; they entered a 10-week dosage escalation period. Pramipexole was taken 3 times per day as 0.25-mg, 0.5-mg, or 1-mg tablets or matching placebo tablets, which were identical in appearance, taste, and smell. Carbidopa/levodopa was taken as 12.5/50-mg or 25/100-mg capsules or matching placebo capsules. Treatment assignments included active drug for one treatment and placebo for the other. All subjects were escalated initially to a daily dosage of 1.5 mg of pramipexole or 75/300 mg of carbidopa/levodopa (level 1 dosage). Subjects requiring additional therapy could escalate to 3 mg of pramipexole or 112.5/450 mg of carbidopa/levodopa (level 2 dosage), or 4.5 mg of pramipexole or 150/600 mg of carbidopa/levodopa (level 3 dosage). Therefore, all patients entered the follow-up phase (week 11) of the trial on dosage level 1, 2, or 3.

Follow-up Phase and Allowable Treatment Options

The follow-up phase of the trial consisted of 2 calendar periods. Through February 2000, subjects were maintained on study drug at the dosage level achieved in the escalation phase, and subjects with emerging disability were prescribed open-label carbidopa/levodopa as needed.[6] Sustained-release carbidopa/levodopa preparations and other antiparkinsonian medications could not be added or altered. From February 2000 to August 2001, subjects had expanded treatment options available, in addition to adding open-label levodopa. If subjects developed wearing off, dyskinesias, or on-off fluctuations (the primary outcome variable), they were permitted to (1) increase or decrease study drug dosages by 1 or 2 levels, (2) add sustained-release carbidopa/levodopa, (3) alter or add amantadine, anticholinergic medications, or selegiline, or (4) add a catechol-*O*-methyltransferase inhibitor after all other treatment options had been used.

OUTCOME VARIABLES

The primary outcome variable was prespecified as the time from randomization until the first occurrence of any of 3 specified dopaminergic complications: wearing off, dyskinesias, or on-off fluctuations, as defined in a prior report.[3] One designated and blinded investigator at each site made the judgment at each visit as to the occurrence of a dopaminergic complication. Subjects who developed a dopaminergic complication continued to be observed for the duration of the trial.

Secondary outcome variables included changes in scores on the UPDRS,[7] the Parkinson's Disease Quality-of-Life scale (PDQUALIF),[8] the EuroQol Visual Analog Scale (VAS),[9] as well as the need for supplemental levodopa. The UPDRS is a standardized, reliable, and valid instrument for assessing the severity of the clinical features of Parkinson disease.[10] The Eu-

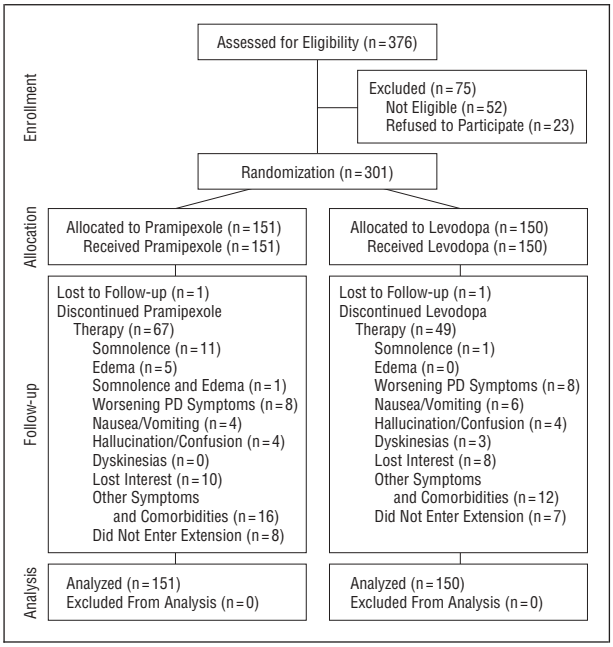

Figure 1. Patient flow. PD indicates Parkinson disease.

roQol VAS is a thermometer-type scale with 100 tick marks on which the subject rates his or her current health state on a scale from 0 to 100, with 0 corresponding to the worst imaginable health and 100 corresponding to the best imaginable health. We used 2 questions (questions 32 and 33) from part IV of the UPDRS to assess the duration and disability of dyskinesias. Measures of safety included incidence of adverse events. In a post hoc analysis, for those patients with somnolence or edema, we used the adverse event start and stop dates to estimate the time spent in the trial either with somnolence or edema. In addition, we report on the severity of all somnolence and edema events as judged by the site investigator and coordinator.

The presence of dopaminergic events was assessed every 3 months until month 58 (4 years and 10 months). Parts I-III of the UPDRS were assessed every 3 months until month 48. The quality-of-life measures were obtained every 6 months until month 48. Part IV of the UPDRS was obtained only at months 42, 45, and 48.

