ORIGINAL ARTICLE

Levodopa and the Progression of Parkinson's Disease

The Parkinson Study Group*

ABSTRACT

BACKGROUND

Despite the known benefit of levodopa in reducing the symptoms of Parkinson's disease, concern has been expressed that its use might hasten neurodegeneration. This study assessed the effect of levodopa on the rate of progression of Parkinson's disease.

METHODS

In this randomized, double-blind, placebo-controlled trial, we evaluated 361 patients with early Parkinson's disease who were assigned to receive carbidopa–levodopa at a daily dose of 37.5 and 150 mg, 75 and 300 mg, or 150 and 600 mg, respectively, or a matching placebo for a period of 40 weeks, and then to undergo withdrawal of treatment for 2 weeks. The primary outcome was a change in scores on the Unified Parkinson's Disease Rating Scale (UPDRS) between baseline and 42 weeks. Neuroimaging studies of 142 subjects were performed at baseline and at week 40 to assess striatal dopamine-transporter density with the use of iodine-123–labeled 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane ([^{123}I]β-CIT) uptake.

RESULTS

The severity of parkinsonism increased more in the placebo group than in all the groups receiving levodopa: the mean difference between the total score on the UPDRS at baseline and at 42 weeks was 7.8 units in the placebo group, 1.9 units in the group receiving levodopa at a dose of 150 mg daily, 1.9 in those receiving 300 mg daily, and −1.4 in those receiving 600 mg daily ($P<0.001$). In contrast, in a substudy of 116 patients the mean percent decline in the [^{123}I]β-CIT uptake was significantly greater with levodopa than placebo (−6 percent among those receiving levodopa at 150 mg daily, −4 percent in those receiving it at 300 mg daily, and −7.2 percent among those receiving it at 600 mg daily, as compared with −1.4 percent among those receiving placebo; 19 patients with no dopaminergic deficits on the baseline scans were excluded from the analysis) ($P=0.036$). The subjects receiving the highest dose of levodopa had significantly more dyskinesia, hypertonia, infection, headache, and nausea than those receiving placebo.

CONCLUSIONS

The clinical data suggest that levodopa either slows the progression of Parkinson's disease or has a prolonged effect on the symptoms of the disease. In contrast, the neuroimaging data suggest either that levodopa accelerates the loss of nigrostriatal dopamine nerve terminals or that its pharmacologic effects modify the dopamine transporter. The potential long-term effects of levodopa on Parkinson's disease remain uncertain.

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PARKINSON'S DISEASE IS A PROGRESSIVELY disabling neurodegenerative disorder that is manifested clinically by bradykinesia, tremor, rigidity, flexed posture, postural instability, and freezing of gait. It is characterized pathologically by the loss of pigmented dopaminergic neurons in the substantia nigra. The course of the clinical decline parallels that of the progressive degeneration of the remaining dopaminergic neurons.[1] The use of levodopa as dopamine-replacement therapy is highly effective in ameliorating the symptoms of the disease and remains the standard drug with which other therapies are compared.[2,3]

Because levodopa and dopamine can generate reactive oxygen species and induce the degeneration of cultured dopamine neurons, concern has been raised that levodopa could enhance oxidative stress and hasten the degeneration of residual dopamine neurons in patients with Parkinson's disease.[4-6] However, levodopa is not toxic in animals and may be trophic and promote the functional recovery of damaged nigral neurons.[7-10] Humans without Parkinson's disease who are exposed to levodopa do not develop nigral damage,[11,12] but such persons do not have increased oxidative stress in their substantia nigra neurons.

Whether levodopa is detrimental, beneficial, or without effect on the rate of the progression of Parkinson's disease is unknown and extremely important, both scientifically and clinically. We therefore conducted a controlled clinical trial to assess the effect of levodopa on the course of Parkinson's disease.

METHODS

STUDY DESIGN

Our multicenter, placebo-controlled, randomized, dose-ranging, double-blind clinical trial, called the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study, was conceived, organized, and implemented by the Parkinson Study Group and sponsored by the National Institute of Neurological Disorders and Stroke. The Department of Defense sponsored the single-photon-emission computed-tomography (SPECT) substudy. The subjects were enrolled between September 1998 and August 2001 at 33 sites in the United States and 5 sites in Canada. The study was approved by the institutional review boards at the participating sites, and all subjects gave written informed consent. An independent safety monitoring committee monitored the data, subjects' safety, and the tolerability of the study drug. There was no prespecified formal guideline for recommending either modification or termination of the trial.

