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RESEARCH ARTICLE

Long-Term Follow-Up of the LEAP Study: Early Versus Delayed Levodopa in Early Parkinson's Disease

CME

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ABSTRACT: Background and Objective: The Levodopa in EArly Parkinson's disease study showed no effect of earlier versus later levodopa initiation on Parkinson's disease (PD) progression over 80 weeks. We now report the effects over 5 years.

Methods: The Levodopa in EArly Parkinson's disease study randomly assigned patients to levodopa/carbidopa 300/75 mg daily for 80 weeks (early start) or to placebo for 40 weeks followed by levodopa/carbidopa 300/75 mg daily for 40 weeks (delayed start). Follow-up visits were performed 3 and 5 years after baseline. We assessed the between-group differences in terms of square root transformed total Unified Parkinson's Disease Rating Scale score at 3 and 5 years with linear regression. We compared the prevalence of dyskinesia, prevalence of wearing off, and the levodopa equivalent daily dose.

Results: A total of 321 patients completed the 5-year visit. The adjusted square root transformed total Unified Parkinson's Disease Rating Scale did not differ between treatment groups at 3 (estimated difference, 0.17; standard error, 0.13; $P = 0.18$) and 5 years (estimated difference, 0.24; standard error, 0.13; $P = 0.07$). At 5 years, 46 of 160 patients in the early-start group and 62 of 161 patients in the delayed-start group experienced dyskinesia ($P = 0.06$). The prevalence of wearing off and the levodopa equivalent daily dose were not significantly different between groups.

Conclusions: We did not find a difference in disease progression or in prevalence of motor complications between patients with early PD starting treatment with a low dose of levodopa 40 weeks earlier versus 40 weeks later over the subsequent 5 years. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: early Parkinson's disease; levodopa; disease-modifying; motor symptoms; motor response fluctuations

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Introduction

To date, there is no treatment that slows Parkinson's disease (PD) progression. Levodopa remains the most effective symptomatic oral treatment for PD motor symptoms.[1] An earlier trial investigating levodopa's effect on PD progression showed inconclusive results[2]; therefore, the Levodopa in EArly Parkinson's disease (LEAP) study was initiated.[3] The LEAP study used a randomized, double-blind, placebo-controlled, delayed-start design.[3,4] Treatment-naive early PD patients were randomly assigned to receive levodopa for 80 weeks (early-start group) or placebo for 40 weeks followed by levodopa for 40 weeks (delayed-start group). At 80-week follow-up, the study showed no evidence that levodopa had a disease-modifying effect.[3] In addition, there was no between-group difference at week 80 in the prevalence of dyskinesia, but there was a higher prevalence of early signs of motor response fluctuations in the delayed-start group.[5] A substantial limitation of these results was the relatively short follow-up. Another limitation, although closely resembling clinical practice, was the risk of misclassification because of enrollment of patients with a clinically based diagnosis of PD. Because the clinical diagnostic accuracy of PD by movement disorder specialists is about 84% and lower by non–movement disorder neurologists,[6] this method inevitably must have resulted in the enrollment of patients who did not have PD. Because of these limitations, we conducted follow-up visits 3 and 5 years after baseline of the LEAP study. After exclusion of patients who did not have PD 5 years after baseline, we studied the effect of a 40-week earlier start of levodopa versus placebo on PD progression over 5 years' time.

Patients and Methods

LEAP Study Design

The methods of the LEAP study have been published previously.[3] To separate a possible disease-modifying effect of levodopa from an effect on symptoms, it used a randomized, double-blind, placebo-controlled, delayed-start study design.[3,4] Patients assigned to the early-start group received a 2-week dose-escalation schedule of levodopa/carbidopa and thereafter 300/75 mg/day for 78 weeks. Patients assigned to the delayed-start group received placebo for 40 weeks followed by a 2-week dose-escalation schedule of levodopa/carbidopa and thereafter 300/75 mg/day for 38 weeks. If patients from either arm developed the need for extra medication during the placebo-controlled phase, the medication was converted to unblinded study medication (levodopa/carbidopa 300/75 mg/day). This meant that the patients from the early-start group continued the same dose but knew for sure they were taking levodopa, and the patients from the delayed-start group switched from placebo to levodopa. In this way, patients and investigators remained blinded regarding the initial randomization.

