# Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease

## A Randomized Controlled Trial

Parkinson Study Group

**Context** Pramipexole and levodopa both ameliorate the motor symptoms of early Parkinson disease (PD), but no controlled studies have compared long-term outcomes after initiating dopaminergic therapy with pramipexole vs levodopa.

**Objective** To compare the development of dopaminergic motor complications after initial treatment of early PD with pramipexole vs levodopa.

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

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

**Patients** Three hundred one patients with early PD who required dopaminergic therapy to treat emerging disability, enrolled between October 1996 and August 1997.

**Interventions** Subjects were randomly assigned to receive pramipexole, 0.5 mg 3 times per day, with levodopa placebo (n=151); or carbidopa/levodopa, 25/100 mg 3 times per day, with pramipexole placebo (n=150). For patients with residual disability, the dosage was escalated during the first 10 weeks. From week 11 to month 23.5, investigators were permitted to add open-label levodopa to treat continuing or emerging disability.

**Main Outcome Measures** Time to the first occurrence of any of 3 dopaminergic complications: wearing off, dyskinesias, or on-off motor fluctuations; changes in scores on the Unified Parkinson's Disease Rating Scale (UPDRS), assessed at baseline and follow-up evaluations; and, in a subgroup of 82 subjects evaluated at baseline and 23.5 months, ratio of specific to nondisplaceable striatal iodine 123 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane (β-CIT) uptake on single photon emission computed tomography imaging of the dopamine transporter.

**Results** Initial pramipexole treatment resulted in significantly less development of wearing off, dyskinesias, or on-off motor fluctuations (28%) compared with levodopa (51%) (hazard ratio, 0.45; 95% confidence interval [CI], 0.30-0.66; $P<.001$). The mean improvement in total UPDRS score from baseline to 23.5 months was greater in the levodopa group than in the pramipexole group (9.2 vs 4.5 points; $P<.001$). Somnolence was more common in pramipexole-treated patients than in levodopa-treated patients (32.4% vs 17.3%; $P=.003$), and the difference was seen during the escalation phase of treatment. In the subgroup study, patients treated initially with pramipexole (n=39) showed a mean (SD) decline of 20.0% (14.2%) in striatal β-CIT uptake compared with a 24.8% (14.4%) decline in subjects treated initially with levodopa (n=39; $P=.15$).

**Conclusions** Fewer patients receiving initial treatment for PD with pramipexole developed dopaminergic motor complications than with levodopa therapy. Despite supplementation with open-label levodopa in both groups, the levodopa-treated group had a greater improvement in total UPDRS compared with the pramipexole group.

*JAMA. 2000;284:1931-1938* www.jama.com

PARKINSON DISEASE (PD) IS A PROgressively disabling neurodegenerative disorder treated most commonly by dopamine replacement with the precursor levodopa, but agonists at dopamine-receptor sites have recently been proposed as initial therapy in early stages of the disease.[1] The rationale for initial dopamine agonist treatment derives from the belief that early levodopa exposure adversely affects the course of disease and leads to disabling dyskinesias and motor fluctuations (ie, dopaminergic complications).[2] These dopaminergic complications are likely a consequence of underlying nigrostriatal degeneration, elicited by exposure to dopaminergic treatments, including levodopa and dopamine agonists.

Two reports have shown a reduced incidence of dyskinesias by initiating treatment with dopamine agonists ropinirole or cabergoline compared with levodopa.[3,4] The ropinirole trial found no statistical differences in the occurrences of adverse events or in changes in the activities of daily living (ADL) between the 2 groups, despite absolute differences in favor of levodopa, leaving the relative benefits of these drugs in question.

Pramipexole is a nonergoline dopaminergic agonist[5] that has been shown to be safe and effective compared with

**See also p 1971 and Patient Page.**

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placebo in early PD,[6,7] but has not yet been compared with levodopa. Accordingly, members of the Parkinson Study Group (PSG), an independent academic consortium of investigators, conducted a multicenter randomized clinical trial comparing initial treatment of early PD with pramipexole vs levodopa. Given recent in vitro and animal data that have suggested that pramipexole may be neuroprotective for dopamine neurons, we also explored, in a subset of the subjects, the effects of these treatment strategies on dopamine transporter density, a marker of the dopaminergic neuron terminal, as measured by single photon emission computed tomography and iodine 123 [$^{123}$I] 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane (β-CIT).[8,9]

## METHODS

A report detailing the methods of this trial has been published.[10]

### Organization

This multicenter study was organized by the PSG in conjunction with the sponsor, Pharmacia Corp (Peapack, NJ; formerly Pharmacia & Upjohn Inc, Kalamazoo, Mich). Subjects were enrolled in the trial between October 1996 and August 1997 at 22 sites in the United States (17) and Canada (5). The study was reviewed and approved by the institutional review board at each of the participating sites, and all subjects gave written informed consent. An independent safety monitoring committee was responsible for unblinded monitoring of data concerning patient safety, with particular attention to patient death, serious adverse events, and adverse events resulting in subject withdrawal from the trial. There were no prespecified formal guidelines for recommending modification or termination of the trial, and any decision regarding early modification or termination would have been based on clinical judgment in light of the results of significance tests.