STATISTICAL ANALYSIS

The primary statistical analyses were performed according to the intention-to-treat principle.[11] All statistical tests were 2-tailed and performed using a significance level of 5%. The analysis of the primary outcome variable used the Cox proportional hazards regression model, with treatment group as the factor of interest and enrolling investigator as a stratification factor. The hazard ratio comparing the 2 treatment groups and the associated 95% confidence interval were determined from this model. The assumption of proportionality of hazards was examined with the use of time-dependent covariates.[12] Separate analyses of the time from baseline to the first occurrence of each individual dopaminergic complication, including freezing and the need for supplemental levodopa, were performed. The cumulative probabilities of reaching the primary end point and other end points were estimated using Kaplan-Meier survival curves.

Mean changes in the total UPDRS score, as well as the mental, motor, and activities of daily living (ADL) UPDRS scores, between randomization and 48 months were compared among the treatment groups using analysis of covariance, with treatment group, enrolling investigator, and the baseline total UPDRS score included in the model. A 95% confidence interval was computed for the difference between the adjusted treatment group means. Changes in UPDRS scores between baseline and the other visits were analyzed similarly. These analyses were also used to examine score changes in the quality-of-life measures. The interactions between treatment and enrolling investigator were tested by including the appropriate interaction terms in the model, but no such interactions were found. Two-tailed Fisher exact tests were used to compare proportions of subjects experiencing adverse events between the 2 treatment groups.

For the analyses of the UPDRS scores, if a subject was missing a response at a particular visit, missing data were imputed using a multiple imputation algorithm similar to that described by Little and Yau.[13] For subjects with complete data up to a particular visit, a multiple regression model was fit that included the UPDRS score at that visit as the dependent variable and UPDRS scores at previous visits, treatment group, and site as independent variables. Separate models were similarly constructed for each visit. Using these regression models, a missing value for a subject at a particular visit was imputed as a draw from the predictive distribution given the UPDRS scores at previous visits (some possibly imputed), treatment group, and site of the subject.[13] This was done sequentially starting with the week 4 visit and ending with the month 48 visit. This process was repeated 10 times, resulting in 10 complete analysis data sets. The analyses of covariance were performed separately for each of the 10 complete analysis data sets, and the results were combined into 1 multiple imputation inference (estimated treatment effect and associated confidence interval and *P* value), as described by Little and Yau.[13] Analyses of quality-of-life outcomes were performed in a similar fashion. For the total UPDRS score, missing values were imputed in 1104 (19%) of the 5719 person-visits in the trial, the vast majority of which were because of subject withdrawal.

We performed additional exploratory analyses to determine if the risk of developing dopaminergic complications was related to the degree of total UPDRS improvement during the first 13 weeks of the trial. For this analysis, we used Cox proportional hazards regression models for time to wearing off and time to dyskinesias that included treatment group and 13-week change from baseline in the total UPDRS score as independent variables and enrolling investigator as a stratification factor.

RESULTS

PATIENT FLOW

Of the 376 patients who were identified as potential participants, 52 were found to be ineligible and 23 declined for no specific reason (**Figure 1**). The remaining 301 patients were randomized in the study. Sixty-eight (45%) of the 151 subjects in the pramipexole group withdrew prior to the planned final follow-up visit, compared with 50 (33%) of the 150 subjects in the levodopa group. In the pramipexole group, 11 withdrew because of somnolence, 5 because of edema, and 1 because of both. In the levodopa group, 1 withdrew because of somnolence and none because of edema. Other reasons for study withdrawal were similar between the 2 groups. There were 5 deaths, 3 in the levodopa-treated group and 2 in the pramipexole-treated group, all judged not to be related to the study drug. Two subjects, 1 in each treatment group, were lost to follow-up; both occurred after the month 48 visit.