Prospective Follow-Up Study

After completion of the first 80 weeks of the study, treatment was no longer dictated by a study protocol. During the follow-up study, patients and investigators remained blinded to the patient's initial treatment allocation (ie, early-start group, delayed-start group). The prospective follow-up comprised study visits 3 and 5 years after baseline. However, because of a delay in funding, the 3-year follow-up visits started after some of the patients had already passed the 3-year follow-up time frame. At the 3-year and 5-year visits, the Unified Parkinson's Disease Rating Scale (UPDRS)[7] was administered regardless of *on* or *off* drug state, and the amount of antiparkinson medication was assessed. Only at the 5-year visit were the Scales for Outcomes in Parkinson's Disease—Autonomic (SCOPA-AUT) and the Montreal Cognitive Assessment (MoCA) administered.[8,9] During the first 80 weeks, the Mini-Mental State Examination was used,[10] but because of its higher sensitivity for cognitive decline we chose to use the MoCA during the follow-up. In addition, we inquired after the current diagnoses (ie, PD or another diagnosis) of all included patients with their treating neurologist 5 years after baseline. The treating neurologists were either general neurologists or movement disorder specialists.

Patients

Patients who were included in the LEAP study had received a diagnosis of PD within the previous 2 years based according to standard clinical criteria, had insufficient disability to warrant treatment with antiparkinson medication, were 30 years of age or older, and had a life expectancy of more than 2 years. Patients were not eligible if they had been treated with antiparkinson medication previously; if their most prominent symptom was tremor, such as a severe resting tremor that was present almost continuously or resulted in disability; if they had dementia; and if they had features that indicated atypical or secondary parkinsonism.[3] Patients were eligible for follow-up if they completed the first 80 weeks of the study and consented to participation in the follow-up.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients enrolled in the follow-up study provided written informed consent before participation. The study protocol was approved by the ethics committee at the Amsterdam University Medical Centers in the Netherlands. The study was conducted in accordance with the principles of the Declaration of Helsinki. Trial monitoring and data management were performed in

accordance with the International Conference on Harmonization Good Clinical Practice guidelines. The LEAP study was registered at the ISRCTN registry with number ISRCTN30518857, and the LEAP study including the follow-up study were registered at the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) with number 2011-000678-72.

Statistical Analysis

We used only data from patients with a confirmed PD diagnosis 5 years after baseline and from patients for whom this information was not available, assuming a diagnosis of PD. We performed a between-treatment group comparison of the clinical characteristics at baseline of all patients included in the LEAP study and of the patients who remained in the follow-up study at 5 years. We used independent sample *t* tests, χ^2 tests, and Mann–Whitney tests. Two-sided *P* values of less than 0.05 were considered to indicate statistical significance. Using logistic regression, we analyzed the difference in sex, age, and total UPDRS score at baseline between the patients included in the follow-up and the patients who did not participate in the follow-up. For the main analysis of the follow-up study, the difference between the treatment groups in total UPDRS score at 5 years was analyzed using linear regression, taking into account sex, baseline age, baseline total UPDRS scores, and levodopa equivalent daily dose (LEDD) 5 years after baseline.[11] In this analysis, the square root of UPDRS was used to adjust for skewness, which makes the interpretation of the results less intuitive; however, it provides the most correct inference. Possible nonlinear relations were allowed for using smoothing splines. A positive estimate indicates a higher score in the early-start group compared with the delayed-start group. We performed the same analyses for the total UPDRS score at 3 years and separately for Parts I, II, III, and IV of the UPDRS and the Levy A and Levy B scores at 3 and 5 years. Levy A refers to a sum of the UPDRS Part III items for "facial expression," "tremor," "rigidity," "hand movements," "pronation-supination movements of hands," "leg agility," and "global spontaneity of movement" (range 0–80 points). Levy B (highlighting axial features of the disease) refers to a sum of UPDRS Part III items for "speech," "arising from chair," "posture," "gait," and "postural stability" (range 0–20 points).[12] Analogously, the difference in square root transformed LEDD between the treatment groups at 3 and 5 years was analyzed using linear regression, taking into account sex, baseline age, and baseline total UPDRS scores. As a more in-depth analysis, we evaluated the between-group difference in slopes of (the square root of) total UPDRS progression over time from week 56 onward, using a linear mixed effects model allowing for patient-specific intercepts and slopes, and accounting for the same variables as in the main analysis. We analyzed the between-group difference in prevalence of dyskinesia (UPDRS item 32) and wearing off (UPDRS item 39) at 3 and 5 years with χ^2 test. The between-group differences in SCOPA-AUT and MoCA at 5 years were analyzed with Mann–Whitney tests.