### Recruitment, Randomization, and Enrollment

Eligible subjects were adults aged 30 years or older who had idiopathic PD for fewer than 7 years and who 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, a scale that classifies PD into 5 clinical stages ranging from mild unilateral (stage I) to severe, bed-bound illness (stage V).[11] Subjects were excluded if they had (1) history of a previous dopaminergic complication, (2) atypical parkinsonian syndromes, (3) serious concurrent illness, (4) treatment with methylphenidate, cinnarizine, reserpine, amphetamine, or monoamine oxidase type A inhibitors in the past 3 months, (5) treatment with pramipexole in the past 4 months, (6) treatment with neuroleptics, metoclopramide, alphamethyldopa, or flunarizine in the past 6 months, or (7) an unstable dosage of selegiline, amantadine, anticholinergic therapy, or other central nervous system active therapies (eg, hypnotics, antidepressants, anxiolytics) in the past 2 months.

Eligible patients were randomized 1:1 to pramipexole or levodopa, in combination with carbidopa, using a computer-generated randomization plan that included stratification by investigator and blocking. A programmer at the Pharmacia Corp generated a list of the subject identification numbers and corresponding treatment assignments. The subject identification numbers were sent to the PSG Biostatistics Center (Rochester, NY) and incorporated in a computer interactive randomization module at the PSG Coordination Center (Rochester, NY). Access to the randomization code was restricted to 2 programmers, 1 at the Pharmacia Corp and the other at the PSG Biostatistics Center. When a patient was judged eligible and consented to be enrolled, a telephone call was made to the Coordination Center, which provided a unique subject identification number from the randomization module.

### Study Intervention

Pramipexole was taken as 0.25-mg, 0.5-mg, or 1.0-mg tablets or matching placebo tablets, 3 times daily, 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 3 times a day. Treatment assignments included active drug for one treatment and placebo for the other.

Subjects entered a 10-week dosage escalation period followed by a 21-month maintenance period. All subjects were escalated initially to a daily dosage of 1.5-mg pramipexole or 75/300-mg carbidopa/levodopa (level 1 dosage). Subjects requiring additional therapy could escalate to 3.0-mg pramipexole or 112.5/450-mg carbidopa/levodopa (level 2 dosage), or 4.5-mg pramipexole or 150/600-mg carbidopa/levodopa (level 3 dosage). Therefore, all patients entered into the maintenance phase (week 11) of the trial on level 1, 2, or 3 dosing. The pramipexole dosages were determined from a previous dosage-ranging tolerability study in patients with early PD.[6] Levodopa and pramipexole dosages were chosen as those commonly used in clinical practice and judged to be near equivalent.

Throughout the maintenance period (week 11 through month 23.5), subjects maintained on study dosage level achieved in the escalation phase. Subjects with emerging disability were prescribed open-label carbidopa/levodopa as needed.[12] Sustained-release carbidopa/levodopa preparations were not permitted.

### Outcome Variables

Subjects were randomly assigned to the intervention groups at the baseline visit and were evaluated at 4 and 10 weeks, and at 3, 6, 9, 12, 15, 18, 21, and 23.5 months. 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.

Dyskinesias were defined as an abnormal involuntary movement that includes chorea, dystonia, myoclonus, or tics that could be either peak dose or end of dose. Dyskinesias did not include early

morning dystonia or other "off" dystonias. Wearing-off was defined as a perception of loss of mobility or dexterity, usually taking place gradually over minutes and usually bearing close relationship to the timing of antiparkinsonian medications. On-off effects were defined as an unpredictable and generally sudden (seconds to minutes) shift between "on" (mobility) and "off" (immobility) not apparently related to the timing of antiparkinsonian medications.[10] One blinded investigator at each site made the judgment as to the occurrence of a dopaminergic complication. Subjects reaching the primary end point continued to be followed up throughout the 23.5 months of the trial.

Secondary outcome variables included changes in scores on the Unified Parkinson's Disease Rating Scale (UPDRS),[13] the Parkinson's Disease Quality of Life scale (PDQUALIF),[14] the EuroQol,[15] and the need for supplemental carbidopa/levodopa. Measures of safety included the frequency and severity of individual adverse experiences. The UPDRS is a standardized, reliable, and valid instrument for assessing the severity of the clinical features of PD.[16] The PDQUALIF and EuroQol are disease-specific and generic quality-of-life instruments, respectively. The PDQUALIF consists of 32 items and is scored on a 100-point scale including 7 domains: social/role function, self-image/sexuality, sleep, outlook, physical function, independence, and urinary function.