Table 1. Baseline Characteristics

Variable	Completed Trial		Withdrew From Trial	
	Pramipexole (n = 83)	Levodopa (n = 100)	Pramipexole (n = 68)	Levodopa (n = 50)
Age, y	61.1 (9.6)	60.8 (9.8)	62.1 (10.8)	61.0 (11.9)
No. (%) of male patients	50 (60.2)	68 (68.0)	46 (67.7)	31 (62.0)
No. (%) of white patients	79 (95.2)	96 (96.0)	65 (95.6)	47 (94.0)
Years since diagnosis	1.4 (1.3)	1.8 (1.7)	1.6 (1.6)	1.8 (1.7)
No. (%) of patients with prior levodopa use	20 (24.1)	15 (15.0)	20 (29.4)	15 (30.0)
No. (%) of patients with baseline eldepryl use	14 (16.9)	21 (21.0)	16 (23.5)	13 (26.0)
No. (%) of patients with baseline amantadine use	12 (14.5)	15 (15.0)	9 (13.2)	8 (16.0)
No. (%) of patients with baseline anticholinergic use	5 (6.0)	6 (6.0)	3 (4.4)	1 (2.0)
Unified Parkinson's Disease Rating Scale score				
Total	31.6 (12.4)	29.3 (12.2)	33.7 (13.0)	34.7 (13.5)
Mental	1.1 (1.2)	0.7 (1.0)	1.5 (1.4)	1.2 (1.2)
Activities of daily living	8.7 (4.1)	7.8 (3.8)	9.5 (4.0)	9.2 (4.2)
Motor	21.9 (8.9)	20.8 (9.4)	22.7 (9.5)	24.3 (9.8)
No. (%) of patients in Hoehn and Yahr Stage				
1.0	12 (14.5)	18 (18.0)	8 (11.8)	5 (10.0)
1.5	11 (13.3)	16 (16.0)	12 (17.7)	4 (8.0)
2.0	43 (51.8)	58 (58.0)	35 (51.5)	26 (52.0)
2.5	16 (19.3)	7 (7.0)	9 (13.2)	9 (18.0)
3.0	1 (1.2)	1 (1.0)	4 (5.9)	6 (12.0)
Quality-of-life scales				
Parkinson's Disease Quality-of-Life Scale	28.2 (9.9)	24.5 (10.4)	30.6 (13.6)	31.0 (12.2)
EuroQol visual analog scale	76.3 (14.3)	79.2 (11.5)	73.6 (17.1)	74.4 (12.4)

*Values are expressed as mean (SD) unless otherwise indicated. The scale ranges are as follows for the Parkinson's Disease Quality-of-Life Scale, 0 to 100 (lower scores reflect better quality of life); and EuroQol visual analog scale, 0 to 100 (higher scores reflect better quality of life).

BASELINE CHARACTERISTICS

The 2 treatment groups were similar at baseline with regard to demographic and clinical variables, except for lower quality-of-life scores in the pramipexole group.[2] **Table 1** shows that the baseline UPDRS and quality-of-life scores of subjects who completed the planned follow-up were better than the baseline scores of subjects who prematurely withdrew.

STUDY DRUG USE AND CONCOMITANT MEDICATIONS

Table 2 shows dosage-level changes and baseline and trial-emergent use of medications during the trial. One hundred nine subjects (72%) in the pramipexole group required open-label levodopa compared with 89 (59%) in the levodopa group (hazard ratio, 1.64; 95% CI, 1.22-2.21; $P=.001$). The mean total daily levodopa dosage in the pramipexole subjects was 434±498 mg/d (supplemental only) compared with 702±461 mg/d (experimental: 427±112 mg plus supplemental: 274±442 mg) in the levodopa group. Subjects allocated to pramipexole took an average of 2.78±1.1 mg/d by the end of the trial.

DOPAMINERGIC END POINTS

Table 3 and **Figure 2** show that 52% of subjects assigned to pramipexole treatment reached the primary end point of developing dyskinesias, wearing off, or on-off fluctuations compared with 74% of the levodopa group (hazard ratio, 0.48; 95% CI, 0.35-0.66; $P<.001$). A reduced risk was observed for those subjects assigned to pramipexole for wearing-off (hazard ratio, 0.68; 95% CI, 0.49-0.93; $P=.02$) and dyskinesias (hazard ratio, 0.37; 95% CI, 0.25-0.56; $P<.001$) but not for on-off fluctuations (hazard ratio, 0.64; 95% CI, 0.26-1.59; $P=.34$). In contrast, an increased risk of freezing was observed in the pramipexole group compared with the levodopa group (hazard ratio, 1.7; 95% CI, 1.11-2.59; $P=.01$). In the pramipexole group, the majority of the dopaminergic complications occurred after initiating open-label levodopa treatment, whereas in the levodopa group, the majority of complications occurred prior to initiating open-label levodopa treatment. Of the 10 subjects in the pramipexole group who developed dyskinesias before starting open-label levodopa treatment, 7 had no history of prior levodopa exposure.

The development of dopaminergic complications by treatment group was not significantly influenced by age (≤60, >60 years), sex, years since onset of Parkinson disease (<2, ≥2 years), dosage level, or baseline UPDRS score (≤30, >30 units). Pramipexole tended to be particularly effective in reducing the risk of developing dyskinesias in subjects with baseline Hoehn and Yahr scores of less than 2 compared with subjects with baseline Hoehn and Yahr scores of 2 or higher (hazard ratio, 0.15 vs 0.46; $P=.06$).