SUBJECTS

The subjects were 30 years of age or older, had received a diagnosis of Parkinson's disease within the past two years, had a rating on the modified Hoehn–Yahr scale[13,14] of less than stage 3 (with stage 1 indicating unilateral disease, stage 2 mild bilateral disease, and stage 3 more advanced bilateral disease), and were considered not likely to require therapy for symptoms of the disease within the nine months after enrollment in the study. Patients were excluded if they were receiving antiparkinson medication, had been exposed to levodopa or to any dopamine agonist for more than 14 days, had an identifiable cause of parkinsonism, or had a tremor in any limb that was given a score of 3 or more on the Unified Parkinson's Disease Rating Scale (UPDRS),[14] freezing of gait, loss of postural reflexes, major depression, or dementia.

Potential subjects were informed that only the assigned study drug would be permitted during the nine months of the study and that if they needed additional antiparkinson medication during this period, they would have to withdraw from the study. Subjects were randomly assigned to receive placebo or carbidopa–levodopa at a dose of 12.5 and 50 mg three times daily, 25 and 100 mg three times daily, or 50 and 200 mg three times daily, respectively. The doses were increased to the full amount over a period of nine weeks in a blinded fashion.

After 40 weeks, the subjects underwent a 3-day period of step-down withdrawal from the study drug. After two weeks without the study drug, a final assessment of the severity of the symptoms of Parkinson's disease was made. The selection of the 2-week duration for the washout period was based on reports that withdrawal from levodopa for a period up to 14 days resulted in a worsening of parkinsonism mainly within the first 7 days, with nonsignificant worsening beyond that point.[15-17]

CLINICAL EVALUATION

The treating investigator, who was blinded to the treatment assignment, performed a clinical evaluation with the use of the UPDRS[14] at the screening, baseline, and interim visits (at the end of weeks 3, 9, 24, and 40) and during each of the two weeks of the washout phase. During the four interim visits,

the evaluations were performed before the administration of the first dose of the study drug. At every visit the treating investigator inquired about adverse events. The primary rater, who was also blinded to the treatment assignment and was kept unaware of information obtained during the course of the study, performed the examination with the use of the UPDRS only at the baseline evaluation, which took place within four weeks after screening, and again at the final evaluation, two weeks after the subject had undergone complete withdrawal from the study treatment (week 42). The study coordinators and the subjects also were blinded to the treatment assignments. An emergency unblinding procedure was established but was never used.

OUTCOME

The prespecified primary outcome was the change in the severity of parkinsonism between the baseline visit and week 42, as measured with the use of the total score on the UPDRS that was obtained by the primary rater; week 42 was 14 days after the withdrawal of the study drug. The expected result was a dose-related deterioration during washout if levodopa were shown to hasten the progression of Parkinson's disease. The change in the total scores on the UPDRS measured by the treating investigator at each visit was a prespecified secondary outcome. The treating investigator assessed adverse events with the use of open-ended questioning at each visit.

SUBSTUDY

After the clinical trial was begun, we conducted a substudy with the use of SPECT to measure striatal dopamine-transporter density with the use of iodine-123–labeled 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane ([^{123}I]β-CIT). The methods have been reported previously.[18] The subjects who gave consent underwent SPECT imaging just before the baseline visit and then again before the visit at week 40. The imaging studies were performed at