### Single Photon Emission Computed Tomography and β-CIT Substudy

A subset of subjects (n=82) were enrolled from 17 of the 22 participating study sites to undergo single photon emission computed tomography imaging with [$^{123}$I] β-CIT using methods reported previously.[17] The imaging outcome measure was the ratio of specific to nondisplaceable striatal [$^{123}$I] β-CIT uptake. Subjects were imaged before the baseline visit and just before the final 23.5-month visit. All imaging evaluations took place at Yale University (New Haven, Conn).

### Sample Size

The planned sample size of 300 subjects (150 per treatment group) was chosen to provide 94% power to detect a 20% difference (70% vs 50%; hazard ratio [HR], 0.57) and 77% power to detect a 15% difference (70% vs 55%; HR, 0.66) in the proportions of subjects reaching the primary end point between the treatment groups. The assumptions underlying these calculations are detailed elsewhere.[10]

### Statistical Analysis Plan

The primary statistical analyses were performed by intention-to-treat.[18] All statistical tests were 2-tailed and were 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 stratified by the enrolling investigator. The HR and 95% confidence interval (CI) comparing the 2 treatment groups were determined from this model. The assumption of proportionality of hazards was examined with the use of time-dependent covariates.[19] Separate analyses of the time from baseline to the first occurrence of individual dopaminergic complications and the need for supplemental levodopa were performed. The cumulative probabilities of reaching the primary outcome and other end points were estimated using Kaplan-Meier curves.

Mean changes in the total UPDRS score, as well as the mental, motor, and ADL UPDRS scores, between randomization and 23.5 months were compared among the treatment groups using analysis of covariance, with treatment group, enrolling investigator, and the baseline UPDRS score included in the model. A 95% CI 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 also were used to examine change scores in the quality-of-life measures. Interactions between treatment and enrolling investigator were tested but not found. Two-tailed Fisher exact tests were used to compare proportions of subjects experiencing adverse events between the 2 groups. Changes in [$^{123}$I] β-CIT uptake (striatum, caudate, and putamen) were expressed as percentage changes from baseline, and means were compared between the 2 groups using *t* tests.

For the analyses of continuous efficacy variables, if a subject was missing a response at a particular visit, the last available observation for that subject was carried forward and imputed for that visit. To determine the impact of dropouts on the results, the analyses were repeated including only subjects who had complete data for the response variable of interest. The results of the latter analyses did not differ materially from the analyses of the imputed data and hence are not reported here.

## RESULTS

### Patients Enrolled

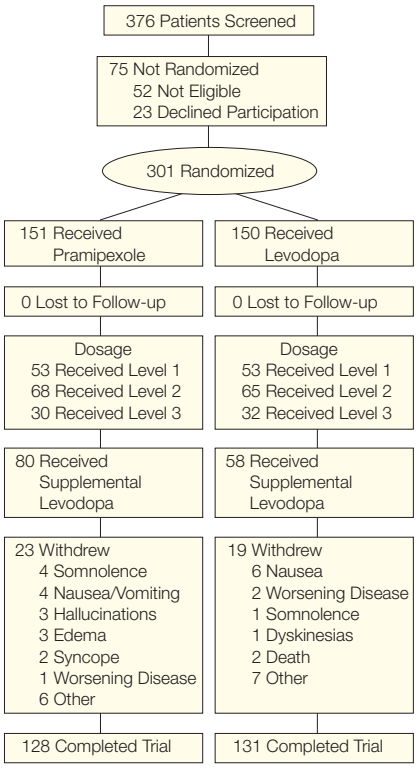
Of the 376 patients who were identified as potential participants, 52 were found to be ineligible and 23 declined for no specific reason (FIGURE 1). The remaining 301 patients were randomized in the study, 82 of whom also enrolled in the [$^{123}$I] β-CIT substudy. No patients were lost to follow-up. Twenty-three subjects in the pramipexole group (15.1%) withdrew prior to the planned 23.5 months of follow-up compared with 19 subjects in the levodopa group (12.7%). In the pramipexole group, 4 withdrew due to somnolence and nausea/vomiting, and 3 due to hallucinations and edema. Six subjects in the levodopa group withdrew due to nausea. Two deaths occurred in the levodopa-treated group and neither were judged to be related to the study drug.

The 2 treatment groups were similar at baseline with regard to demographic and clinical variables and the baseline characteristics for the 82 subjects enrolled in the [$^{123}$I] β-CIT substudy cohort were similar to those for the entire study cohort (TABLE 1).

### Pramipexole and Levodopa Use

The numbers of subjects at each dosage level were nearly identical in the 2 treatment groups (Figure 1). Subjects allocated to pramipexole took an average of 2.78 mg/d by the end of the trial. Subjects allocated to levodopa took an average of 406 mg/d of levodopa as experimental therapy. Fifty-three percent of subjects in the pramipexole group required supplemental levodopa compared with 39% in the levodopa group (HR, 1.54; 95% CI, 1.09-2.17; $P=.02$). At the end of the trial, subjects in the pramipexole group who required supplemental levodopa (n=80) were taking a mean (SD) of 264 (245) mg/d of supplemental levodopa compared with 252 (245) mg/d for subjects in the levodopa group requiring supplementation (n=58). Subjects in the levodopa group thus took an average total daily dosage of 509 mg of levodopa (experimental plus supplemental).