SEVERITY OF DYSKINESIAS

At the month 48 visit, 12 (13%) of 91 subjects in the pramipexole group indicated the presence of dyskinesias, and 4 of the 12 indicated that the dyskinesias were mildly disabling. In the levodopa group, 32 (32%) of 101 subjects indicated the presence of dyskinesias; 6 indicated

Table 2. Drug Use During Trial

	Pramipexole (n = 151)	Levodopa (n = 150)
Dosage level changes		
Up 1 level	14	14
Up 2 levels	2	5
Down 1 level	6	2
Down 2 levels	2	0
Open-label levodopa		
Baseline use	0	0
Trial-emergent use	109	89
Eldepryl		
Baseline use	30	34
Trial-emergent use	21	22
Amantadine		
Baseline use	21	23
Trial-emergent use	11	21
Anticholinergics		
Baseline use	8	7
Trial-emergent use	4	7
Catechol-*O*-methyl transferase inhibitors		
Baseline use	0	0
Trial-emergent use	3	4
Antidepressants		
Baseline use	6	6
Trial-emergent use	46	45
Anxiolytics		
Baseline use	2	3
Trial-emergent use	18	22
Antipsychotics		
Baseline use	0	0
Trial-emergent use	7	2

Table 3. Treatment Effects on Dopaminergic End Points*

End Points	Pramipexole, No. (%) (n = 151)	Levodopa, No. (%) (n = 150)	HR (95% CI)	*P* Value
First dopaminergic complication†	78 (51.7)	111 (74.0)	0.48 (0.35-0.66)	<.001
Wearing off	71 (47.0)	94 (62.7)	0.68 (0.49-0.93)	.02
Dyskinesias	37 (24.5)	81 (54.0)	0.37 (0.25-0.56)	<.001
On-off fluctuations	10 (6.6)	12 (8.0)	0.64 (0.26-1.59)	.34
Freezing	56 (37.1)	38 (25.3)	1.70 (1.11-2.59)	.01
Off-period dystonia	53 (35.1)	69 (46.0)	0.73 (0.51-1.06)	.10

Abbreviations: CI, confidence interval; HR, hazard ratio.
*All analyses are stratified by the enrolling investigator. The hazard ratio is the ratio of the risk of reaching the end point per unit of time for patients assigned to initially receive pramipexole treatment, to the corresponding risk for patients assigned to initially receive levodopa treatment.
†Defined as the first occurrence of wearing off, dyskinesia, or on-off fluctuations.

that the dyskinesias were mildly disabling, and 1 indicated that the dyskinesias were moderately disabling. The remainder of both groups indicated no disability from their dyskinesias: 8 in the pramipexole group and 25 in the levodopa group. Similar patterns of dyskinesia frequency and disability were seen at the month 42 and month 45 visits.

OTHER ADVERSE EVENTS

Table 4 shows that significantly more patients in the pramipexole group experienced edema ($P<.001$), somnolence ($P=.005$), and cellulitis ($P=.01$). Urinary frequency ($P=.01$) and hernia ($P=.002$) were more common in the levodopa group. Somnolence most commonly developed during the escalation phase in the pramipexole group as compared with edema and cellulitis, which tended to occur later in the trial.

For subjects randomized to pramipexole who experienced 1 or more episodes of somnolence, a mean±SD of 46.4%±36.2% of their total days in the trial were spent somnolent compared with a mean of 17.5%±32.9% for subjects in the levodopa group. Of the total 103 somnolence events recorded in those randomized to the pramipexole group, 39 (38%) were judged by the site investigator or coordinator to be of moderate or severe intensity compared with 12 (22%) of the total 48 somnolence events in the levodopa group. Of the 12 subjects in the pramipexole group who withdrew because of somnolence, 8 described their somnolence as "sudden" or "unexpected," and 5 said these episodes occurred while driving. The 1 subject in the levodopa group who withdrew because of somnolence was described as having "increased daytime drowsiness."

For subjects randomized to pramipexole who experienced 1 or more episodes of edema, a mean±SD of 46.1%±37.4% of their total days spent in the trial were spent with edema, compared with a mean of 30.6%±31.7% for subjects in the levodopa group. Of the total 125 edema events recorded in subjects randomized to the pramipexole group, 49 (35%) were judged to be of moderate or severe intensity compared with 11 (23%) of the total 41 edema events in the levodopa group.

There were 7 serious adverse events relating to driving. Two events occurred in 2 subjects randomized to levodopa, and 5 events occurred in 4 subjects randomized to pramipexole. Of the 2 events in the levodopa group, 1 subject described "falling asleep at the wheel." Of the 5 events in the pramipexole group, 3 events in 2 subjects were described as "falling asleep" or "sudden onset of sleep" while driving.