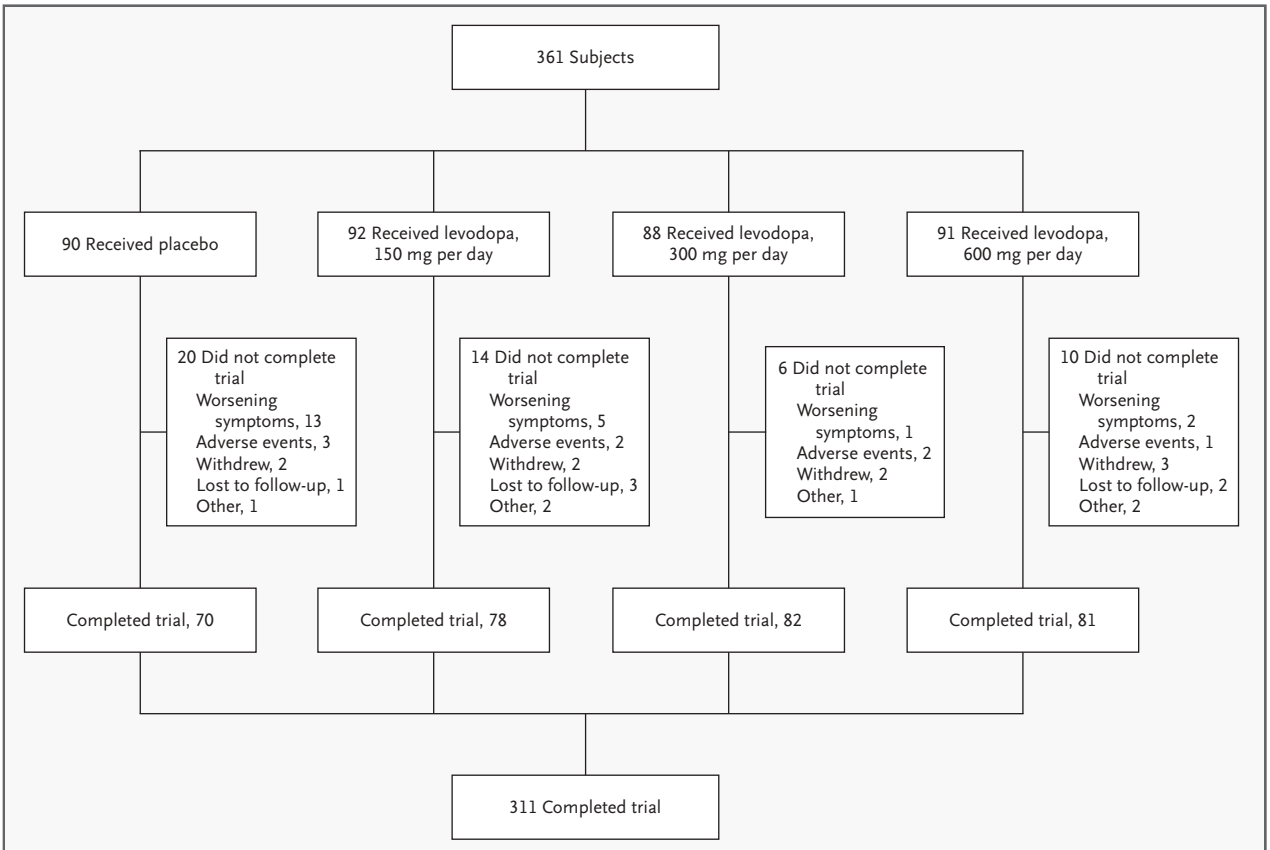

Figure 1. Random Assignments to Treatment, Completion of the Trial, and Reasons for Not Completing It.

that point rather than after the subjects had undergone withdrawal from levodopa, at week 42, because it was thought that the subjects would not be able to tolerate the procedure (including the necessary travel) after the return of parkinsonism or after its worsening. Another reason was that there was no clear evidence of a short-term effect of levodopa on dopamine-transporter imaging.

All imaging studies were performed at Yale University or the Institute for Neurodegenerative Disorders (both in New Haven, Connecticut). The neuroimaging personnel were blinded to the treatment assignment of the subjects. The results of the SPECT studies were transferred to and analyzed by the biostatistics center of the Parkinson Study Group. The prespecified outcome was the percent change in the ratio of the specific striatal [^{123}I]β-CIT uptake to the nondisplaceable striatal [^{123}I]β-CIT uptake between the two images.

STATISTICAL ANALYSIS

Allowing for a dropout rate of 10 percent of the subjects enrolled, we chose a sample size of 360 subjects (i.e., 90 subjects in each of the four treatment