**Figure 1.** Patient Flow Chart




For explanation of dosage levels, see the "Study Intervention" section.

### Dopaminergic End Points

TABLE 2 shows that 28% of subjects assigned to pramipexole treatment reached the primary end point by 23.5 months compared with 51% in the levodopa group (HR, 0.45; 95% CI, 0.30-0.66; $P<.001$). The reduced risk was observed in each of the four 6-month study periods (0-6 month HR, 0.46; 6-12 month HR, 0.27; 12-18 month HR,

**Table 1.** Baseline Characteristics*

| Variable | Main Trial | | β-CIT Substudy | |
|---|---|---|---|---|
| | Pramipexole (n = 151) | Levodopa (n = 150) | Pramipexole (n = 42) | Levodopa (n = 40) |
| Age, y | 61.5 (10.1) | 60.9 (10.5) | 61.9 (10.8) | 60.1 (11.1) |
| No. (%) of male patients | 96 (63.6) | 99 (66.0) | 27 (65.9) | 24 (58.5) |
| No. (%) of white patients | 144 (95.4) | 143 (95.3) | 39 (92.7) | 38 (95.1) |
| Years since diagnosis | 1.5 (1.4) | 1.8 (1.7) | 1.3 (1.4) | 1.6 (1.9) |
| No. (%) of patients with prior levodopa use | 40 (26.5) | 30 (20.0) | 11 (26.2) | 11 (27.5) |
| No. (%) of patients with selegiline use | 50 (33.1) | 56 (37.3) | 19 (45.2) | 14 (35.0) |
| No. (%) of patients with amantandine use | 31 (20.5) | 34 (22.7) | 6 (14.3) | 8 (20.0) |
| No. (%) of patients with anticholinergic use | 7 (4.6) | 12 (8.0) | 2 (4.8) | 2 (5.0) |
| Unified Parkinson's Disease Rating Scale | | | | |
| Mental | 1.3 (1.3) | 0.9 (1.1) | 1.5 (1.6) | 0.9 (1.1) |
| Activities of daily living | 9.1 (4.1) | 8.3 (4.0) | 9.9 (4.2) | 8.3 (4.0) |
| Motor | 22.3 (9.2) | 22.0 (9.6) | 23.2 (9.7) | 21.5 (8.8) |
| Total | 32.5 (12.7) | 31.1 (12.8) | 34.6 (13.1) | 30.6 (11.4) |
| No. (%) of patients in Hoehn and Yahr Stage | | | | |
| 1.0 | 27 (17.9) | 33 (22.0) | 1 (2.4) | 7 (17.1) |
| 1.5 | 23 (15.2) | 17 (11.3) | 4 (9.8) | 4 (9.8) |
| 2.0 | 75 (49.7) | 78 (52.0) | 25 (58.5) | 20 (48.8) |
| 2.5 | 21 (13.9) | 13 (8.7) | 10 (24.4) | 4 (9.8) |
| 3.0 | 5 (3.3) | 9 (6.0) | 2 (4.9) | 5 (12.2) |
| Mini-Mental State Examination | 29.2 (1.4) | 29.3 (1.1) | 29.3 (1.2) | 29.2 (1.2) |
| Parkinson's Disease Quality of Life Scale | 30.5 (10.7) | 28.1 (10.4) | 31.3 (10.3) | 28.4 (9.2) |
| EuroQol visual analog scale | 75.1 (15.6) | 77.6 (12.0) | 75.6 (15.2) | 79.5 (11.5) |
| Striatal β-CIT uptake | NA | NA | 3.8 (1.0) | 3.6 (0.8) |
| Caudate β-CIT uptake | NA | NA | 4.3 (1.1) | 4.2 (1.0) |
| Putamen β-CIT uptake | NA | NA | 3.3 (1.0) | 3.1 (0.7) |

*Values are expressed as mean (SD) unless otherwise indicated. CIT indicates carboxymethoxy-3-β-(4-iodophenyl) tropane; NA, not applicable. The scale ranges are as follows for the Mini-Mental State Examination, 0-30; Parkinson's Disease Quality of Life Scale, 0-100; and EuroQol visual analog scale, 0-100.