UNIFIED PARKINSON'S DISEASE RATING SCALE

The mean improvements in total, motor, and activities of daily living UPDRS scores from baseline to 48 months were greater in the levodopa group than in the pramipexole group (**Table 5**). In each treatment group, the initial improvements achieved in UPDRS scores slowly decayed across time, with an approximate decay rate of 3 total UPDRS units per year, although the difference between the groups remained relatively constant (**Figure 3**). The mean improvement in the mental UPDRS score from baseline was greater at each study visit in the pramipexole group compared with the levodopa group but did not reach statistical significance (Figure 3, Table 5).

The 13-week change from baseline in total UPDRS score was significantly associated with time to dyskinesias (hazard ratio, 0.97; 95% CI, 0.95-1; $P=.05$) but not significantly associated with time to wearing off (hazard ratio, 1; 95% CI, 0.98-1.03; $P=.82$). After adjusting for

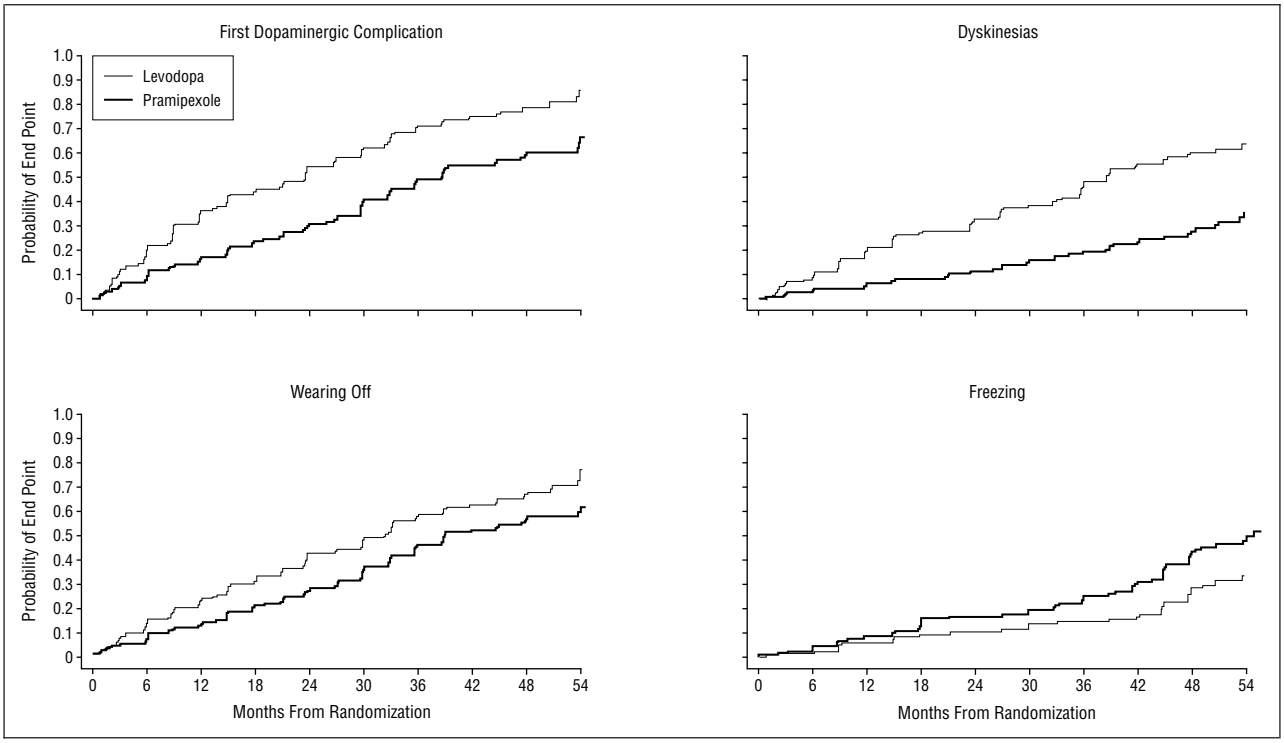

Figure 2. Cumulative probability of reaching the first dopaminergic complication (A) and the individual complications wearing off (B), dyskinesias (C), and freezing (D) by treatment assignment. First dopaminergic complication is defined as the first occurrence of wearing off, dyskinesias, or on-off fluctuations.

short-term UPDRS improvement, the treatment group hazard ratio for time to dyskinesia remained similar to that reported in Table 3 (hazard ratio, 0.39; 95% CI, 0.26-0.6; $P<.001$).