Results

Patients

From August 2011 through May 2016, 446 patients were recruited for the LEAP study from 50 community hospitals and 7 academic hospitals in the Netherlands. One patient withdrew from the trial before the baseline assessment. We successfully inquired after the diagnoses (ie, PD or another diagnosis) of 440 patients 5 years after baseline. For five patients, this information was not available. A total of 413 patients (93%) still had the diagnosis PD, and 27 patients (6%) did not have PD. Table 1 shows the alternative diagnoses. In all further analyses, only patients with PD and patients for whom no information was available, assuming the diagnosis was still PD, were included. Figure 1 shows the patient disposition during the study. A total of 418 patients were enrolled in the LEAP study, and 397 patients (95%) completed the first 80 weeks of the trial. From October 2016 through July 2021, patients underwent the follow-up visits 3 and 5 years after baseline. A total of 207 patients completed the 3- and 5-year visits, 29 patients completed only the 3-year visit, and 114 patients completed only the 5-year visit.

TABLE 1 *Diagnosis 5 years after baseline*

Diagnosis characteristics	Patients, n (%)
Total randomly assigned in LEAP study	445 (100)
Diagnosis	440 (99)
No information available	5 (1)
Parkinson's disease	413 (93)
Multiple system atrophy	13 (3)
Progressive supranuclear palsy	5 (1)
Corticobasal syndrome	1 (0.2)
Essential tremor	1 (0.2)
Dystonic tremor	1 (0.2)
Lower body parkinsonism	1 (0.2)
Primary lateral sclerosis	1 (0.2)
Other diagnosis	4 (1)

Diagnosis refers to the number of patients for whom the diagnosis was successfully inquired after with their treating neurologist.
Abbreviation: LEAP, Levodopa in EArly Parkinson's disease.