**Table 2.** Treatment Effects on Dopaminergic End Points*

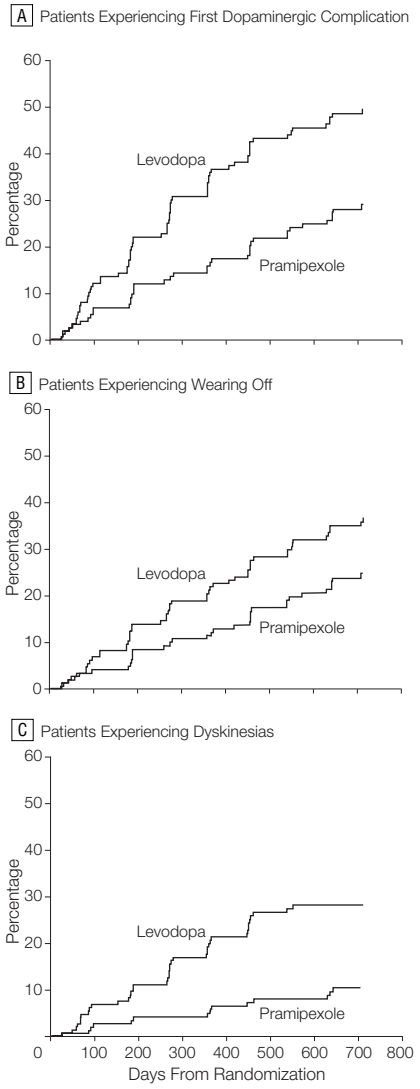
| End Points | No. (%) | | HR (95% CI)† | *P* Value |
|---|---|---|---|---|
| | Pramipexole (n = 151) | Levodopa (n = 150) | | |
| First dopaminergic complications‡ | 42 (27.8) | 76 (50.7) | 0.45 (0.30-0.66) | <.001 |
| Wearing off | 36 (23.8) | 57 (38.0) | 0.57 (0.37-0.88) | .01 |
| Dyskinesias | 15 (9.9) | 46 (30.7) | 0.33 (0.18-0.60) | <.001 |
| On-off fluctuations | 2 (1.3) | 8 (5.3) | 0.27 (0.06-1.32) | .11 |

*All analyses are stratified by enrolling investigator.
†HR indicates hazard ratio; CI, confidence interval. The HR 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 first occurrence of wearing off, dyskinesia, or on-off fluctuations.

0.56; 18-24 month HR, 0.65) and for specific dopaminergic complications of wearing off and dyskinesias (Table 2; FIGURE 2).

TABLE 3 shows treatment effects on dopaminergic end points vs timing of supplemental levodopa. The absolute numbers of end points were larger in the levodopa group. Most of the end points occurred after the use of supplemental levodopa, but in similar proportions between the treatment groups.

**Figure 2.** Percentages of Patients Experiencing Dopaminergic Complications




First dopaminergic complication is defined as the first occurrence of wearing off, dyskinesias, or on-off fluctuations.

Of the 5 subjects taking pramipexole who developed dyskinesias before the supplemental levodopa, 4 had no prior levodopa exposure.

### Unified Parkinson's Disease Rating Scale

The mean improvement in total, motor, and ADL UPDRS scores from baseline to 23.5 months was greater in the levodopa group compared with the pramipexole group (TABLE 4). The levodopa group improved significantly from baseline to each follow-up visit relative to the pramipexole group ($P \leq .002$) in mean total, motor, and ADL UPDRS scores (FIGURE 3).

### Quality-of-Life Outcomes

Quality-of-life scores improved in both groups initially and then declined over time (FIGURE 4). At 23.5 months (102 weeks), the mean change scores were significantly different ($P = .006$) for the PDQUALIF with the scores higher (ie, better) for those in the levodopa group. Mean change scores did not differ among the groups at other time points. Analyses of the 7 PDQUALIF subscales revealed significant differences at 23.5 months for 2 subscales in favor of the levodopa group: sleep ($P = .004$) and self-image/sexuality ($P = .02$). Quality-of-life scores on the EuroQol scale showed a similar divergence between the 2 groups at the 23.5-month visit ($P = .06$; Figure 4).

### Adverse Events

Significantly more patients in the pramipexole group experienced somnolence ($P = .003$), hallucinations ($P = .03$), and both generalized ($P = .01$) and peripheral edema ($P = .002$) compared with those in the levodopa group (TABLE 5). Of note, the differences in somnolence and hallucinations between the 2 groups emerged during the

**Table 3.** Treatment Effects on Dopaminergic End Points vs Timing of Supplemental Levodopa

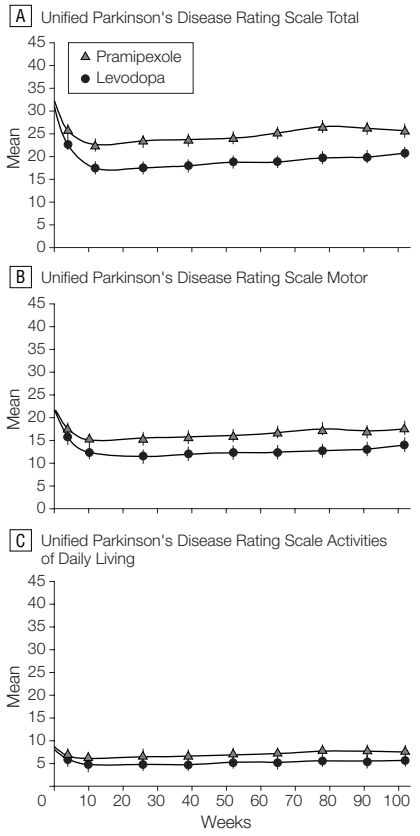
| End Point | Pramipexole (n = 151) | Levodopa (n = 150) |
|---|---|---|
| First dopaminergic complication | | |
| Total receiving open-label levodopa | 42 | 76 |
| Before open-label levodopa | 13 | 24 |
| After open-label levodopa | 29 | 52 |
| Wearing off | | |
| Total receiving open-label levodopa | 36 | 57 |
| Before open-label levodopa | 11 | 22 |
| After open-label levodopa | 25 | 35 |
| Dyskinesias | | |
| Total receiving open-label levodopa | 15 | 45 |
| Before open-label levodopa | 5 | 7 |
| After open-label levopoda | 10 | 38 |
| On-off fluctuations | | |
| Total receiving open-label levodopa | 2 | 7 |
| Before open-label levodopa | 0 | 2 |
| After open-label levodopa | 2 | 5 |