QUALITY-OF-LIFE OUTCOMES

The total scores on the PDQUALIF and the EuroQol VAS improved in both groups by approximately 2 units during the first 6 months and then worsened across time at a decay rate of approximately 1 unit per year. At 48 months, the mean change scores were not significantly different between the treatment groups for either the PDQUALIF or the EuroQol VAS. Analyses of the 7 PDQUALIF subscales revealed no significant treatment group differences.

COMMENT

Our findings show that after 4 years of treatment, 74% of subjects assigned to initial levodopa experienced a dopaminergic motor complication (wearing off, dyskinesia, or on-off fluctuations) compared with 52% of subjects assigned to initial pramipexole. The treatment differential was most striking for dyskinesias (54% of subjects in the levodopa group vs 25% of subjects in the pramipexole group) and wearing off (63% vs 47%, respectively). The differences in the risks of developing dyskinesias and wearing off persisted even after we controlled for early symptomatic changes in UPDRS, which suggests that these complications are mediated via mechanisms other than the magnitude of early UPDRS improvement.

Our dyskinesia severity data differ from those of a prior study comparing the severity of dyskinesias after 5 years of treatment among subjects initially treated with ropinirole vs levodopa.[14] The ropinirole study reported the incidence of "disabling" dyskinesias as measured by a response of mildly, moderately, severely, or completely disabling on question 33 of the UPDRS at any time during the month 60 trial: 14 (7.8%) of 179 patients in the ropinirole group and 20 (22.4%) of 89 patients in the levodopa group. We report the point prevalence of disabling dyskinesias at month 48: 4 (4.4%) of 91 patients in the pramipexole group and 7 (6.9%) of 101 patients in the levodopa group at the month 48 visit. These trial differences occurred despite similar mean amounts±SD of total levodopa in the levodopa groups at the end of both studies: 753±398 mg/d in the ropinirole trial vs 702±461 mg/d in the pramipexole trial. The lower frequency of disabling dyskinesias in our trial compared with that in the ropinirole trial may be partly explained if early-onset dyskinesias were transient and successfully treated with medication adjustments.

The observation that the development of freezing was more common in the pramipexole group than in the levodopa group has been previously reported for other dopamine agonists.[14] In the ropinirole trial, 57 (32%) of 178 subjects in the ropinirole group and 22 (25%) of 88 subjects in the levodopa group reported an increase in freezing when walking. More research is needed on the relative value that patients place on early motor complications, on the impact of early motor complications on short-term patient function, and on their ability to predict long-term disability.

Table 4. Adverse Events by Treatment Group and Study Phase

	No. (%)		
	Pramipexole (n = 151)	Levodopa (n = 150)	*P* Value
Edema*	64 (42.4)	22 (14.7)	<.001
Escalation	11	3	
Week 11 through month 23.5	39	13	
Month 23.5 through month 48+	14	6	
Peripheral edema	34 (22.5)	9 (6.0)	<.001
Escalation	7	2	
Week 11 through month 23.5	17	4	
Month 23.5 through month 48+	10	3	
Somnolence	56 (36.4)	32 (21.3)	.005
Escalation	35	13	
Week 11 through month 23.5	13	13	
Month 23.5 through month 48+	7	6	
Hallucination	22 (14.6)	12 (8.0)	.10
Escalation	10	2	
Week 11 through month 23.5	4	3	
Month 23.5 through month 48+	8	7	
Cellulitis	7 (4.6)	0 (0.0)	.01
Escalation	0		
Week 11 through month 23.5	3		
Month 23.5 through month 48+	4		
Urinary frequency	5 (3.3)	16 (10.7)	.01
Escalation	1	5	
Week 11 through month 23.5	3	5	
Month 23.5 through month 48+	1	6	
Hernia	1 (0.7)	12 (8.0)	.002
Escalation	0	1	
Week 11 through month 23.5	0	2	
Month 23.5 through month 48+	1	9	

*Edema includes peripheral edema, localized edema, generalized edema, facial edema, tongue edema, periorbital edema, and lymphedema.

Table 5. Mean Changes From Baseline to Month 48 in Unified Parkinson's Disease Rating Scale Scores (UPDRS)*

Scale Score	Pramipexole (n = 151)	Levodopa (n = 150)	Treatment Effect† (95% CI)	*P* Value
Total UPDRS	−3.2 (17.3)	2.0 (15.4)	−5.9 (−9.6, −2.1)	.003
Motor	−1.3 (13.3)	3.4 (12.3)	−4.9 (−7.8, −1.9)	.001
ADL	−1.7 (5.4)	−0.5 (4.7)	−1.4 (−2.5, −0.2)	.02
Mental	−0.3 (1.6)	−0.8 (1.6)	0.3 (−0.1, 0.7)	.10

Abbreviation: ADL, activities of daily living.
*Values are mean (SD). Negative values indicated worsening and positive values indicated improvement.
†Treatment effect is the difference in mean change between the groups (pramipexole, levodopa), adjusted for investigator effects and the baseline value of the outcome variable in an analysis of covariance model. All analyses are based on multiple imputation for missing values.