Table 1. Baseline Characteristics of the Study Subjects.*

Characteristic	Placebo	Levodopa			Total	P Value
		150 mg/day	300 mg/day	600 mg/day		
Full cohort						
No. of subjects	90	92	88	91		
Male sex (%)	72	63	67	68		0.62
White race (%)	90	91	93	88		0.67
Age (yr)	64.9±10.3	64.3±10.6	63.8±12.1	65.2±10.7		0.84
At onset	64.4±10.4	63.8±10.7	63.1±12.1	64.8±10.6		0.76
Duration of disease (mo)	5.3±5.6	5.7±6.1	7.6±7.5	6.0±6.1		0.10
Severity of disease						
Total UPDRS score	27.7±12.0	27.2±12.6	27.5±11.6	29.4±13.9		0.63
Mental component	1.4±1.5	1.3±1.5	1.3±1.4	1.4±1.6		0.93
ADL component	7.5±3.6	7.5±4.4	7.3±3.7	7.6±4.0		0.94
Motor component	18.8±8.9	18.6±9.1	18.9±8.8	20.5±10.8		0.51
Schwab–England scale score	91.1±7.3	91.1±7.0	91.6±6.1	90.9±6.8		0.89
Hoehn–Yahr scale score	1.8±0.5	1.9±0.6	1.8±0.5	1.9±0.6		0.57
[^{123}I]β-CIT SPECT substudy						
No. of subjects	29	38	37	38	142	
Male sex (%)	76	61	78	71	71	0.34
White race (%)	97	95	97	87	94	0.23
Age (yr)	63.9±10.5	64.5±11.8	63.1±10.2	62.3±9.8	63.4	0.82
At onset	63.4±10.6	64.0±11.7	62.3±10.2	62.0±9.6	62.9	0.84
Duration of disease (mo)	6.4±5.7	6.2±6.6	6.6±6.4	6.9±5.9	6.5	0.98
UPDRS, total score	26.3±12.6	27.8±13.1	26.3±10.3	31.7±13.4	28.2	0.22
[^{123}I]β-CIT uptake						
Striatum	3.42±1.32	3.86±1.45	3.38±0.84	3.68±1.66	3.60	0.38
Putamen	2.38±1.26	2.68±1.38	2.25±0.75	2.59±1.57	2.48	0.47
Caudate nucleus	4.46±1.48	5.05±1.59	4.50±1.03	4.76±1.81	4.71	0.33

* Plus–minus values are means ±SD. The Hoehn–Yahr scale, which ranges from 1 to 5, represents stages of Parkinson's disease. On the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn–Yahr scale, higher numbers indicate a greater severity of the impairment. The Schwab–England scale was used to assess activities of daily living (ADL), which range from 0 to 100, with 100 indicating normal. In the measurement of the uptake of iodine-123–labeled 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane ([^{123}I]β-CIT) uptake, lower numbers indicate greater deficits. Subjects with more than 75 percent of their age-expected[^{123}I]β-CIT uptake in the putamen (the basis of data on healthy subjects) were considered to have scans that showed no dopaminergic deficit. Race was reported by the site coordinators or by the subjects.

groups) in order to provide the study with 85 percent power to detect a dose–response relationship (linear trend) between the assigned doses and the change in the subjects' total score on the UPDRS between the baseline visit and the final visit at week 42. On the basis of the results of one study,[19] we anticipated a rate of worsening in the total score on the UPDRS in the placebo group of 9.5 units over the 9.5 months of the study. The study was powered to detect a linear trend that corresponded to a 4-unit difference (45 percent of 9.5 units) in the score on the UPDRS between the highest dose of levodopa (600 mg per day) and placebo — that is, a change of either 13.5 or 5.5 units from baseline in the group receiving the highest dose of the active study drug.

The primary statistical tests were two-tailed, with an alpha level of 0.05. Only subjects who completed the two-week washout phase were included in this analysis. We used the intention-to-treat principle in the analysis, even if among some subjects the dose of the study drug were to be reduced during the study. The primary analysis assessed the dose–response relationship between the assigned doses and the worsening of parkinsonism, as indicated by the changes in the total score on the UPDRS between the baseline visit and week 42. Statistical comparisons were made by analysis of covariance in a model that adjusted for differences among the investigators performing the evaluations and in baseline values.

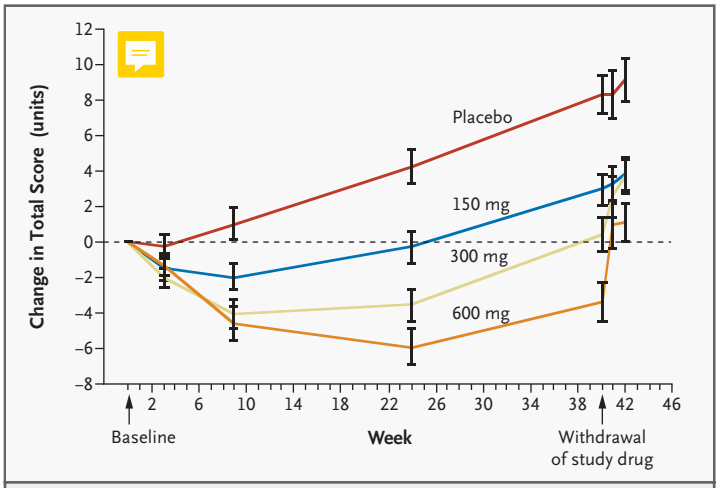

Figure 2. Changes in Total Scores on the Unified Parkinson's Disease Rating Scale (UPDRS) from Baseline through Evaluation at Week 42.