**Table 4.** Mean Changes From Baseline to Month 23.5 in Unified Parkinson's Disease Rating Scale (UPDRS) Scores*

| Variable | Pramipexole (n = 151) | Levodopa (n = 150) | Difference in Treatments (95% CI)† | *P* Value |
|---|---|---|---|---|
| Total UPDRS | 4.5 (12.7) | 9.2 (10.8) | –5.0 (–7.6 to –2.4) | <.001 |
| Motor | 3.4 (8.6) | 7.3 (8.6) | –3.9 (–5.7 to –2.1) | <.001 |
| ADL | 1.1 (4.5) | 2.2 (3.2) | –1.4 (–2.2 to –0.5) | .001 |
| Mental | 0.0 (1.6) | –0.2 (1.2) | 0.1 (–0.2 to 0.3) | .72 |

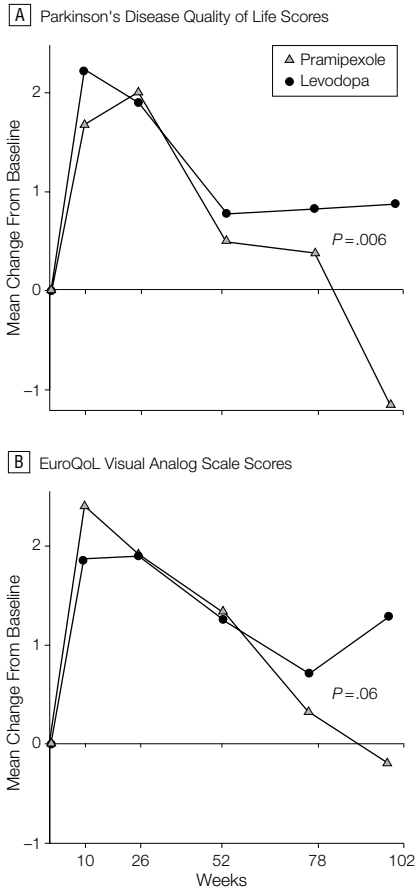
*Values are expressed as mean (SD). Positive values indicate improvement. ADL indicates activities of daily living.
†Difference in treatment is the difference in mean change between the groups (pramipexole minus levodopa) and is adjusted for investigator effects and the baseline value of the outcome variable in an analysis of covariance model.

**Figure 3.** Unified Parkinson's Disease Rating Scale




Scores are expressed as mean (SE). In each case, a lower score indicates less severe features of the disease. Scores were calculated over the course of the trial by treatment assignment. Significant differences ($P \leq .002$) were evident between the pramipexole and levodopa groups at week 10 and at all subsequent visits.

**Figure 4.** Mean Changes in Quality-of-Life Scores Over the Course of the Trial




Quality-of-life scores improved by approximately 2 units during the first 6 months of the trial. At the end of the trial (23.5 months), the group difference in the mean change was statistically significant ($P = .006$) for the Parkinson's Disease Quality of Life Scale and marginally significant for the EuroQol ($P = .06$), with the scores higher for those in the levodopa group. Differences in mean changes were not significant at any other time points.

escalation phase of the trial, whereas the differences for edema emerged during the maintenance phase of the trial.

Three subjects reported falling asleep while driving, 2 of whom had been randomized to pramipexole and 1 to levodopa. None were taking open-label levodopa. These events occurred while the subjects were receiving the level 2 dosing schedule at 2, 5, and 12 months after randomization. Two of these events resulted in motor vehicle crashes, one in a subject randomized to levodopa and the other in a subject randomized to pramipexole. Two additional subjects complained of "abrupt" or "sudden onset" drowsiness unrelated to driving, both were allocated to pramipexole and receiving level 3 dosing.