Those subjects randomized to pramipexole tended to experience somnolence earlier, more frequently, and more severely, as evidenced by the higher discontinuation rates and the greater time spent somnolent during the trial. The precise factors that predict somnolence, irresistible daytime sleepiness, and driving risk are not completely known, but this study suggests that pramipexole-treated subjects had a higher risk for somnolence than levodopa-treated subjects. This contrasts with a recent prospective evaluation of a large number of patients with Parkinson disease that found no relationship between daytime sleepiness and falling asleep at the wheel and any specific antiparkinsonian drug or class of drugs.[15] Patients who do experience generalized drowsiness and falling asleep during periods of inactivity, regardless of their antiparkinsonian medications, should be instructed not to drive or to partake in activities during which falling asleep would present a danger.

We found the frequency of pramipexole-associated edema to be higher than that previously reported.[16] The mechanism of dopamine agonist–induced edema is unknown, but it is reversible with cessation of therapy or reduction in dosage. Prior studies have shown that pramipexole-induced edema can affect function, and 6 patients assigned to pramipexole in this study withdrew early because of edema. More research is needed on the long-term impact of edema, particularly given the fact that 6 of the 7 patients who developed cellulitis in the pramipexole group also had a history of edema.

The levodopa group continued to have less impairment and disability, as measured by the UPDRS, than did the pramipexole group, and the group differences observed in the motor and activities of daily living components remained relatively uniform throughout the 4 years, with a parallel decay in UPDRS scores across time. It remains unclear why the UPDRS scores of subjects assigned to pramipexole never caught up despite the options of open-label levodopa and other antiparkinsonian therapies. A potential explanation is that the initial UPDRS response was deemed satisfactory by patients and physicians and was used as a benchmark to gauge further therapy.[2] Alternatively, the presence of a dopamine agonist may somehow attenuate the dopaminergic potency of levodopa possibly by competitive inhibition or down-regulation of postsynaptic nigrostriatal dopamine receptors.

The mean group difference in the UPDRS activities of daily living scores found in this study was similar to that published in a prior report in which it was concluded that there was no significant difference between the groups initially treated with ropinirole vs levodopa.[14] In the ropinirole study, there was no imputation of missing values, as there was in our study, and the resulting smaller sample sizes may have contributed to the reported lack of statistically significant group differences. In long-term clinical trials, the strategy of including all randomized subjects in an intent-to-treat analysis is accepted to be generally superior to the strategy of performing the analyses based only on subjects who complete the trial. This is particularly true for the present trial, in which the withdrawal rate by 48 months was close to 40% and the rates differed somewhat between the 2 treatment arms. Assuming that the strategy for imputing missing data is reasonable, bias should be reduced through preservation of the randomized groups, and power is increased by retaining all subjects in the analysis. To avoid artificially increasing power through data imputation, we used multiple imputation to account for the uncertainty associated with the imputation.[13]

We did not find significant differences in the quality-of-life scores between the 2 treatment groups during the 4 years of follow-up. Treatment group differences in the occurrence of dopaminergic complications and UPDRS