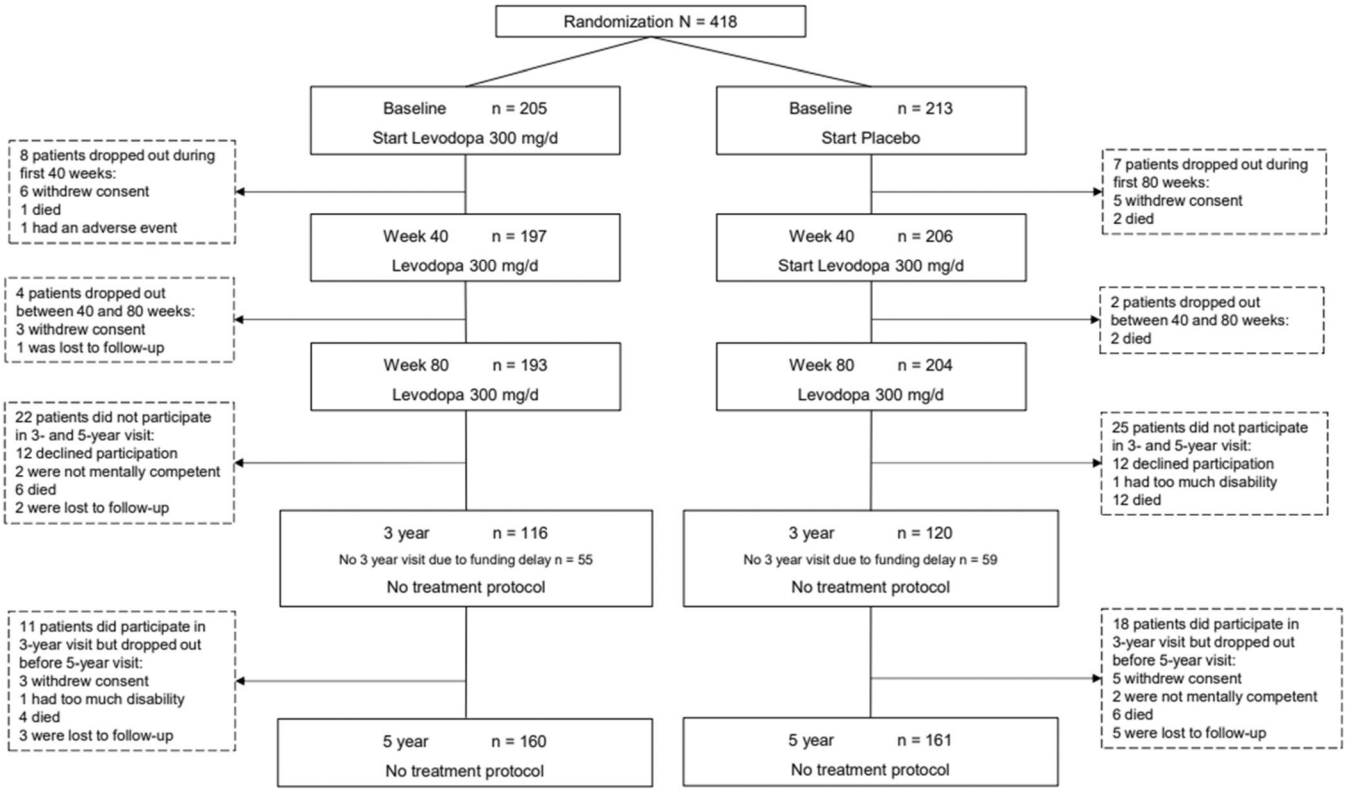

FIG. 1. Study design and patient disposition. This graph includes only the patients with confirmed Parkinson's disease (PD) and the patients for whom this information was not available, still assuming a PD diagnosis, 5 years after baseline.

During the study, 11 of 205 patients (5%) in the early-start group and 22 of 213 patients (10%) in the delayed-start group died ($P = 0.06$). The causes of death in both groups varied. Baseline clinical characteristics of the early- and delayed-start groups were comparable for the included patients (Table 2), as well as

TABLE 2 *Baseline clinical characteristics*

Characteristics	Early-Start Group LEAP Baseline (n = 205)	Early-Start Group with 5-Year Visit (n = 160)	Delayed-Start Group LEAP Baseline (n = 213)	Delayed-Start Group with 5-Year Visit (n = 161)
Age (y), mean ± SD	64.8 ± 8.3	64.3 ± 8.1	65.4 ± 9.0	64.2 ± 8.9
Male sex, n (%)	145 (71)	111 (69)	147 (69)	111 (69)
UPDRS score				
Total, mean ± SD	28.0 ± 11.3	27.2 ± 10.9	29.3 ± 11.9	27.4 ± 10.7
Part I, mean ± SD	2.4 ± 1.4	2.4 ± 1.4	2.3 ± 1.2	2.2 ± 1.2
Part II, mean ± SD	7.2 ± 3.5	7.0 ± 3.3	7.4 ± 3.6	7.1 ± 3.5
Part III, mean ± SD	18.3 ± 8.7	17.8 ± 8.4	19.5 ± 9.4	18.1 ± 8.6
Part IV, mean ± SD	0.6 ± 0.8	0.7 ± 0.8	0.6 ± 0.9	0.6 ± 0.8
MMSE, median (IQR)	29 (28–30)	29 (28–30)	29 (28–30)	29 (28–30)

The total UPDRS concerns mental function (Part I), activities of daily living (Part II), and motor function (Part III); the score ranges from 0 to 176, with higher scores indicating more severe disease. UPDRS Part IV concerns complications of therapy; the score ranges from 0 to 23, with higher scores indicating more severe complications. For the MMSE, the score ranges from 0 to 30, with lower scores indicating less cognitive function. We performed between-treatment group comparisons of the baseline characteristics of patients included in the LEAP study and of patients who remained in the study at 5 years. *P* values ranged between 0.19 and 1.0.