The changes in subjects treated with levodopa at different doses or with placebo were determined on the basis of the total scores on the UPDRS. The scores were obtained by blinded treating investigators who performed the evaluation before the morning dose of the daily dose of the study drug. The points on the curves indicate mean changes from baseline in the total scores at each visit. Improvement in parkinsonism is represented by lower scores, and worsening by higher scores. Negative scores on the curves indicate improvement from baseline. The bars indicate the standard error.

RESULTS

SUBJECTS

Of a total of 361 subjects enrolled in the study, 317 (88 percent) took the study medication for 40 weeks, and 311 (86 percent) completed the 2 weeks of washout (Fig. 1). The neuroimaging substudy was begun after the enrollment of the first 108 subjects. Of the 253 subjects subsequently enrolled, 142 (56 percent) participated in the substudy and underwent the baseline SPECT. Of these, 135 (95 percent) returned for scanning at week 40. The demographic and clinical characteristics of the subjects in the treatment groups were similar at baseline, both in the entire sample and in the neuroimaging substudy (Table 1).

CLINICAL OUTCOME

Levodopa, in a dose–response pattern, significantly ($P<0.001$) reduced the worsening of symptoms of Parkinson's disease as reflected in the change between the total score on the UPDRS at baseline and that at week 42 (i.e., two weeks after washout of the study medication), as compared with the change in the placebo group (Fig. 2 and Table 2). The subjects in the placebo group had mild improvement at the week 3 visit, but after that their symptoms worsened steadily throughout the balance of the study period, including the two-week washout phase. A strong dose–response benefit was detected during the period in which the medication was administered beginning at week 9, when the full dose of 600 mg daily was reached in the group receiving the highest dose of levodopa, and it persisted through week 40. The scores on the UPDRS in the three levodopa groups worsened during the two-week washout period, but these groups did not deteriorate to the level observed in the placebo group, and the group receiving the highest dose of levodopa had the best result (Fig. 2 and Table 2). The adverse events that were significantly more common among those receiving levodopa at 600 mg daily than in the placebo group were dyskinesias, nausea, infection, hypertonia, and headache (Table 3).

SPECT AND [^{123}I]β-CIT SUBSTUDY

The mean [^{123}I]β-CIT uptake in the striatum, caudate, and putamen at baseline was consistent with values previously reported for patients with early Parkinson's disease.[20] The percent decrease in striatal [^{123}I]β-CIT uptake over the 40 weeks of the study treatment was greater among subjects in the levodopa groups than in the placebo group, but this difference was not statistically significant (Table 4). However, 21 of the 142 subjects (14.7 percent) had a putaminal [^{123}I]β-CIT uptake of more than 3.25 at baseline (i.e., more than 75 percent of the age-expected putaminal uptake).[21] An analysis of the results of SPECT after the exclusion of the 19 subjects without a dopaminergic deficit who returned for the neuroimaging study at week 40 showed a significantly greater decrease in [^{123}I]β-CIT uptake among those receiving levodopa than among those receiving placebo (P=0.036) (Table 4).

DISCUSSION

We found no clinical evidence that levodopa accelerated the worsening of Parkinson's disease over the 9.5 months of observation. Rather, levodopa was associated with less worsening of parkinsonism than was placebo, consistent with the notion that it slows disease progression (Table 2 and Fig. 2). In comparison with the scores on the UPDRS at baseline, the final scores, after the washout phase, had worsened by approximately 8 units in the placebo group, whereas the group receiving levodopa at 600 mg daily did not have evidence of deterioration. The groups receiving levodopa at lower doses did have deterioration, as shown by a comparison of their scores at baseline and at week 42, but the deterioration was less than in the placebo group (P<0.001).