### Single Photon Emission Computed Tomography and β-CIT Substudy

In the β-CIT substudy, 39 of the 40 subjects in the levodopa group and 39 of the 42 subjects in the pramipexole group had a follow-up β-CIT scan. The mean [$^{123}$I] β-CIT uptake in the striatum, caudate, and putamen at baseline was well below the uptake values reported for healthy subjects (Table 1).[17] The mean (SD) decline in β-CIT striatal uptake over the 23.5 months did not iffer between the 2 treatment groups and was 20.0% (14.2%) in the pramipexole group compared with 24.8% (14.4%) in the levodopa group ($P = .15$; FIGURE 5). Caudate and putamen-specific β-CIT uptake during the 23.5-month observation period also did not differ between the 2 treatment groups.

## COMMENT

Our findings demonstrate that pramipexole, as initial therapy in patients with early PD, reduced the risk of developing prespecified dopaminergic motor complications by 55% compared with initiating therapy with levodopa over a 2-year period. The absolute risk reduction of 23% suggests that one would need to treat 4 to 5 patients with pramipexole instead of levodopa over a 2-year period to prevent 1 additional dopaminergic complication from occurring.

Both pramipexole and levodopa improved parkinsonian features, as measured by the UPDRS, but pramipexole was not as potent as levodopa in improving these features. The UPDRS scores remained worse in the pramipexole group despite the use of open-label levodopa for treating emerging or continuing disability. Since the maximum benefit was seen during the 10-week escalation phase, research subjects and investigators may have developed a clinical sense of a satisfactory response and used this as a benchmark for measuring the adequacy of subsequent treatment; that is, investigators added or adjusted supplemental levodopa to maintain function rather than to improve it. The findings also suggest that although UPDRS scores are not improved as much with pramipexole as with levodopa, the subjects treated with pramipexole and the blinded investigators judged their illness to be satisfactorily treated.

There are several potential explanations for why initial pramipexole treatment reduced the risk of developing wearing off and dyskinesias compared with initial levodopa treatment. First, the longer half-life of pramipexole com-

**Table 5.** Adverse Events by Treatment Group and Study Phase

| | Total Cohort, No. (%) | | Escalation Phase, No. (%) | | Maintenance Phase, No. (%)* | |
|---|---|---|---|---|---|---|
| | Pramipexole (n = 151) | Levodopa (n = 150) | Pramipexole (n = 151) | Levodopa (n = 150) | Pramipexole (n = 142) | Levodopa (n = 144) |
| Somnolence | 49 (32.4) | 26 (17.3)† | 35 (23.2) | 13 (8.7)† | 14 (9.9) | 13 (9.0) |
| Hallucination | 14 (9.3) | 5 (3.3)‡ | 10 (6.6) | 2 (1.3)‡ | 4 (2.8) | 3 (2.1) |
| Generalized edema | 27 (17.9) | 12 (8.0)‡ | 3 (2.0) | 3 (2.0) | 24 (16.9) | 9 (6.3)† |
| Peripheral edema | 22 (14.6) | 6 (4.0)† | 7 (4.6) | 2 (1.3) | 15 (10.6) | 4 (2.8)† |
| Nausea | 55 (36.4) | 55 (36.7) | 45 (29.8) | 42 (28.0) | 10 (7.0) | 13 (9.0) |
| Dizziness | 39 (25.8) | 36 (24.0) | 21 (13.9) | 18 (12.0) | 18 (12.6) | 18 (12.5) |
| Insomnia | 39 (25.8) | 33 (22.0) | 20 (13.3) | 14 (9.3) | 19 (13.4) | 18 (12.5) |
| Headache | 31 (20.5) | 23 (15.3) | 18 (11.9) | 15 (10.0) | 13 (9.1) | 8 (5.6) |
| Constipation | 31 (20.5) | 19 (12.7) | 24 (15.9) | 6 (4.0)† | 7 (4.9) | 12 (8.3) |
| Depression | 23 (15.2) | 20 (13.3) | 3 (2.0) | 9 (6.0) | 20 (14.0) | 11 (7.6) |
| Abnormal dreams | 21 (13.9) | 19 (12.7) | 3 (1.9) | 1 (0.7) | 2 (1.4) | 1 (0.7) |
| Anxiety | 17 (11.3) | 10 (6.7) | 7 (4.6) | 3 (2.0) | 10 (7.0) | 7 (4.9) |
| Postural hypotension | 9 (6.0) | 15 (10) | 4 (2.7) | 7 (4.7) | 5 (3.5) | 8 (5.6) |

*Refers only to patients entering maintenance.
†$P<.01$ for comparison of pramipexole with levodopa.
‡$P<.05$ for comparison of pramipexole with levodopa.

pared with levodopa (8 to 12 hours vs 1.5 to 2 hours) may reduce the pulsatile stimulation of the striatal dopamine receptors thought to be important in the development of dyskinesias and wearing off.[20] Second, pramipexole and levodopa dosing may not have been equivalent and the observed differences may in part be due to differences in dopaminergic potency between the 2 groups. Finally, a neuroprotective effect of pramipexole, if present, could also reduce the development of dopaminergic complications by preventing the loss of dopamine neurons, although a significant effect in [$^{123}$I] β-CIT uptake was not seen in this study.