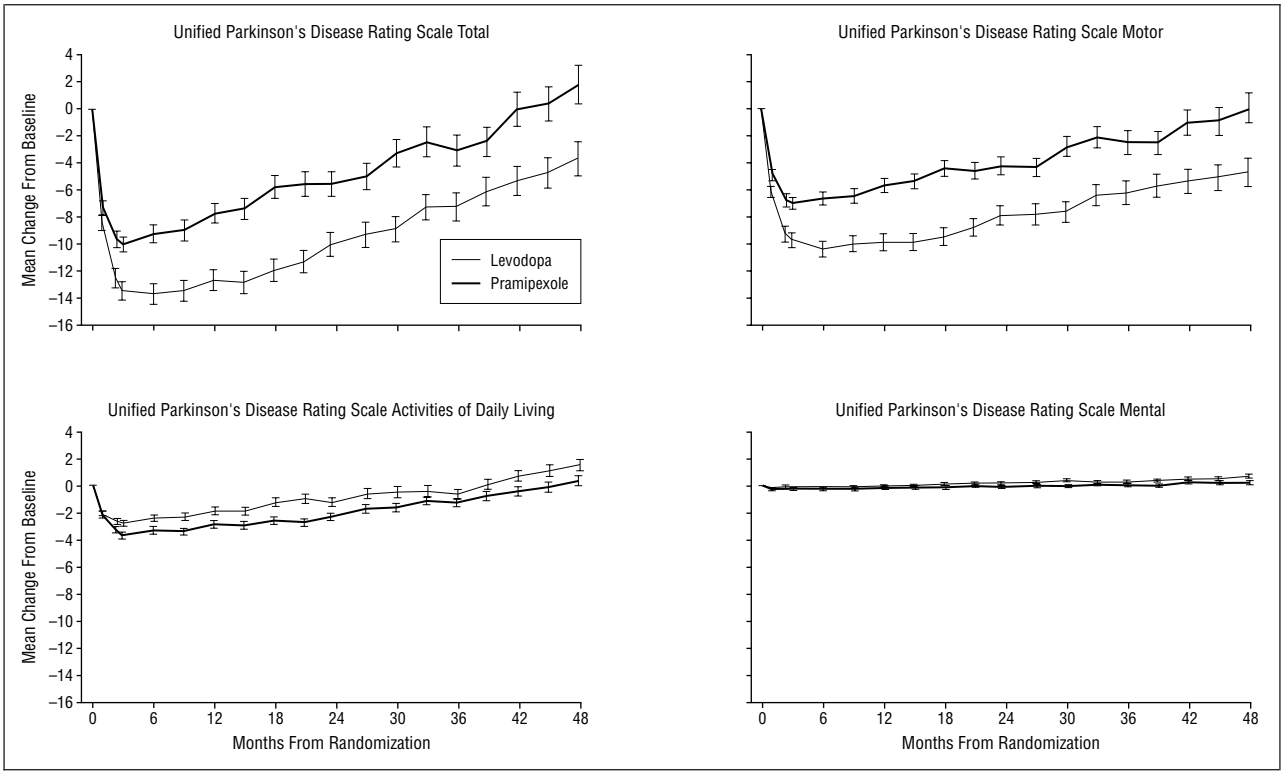

Figure 3. Mean (SE) total (parts I+II+III), motor, activities of daily living, and mental Unified Parkinson's Disease Rating Scale scores during the course of the trial by treatment assignment.

scores did not translate into mean group differences in either the disease-specific health status measure (PDQUALIF) or the generic-based preference measure (EuroQol VAS). We hypothesize that these measures were unable to differentiate between the mean group cumulative health effects for these treatment options, or the quality-of-life differences between the 2 options were inconsequential.

In a subset of this cohort (n=82), patients treated with pramipexole demonstrated a 40% lower rate of loss of striatal ^{123}I–β-CIT uptake, a marker of the dopamine transporter receptor, than those patients initially treated with levodopa during a month 46 evaluation period.[4] It is not yet known, however, if the reduction in the rate of dopamine transporter loss as measured by striatal ^{123}I– β-CIT uptake reflects better neuronal survivability or merely differential regulation of dopamine transporter receptors. No data have yet established a clinical advantage paralleling the biomarker advantage of pramipexole.

This study has several limitations. First, the conclusions to be drawn are limited to comparing the treatment strategies of initial pramipexole followed by open-label levodopa vs initial levodopa followed by open-label levodopa. We did not study the option of initial levodopa followed by a dopamine agonist, which may have mitigated the differences in dopaminergic events between the 2 treatment arms as well as the difference in UPDRS scores. Second, we do not report on the relative cost-effectiveness of pramipexole compared with that of levodopa, which is an important consideration given that pramipexole is substantially more costly than levodopa.[17] This will be the subject of a future report.

In conclusion, during the 4 years of the study, initial treatment with pramipexole resulted in lower incidences of dyskinesias and wearing off and in less relative reduction in striatal ^{123}I–β-CIT uptake compared with initial levodopa. On the other hand, initial treatment with levodopa resulted in lower incidences of freezing, somnolence, and edema, and provided for better symptomatic control, as measured by the UPDRS, compared with initial treatment with pramipexole. Both resulted in similar changes in quality of life. Pramipexole and levodopa are associated with different efficacy and adverse-effect profiles. These differences are insufficient to identify a preferred strategy; hence, both pramipexole and levodopa appear to be reasonable options as initial dopaminergic therapy in Parkinson disease. Long-term follow-up is needed to determine if either treatment strategy is superior to the other in terms of patient impairment, disability, or quality of life.

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Correction

Error in Figure. In Figure 3 of the article titled "Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease: A 4-Year Randomized Controlled Trial," published in the July issue of the ARCHIVES (2004;61:1044-1053), the lines indicating mean change in Unified Parkinson's Disease Rating Scale activities of daily living scores during pramipexole and levodopa treatments should be reversed. The top line should indicate pramipexole, and the bottom line should indicate levodopa.