We need to consider that a two-week washout from levodopa may have been insufficient to eliminate fully the effect of the medication on symptoms, and the results observed may be related to a profound effect of levodopa on symptoms that persists for a long time after the drug has been withdrawn. Indeed, Hauser and Holford,[22] using a modeling technique, analyzed the withdrawal of levodopa in 20 patients and reported that the mean half-life of levodopa as measured by the loss of the clinical benefit was 7.9 days (95 percent confidence interval, 2.2 to 30.4 days). They suggest that a washout

Table 2. Changes in the Scores on the UPDRS between Baseline and Week 42.*

Characteristic	Placebo	Levodopa			P Value for Trend
		150 mg/day	300 mg/day	600 mg/day	
Evaluation by primary rater					
No. of subjects	70	78	82	81	
UPDRS score					
Total score	7.8±9.0	1.9±6.0	1.9±6.9	−1.4±7.7	<0.001
Mental component	0.3±1.5	0.0±1.5	0.1±1.2	0.1±1.4	0.18
ADL component	2.3±3.4	0.5±2.3	0.4±2.9	−0.3±3.0	<0.001
Motor component	5.2±6.4	1.4±5.5	1.4±5.3	−1.4±5.9	<0.001
Evaluation by treating investigator					
No. of subjects	70	78	82	81	
UPDRS score					
Total score	9.0±10.4	4.0±8.2	4.0±8.4	1.0±9.9	<0.001
Mental component	0.5±1.3	−0.1±1.4	0.1±1.4	0.1±1.6	0.31
ADL component	2.5±4.0	0.8±3.1	1.0±2.8	0.3±3.5	<0.001
Motor component	6.0±7.6	3.2±6.4	3.0±6.4	0.6±7.7	<0.001

* Plus–minus values are means ±SD. On the UPDRS, higher scores indicate greater severity of impairment. Negative numbers indicate improvement as compared with the baseline value. The total score on the UPDRS showed a significant trend toward the reduction of symptoms with higher doses of levodopa in the evaluations by both the primary raters and the treating investigators. The post hoc analysis showed that the effects of all three doses of levodopa differed significantly from the effect of the placebo. Scores on the UPDRS showed that treatment effects were significant for activities of daily living (ADL) and the motor component but not for the mental component.

Table 3. Adverse Events.*

Adverse Event	Placebo (N=90)	Levodopa			P Value for Trend
		150 mg/day (N=92)	300 mg/day (N=88)	600 mg/day (N=91)	
	number (percent)				
Dopaminergic effects					
Dyskinesia	3 (3.3)	3 (3.3)	2 (2.3)	15 (16.5)	<0.001
Dystonia	19 (21.1)	19 (20.7)	14 (15.9)	12 (13.2)	0.30
Freezing of gait	13 (14.4)	9 (9.8)	6 (6.8)	5 (5.5)	0.15
On–off	3 (3.3)	1 (1.1)	0	3 (3.3)	0.26
Wearing off	12 (13.3)	15 (16.3)	16 (18.2)	27 (29.7)	0.06
Nondopaminergic effects					
Anxiety	5 (5.6)	3 (3.3)	1 (1.1)	3 (3.3)	0.29
Back pain	5 (5.6)	1 (1.1)	5 (5.7)	4 (4.4)	0.91
Chest pain	1 (1.1)	2 (2.2)	4 (4.5)	3 (3.3)	0.25
Constipation	2 (2.2)	4 (4.3)	7 (8.0)	3 (3.3)	0.49
Coughing	4 (4.4)	5 (5.4)	3 (3.4)	3 (3.3)	0.56
Depression	8 (8.9)	9 (9.8)	7 (8.0)	6 (6.6)	0.50
Diarrhea	5 (5.6)	9 (9.8)	3 (3.4)	4 (4.4)	0.37
Dizziness	6 (6.7)	10 (10.9)	5 (5.7)	14 (15.4)	0.13
Dreaming, abnormal	0	3 (3.3)	0	5 (5.5)	0.06
Dyspepsia	3 (3.3)	2 (2.2)	5 (5.7)	5 (5.5)	0.29
Falls	2 (2.2)	8 (8.7)	4 (4.5)	3 (3.3)	0.91
Fatigue	7 (7.8)	10 (10.9)	7 (8.0)	5 (5.5)	0.44
Fracture	4 (4.4)	0	0	0	0.01
Headache	3 (3.3)	7 (7.6)	5 (5.7)	12 (13.2)	0.03
Hypertension	3 (3.3)	6 (6.5)	2 (2.3)	1 (1.1)	0.19
Hypertonia	1 (1.1)	0	1 (1.1)	5 (5.5)	0.03
Hypoesthesia	1 (1.1)	5 (5.4)	1 (1.1)	3 (3.3)	0.77
Infection	1 (1.1)	0	0	6 (6.6)	0.01
Insomnia	9 (10.0)	8 (8.7)	4 (4.5)	5 (5.5)	0.15
Joint pain	3 (3.3)	3 (3.3)	0	7 (7.7)	0.25
Leg pain	7 (7.8)	6 (6.5)	3 (3.4)	0	0.006
Myalgia	4 (4.4)	1 (1.1)	3 (3.4)	3 (3.3)	0.89
Nausea	12 (13.3)	15 (16.3)	23 (26.1)	29 (31.9)	0.001
Pain	5 (5.6)	4 (4.3)	5 (5.7)	3 (3.3)	0.58
Sinusitis	2 (2.2)	3 (3.3)	4 (4.5)	5 (5.5)	0.22
Skeletal pain	7 (7.8)	5 (5.4)	2 (2.3)	3 (3.3)	0.10
Somnolence	2 (2.2)	0	5 (5.7)	5 (5.5)	0.07
Tremor	7 (7.8)	8 (8.7)	4 (4.5)	4 (4.4)	0.21
Upper respiratory infection	9 (10.0)	12 (13.0)	10 (11.4)	7 (7.7)	0.54
Urinary tract infection	4 (4.4)	5 (5.4)	1 (1.1)	2 (2.2)	0.19
Serious adverse events					
Chest pain	1 (1.1)	0	3 (3.4)	1 (1.1)	0.55
Coronary artery disorder	1 (1.1)	2 (2.2)	2 (2.3)	0	0.55
Malignant melanoma	1 (1.1)	0	0	1 (1.1)	1.00
Pericarditis	0	1 (1.1)	1 (1.1)	0	1.00