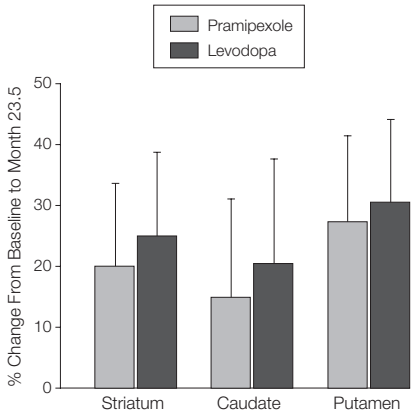
We did not detect significant differences in the quality-of-life scores between the 2 treatment groups during the first 78 weeks of the trial, indicating an initial equal satisfaction with both treatment options. We did detect a significant group difference in the PDQUALIF total score, however, at the end of the trial in favor of levodopa. It is difficult to judge the clinical significance of this difference, which occurred primarily in the sleep subscale of the instrument. A similar trend was seen in the visual analog component of the EuroQol. Although generic and disease-specific quality-of-life scales correlate with disease severity in patients with PD,[21] the responsiveness of these quality-of-life scales to a clinically meaningful change in function and quality of life remains unclear.

Pramipexole use was associated with a greater likelihood of somnolence, hallucinations, and edema. The differences in somnolence and hallucinations almost exclusively occurred when subjects started experimental therapy during the escalation phase of the trial. Risk factors for these adverse effects are not known, but they may be of particular concern for the elderly, those with preexisting sleep disorders, or those receiving multiple concomitant medications.[22]

This study is the first, to our knowledge, to assess the rate of change in striatal [$^{123}$I] β-CIT uptake in a relatively large cohort of patients with early PD over a 2-year period of observation. The rate of decline in β-CIT uptake was similar to that found in smaller PD samples[8] and was less in the pramipexole group than in the levodopa group, but the group difference at 2 years was not significant. We will continue to follow up this cohort to observe the course of neuroimaging outcomes in the next 2 years.

Our findings extend the observations found in the randomized, double-blind trials that compared initial treatment with ropinirole vs levodopa[3] and cabergoline vs levodopa[4] in early PD. The 268 patients in the ropinirole trial were slightly older than our cohort (63 vs 61 years), but had similar UPDRS scores at baseline and were followed up for 5 years. The data in our trial are similar to the data found in the ropinirole trial in terms of dopaminergic and UPDRS outcomes. However, in the ropinirole trial, only 2 comparisons were reported to be statistically significant: occurrences of dyskinesia and mean changes in motor UPDRS scores. The ropinirole trial also showed similar pro-

**Figure 5.** Percentage Reduction in β-CIT Uptake From Baseline to 23.5 Months




Error bars indicate SDs.

portional increases in the occurrence of somnolence (27.4% vs 19.1%) and hallucinations (17.3% vs 5.6%) in the ropinirole-treated subjects.

Our trial revealed significant group differences in the occurrences of wearing off and dyskinesias in favor of pramipexole and in the occurrences of somnolence and hallucinations in favor of levodopa. In addition, our trial revealed significant group differences in the mean change in the ADL component of the UPDRS. The smaller sample size (n=268) and unbalanced allocation ratio (2:1) in the ropinirole trial may have contributed to the differences in statistically significant results seen between the 2 studies despite the similarities in the magnitudes of the group differences.

These studies leave several questions unanswered. Does the trade off between motor complications and efficacy as measured by the UPDRS favor levodopa over agonists? What are the implications of the increased rates of somnolence and hallucinations with agonist treatment? Further study should help address these questions. Until longer-term data are available, the decision to initiate treatment of early PD with pramipexole or levodopa should be made only after considering the favorable dopaminergic motor complication profile associated with pramipexole against the more potent antiparkinsonian effects associated with levodopa.

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**Financial Disclosure:** In keeping with the Parkinson Study Group conflict of interest guidelines, none of the investigators have any personal financial relationship with the sponsor. All compensation received by investigators for trial-related services was paid through a contract between the University of Rochester and the sponsor that was established before the trial began.

**Funding/Support:** This work was supported primarily by the Pharmacia Corp. Support was also provided by the National Parkinson Foundation Center of Excellence to the Parkinson Study Group, and by the National Institutes of Health for Clinical Research Center grants RR00044 and RR01066 to the University of Rochester and Massachusetts General Hospital, respectively.

**Acknowledgment:** We thank the patients and their families who participated in this study. We also thank the Safety Monitoring Committee: W. Jackson Hall, PhD, Pierre Tariot, MD, chair, University of Rochester, Rochester, NY; Carl M. Leventhal, MD, Rockville, Md; Stephen Reich, MD, Johns Hopkins, Baltimore, Md. Contributions from the following individuals of the Pharmacia Corp are gratefully acknowledged: Leona Borchert MD, MPH, Mark Corrigan, MD, Baltazar Gomez-Mancilla, MD, Bruno Musch MD, Rhonda Ragual, MS, Clayton Rowland, PhD, Gene Wright, PhD, Kalamazoo, Mich.

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