* All adverse events considered to be due to an effect on the nigrostriatal dopaminergic system are listed. The nondopaminergic adverse events listed either reached clinical significance or occurred more than three times in any treatment group. All serious adverse events were recorded, and those that occurred more than once are listed. P values for trend were derived with the use of the chi-square test.

Table 4. Change in Striatal [^{123}I]β-CIT Uptake between Baseline and Week 40.*

Variable	Placebo	Levodopa			P Value for Dose–Response
		150 mg/day	300 mg/day	600 mg/day	
Substudy cohort					
No. of subjects	29	33	37	36	
Change (%)	−2.6±11.3	−4.7±10.8	−3.7±9.1	−6.9±8.1	0.15
P value for comparison with placebo		0.46	0.63	0.11	
After exclusion of subjects with baseline scans showing no dopaminergic deficit†					
No. of subjects	26	28	34	28	
Change (%)	−1.4±10.0	−6.0±10.3	−4.0±9.4	−7.2±7.6	0.036
P value for comparison with placebo		0.16	0.40	0.015	

* Plus–minus values are means ±SD.
† The 19 subjects excluded had putaminal [^{123}I]β-CIT uptake levels of 3.25 or greater (i.e., more than 75 percent of the age-expected uptake).

period of 32 days (four half-lives) may be required to eliminate 90 percent of the drug's effects on symptoms. However, we saw little deterioration after one week of washout. Near the end of the study, with the approval of the institutional review boards and of the National Institutes of Health, we asked the last 38 subjects remaining in the study to extend the washout period to four weeks. Among these subjects there was no further worsening of the scores on the UPDRS during the additional two weeks, but the small number of subjects renders this component of the study difficult to interpret.

Muenter and Tyce[23] described motor responses with two types of duration, short and long, with levodopa therapy. The short-duration benefit lasts for a few hours after a single dose, and the long-duration benefit lasts several days. In our study, the long-duration benefit appears to have lasted approximately one to two weeks (Fig. 2). To argue that a longer washout period might have revealed more clinical worsening than was observed, one could propose a hitherto unknown third type of duration of motor response, one that is more sustained than the so-called long-duration benefit. Such an enduring benefit could be envisioned to result from a prolonged pharmacodynamic effect, for example, on dopamine receptors.

If, however, the clinical effects observed offer evidence of neuroprotection, how can we explain the greater loss of dopamine transporter shown in the SPECT imaging studies of the subjects who received levodopa, as compared with those who received the placebo — a result that suggests the possibility of a levodopa-induced toxic effect on dopamine neurons? At the end of the study, when the SPECT neuroimaging studies were performed, the subjects were still taking levodopa, so it is possible to assume that levodopa has a pharmacologic effect on the dopamine transporter that interferes with and reduces the binding of the β-CIT ligand.

Indeed, one study found a reduction in dopamine-transporter binding with the use of positron-emission tomography (PET) and another dopamine-transporter ligand in patients with early Parkinson's disease who were treated for six weeks with levodopa at 300 mg daily.[24] However, the sample size in this study, as in others that have shown no change in dopamine-transporter binding after short-term treatment with levodopa,[25-27] was too small to demonstrate a statistically significant difference between levodopa and placebo. Further indirect support for the absence of a pharmacologic effect of levodopa on imaging studies of the dopamine transporter in the present study was the absence of decline in the [^{123}I]β-CIT uptake by week 40 among the 16 subjects who received levodopa and whose SPECT scans were normal at baseline (i.e., without evidence of a dopaminergic deficit) (data not shown). However, in the absence of studies with larger samples and a longer period of treatment with levodopa, we cannot exclude the possibility that levodopa may simply down-regulate the dopamine transporter. Another consideration is that the falling dopamine concentration in the placebo group may have led to a compensatory increase in the activity of the dopamine transporter that could have increased [^{123}I]β-CIT binding, but evidence for such an interpretation is lacking.

If levodopa has neuroprotective effects, what mechanisms could account for this property? In low concentrations and in the presence of glial cells, levodopa protects cultured dopaminergic neurons[28-31] and up-regulates antioxidant and antiapoptotic proteins.[29,32] Furthermore, in vivo studies suggest that levodopa can promote survival and enhance the sprouting of nigral dopamine neurons in rodents treated with the toxin 6-hydroxydopamine.[9,10] The question of whether levodopa has a protective or a toxic effect in Parkinson's disease — reflecting the results of clinical examination and neuroimaging studies, respectively — cannot be answered with certainty, and future studies will be needed.

This dose–response, placebo-controlled clinical trial evaluating the effect of levodopa in patients with early Parkinson's disease showed a strikingly impressive dose–response clinical benefit: the higher the dose, the stronger and more lasting the benefit, and the benefit was greater even after the drug was withdrawn (Fig. 2).

During withdrawal, we did not encounter the neuroleptic malignant-like effect (i.e., high fever, obtundation, and rigidity) that can occur with the sudden withdrawal of levodopa.[33,34] Its absence may be related to the down-titration procedure employed; however, this complication is so rare that it might not have occurred in a study of this size even had levodopa been withdrawn suddenly, particularly in patients with early-stage disease.

Our study calls into question interpretations of the functional neuroimaging of the dopamine system. It has generally been assumed that imaging studies performed with ^{18}F-fluorodopa PET and [^{123}I]β-CIT SPECT can provide reliable information on the integrity of the nigrostriatal dopamine pathway. Our study and other recent clinical trials[25,35] raise the possibility of a pharmacologic influence of dopaminergic therapy on these neuroimaging targets and point to the need for clarification of this issue.

Although the absence of evidence of a dopaminergic deficit in the imaging in our study and two other studies[25,35] may simply represent a limitation of the sensitivity of the imaging techniques, the scans without a dopaminergic deficit raise doubt about whether the subjects had Parkinson's disease.[35] In our study, the subjects with such scans at baseline had no worsening of the [^{123}I]β-CIT uptake at week 40 (data not shown), nor did subjects with such scans in the group receiving the highest dose of levodopa have an improvement in the scores on the UPDRS (i.e., a change between the score at baseline and at week 40 of 3.38±4.25 units, as compared with a change of −4.95±10.4 units in the subjects receiving levodopa at 600 mg daily whose baseline SPECT scans showed abnormalities; P= 0.002). Whether the subjects with no evidence of dopaminergic deficit on scanning do or do not have classic Parkinson's disease remains uncertain. The fact that scans of some patients with early Parkinson's disease do not have evidence of a dopaminergic deficit needs to be taken into consideration in the planning of future trials to test drugs for neuroprotective effects.

Finally, even though we cannot reconcile the clinical and imaging findings in our study, we can assure both patients with early Parkinson's disease and their physicians that, from a clinical perspective, our study did not find that levodopa hastens the progression of Parkinson's disease. On the basis of the study, we can recommend that the doses of levodopa be adjusted to fit the needs of the patient. Small doses were found to be effective, although less so than higher doses. High doses, however, were associated with a greater frequency of adverse events such as dyskinesia. For the present, until more evidence is available, we recommend customizing the dose of levodopa to the needs of the individual patient on the basis of the clinical response and the profile of adverse events.

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APPENDIX

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