Abbreviations: LEAP, Levodopa in EArly Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; SD, standard deviation; MMSE, Mini-Mental State Examination; IQR, interquartile range.

the patients who remained in the follow-up study at the 3-year (Supporting Information Table S1) and 5-year visits (Table 2). Patients with a 3-year follow-up visit were more often female compared with patients who did not participate in this follow-up visit. Patients with a 5-year follow-up visit were younger at baseline and had a lower baseline UPDRS score compared with patients who did not participate in this follow-up visit (Supporting Information Table S2).

Outcomes

The unadjusted UPDRS and Levy scores and LEDD at 3 and 5 years for both groups are shown in Supporting Information Table S3. The unadjusted UPDRS and Levy change scores and LEDD change from baseline to 3 and 5 years are shown in Table 3. The linear regression taking into account sex, baseline age, baseline total UPDRS, and 5-year LEDD did not show a significant effect of treatment group on the square root of total UPDRS score at 3 (estimate, 0.17; standard error [SE], 0.13; $P = 0.18$) and 5 years (estimate, 0.24; SE, 0.13; $P = 0.07$) (Table 3). The results concerning the same analyses of the separate UPDRS Parts I, II, III, and IV, the Levy A and Levy B, and LEDD also did not show a significant effect of treatment group on these outcomes at 3 and 5 years (Table 3). The mixed effects model for the square root of total UPDRS progression after week 56, adjusted for baseline UPDRS, age, and sex, did not show a significant difference in progression between the early and late treatment groups. Specifically, testing whether separate slopes were required for both treatment groups by means of a likelihood ratio test again was not significant ($\chi^2 = 4.40$; $P = 0.07$). A graphical representation is shown in Figure S2. Fewer patients in the early-start group experienced dyskinesia at 5 years (46/160 patients, 29%) compared with the delayed-start group (62/161 patients, 39%); the between-group difference did not

TABLE 3 *Outcomes at 3- and 5-year follow-up*

Outcomes	Unadjusted Change from Baseline		Estimated Difference (SE)	*P* Value
	Early-Start Group	Delayed-Start Group		
3-Year follow-up				
UPDRS total (I + II + III)	2.6 ± 11.4	0.9 ± 12.8	0.17 (0.13)	0.18
UPDRS I	−0.2 ± 1.8	−0.3 ± 1.8	0.07 (0.09)	0.45
UPDRS II	1.3 ± 4.2	1.1 ± 3.7	0.03 (0.08)	0.68
UPDRS III	1.5 ± 8.8	0.1 ± 9.7	0.16 (0.11)	0.18
UPDRS IV	1.0 ± 1.9	1.4 ± 2.4	−0.13 (0.09)	0.18
Levy A	0.6 ± 7.2	−0.4 ± 8.1	0.14 (0.11)	0.20
Levy B	0.7 ± 2.1	0.6 ± 2.2	0.02 (0.08)	0.83
LEDD	400 (300–600)	450 (300–600)	−0.61 (0.69)	0.38
5-Year follow-up				
UPDRS total (I + II + III)	11.5 ± 17.0	8.2 ± 16.2	0.24 (0.13)	0.07
UPDRS I	0.4 ± 2.2	0.2 ± 1.9	0.11 (0.08)	0.17
UPDRS II	3.7 ± 4.7	3.2 ± 5.3	0.09 (0.08)	0.25
UPDRS III	7.4 ± 13.7	4.7 ± 11.9	0.21 (0.12)	0.09
UPDRS IV	2.4 ± 2.9	2.2 ± 2.4	<0.01 (0.09)	0.97
Levy A	4.7 ± 10.9	2.9 ± 9.4	0.15 (0.12)	0.20
Levy B	2.1 ± 3.0	1.5 ± 2.4	0.11 (0.08)	0.16
LEDD	600 (400–800)	600 (450–800)	−0.16 (0.78)	0.84

The unadjusted UPDRS and Levy change scores are expressed as mean ± standard deviation. Positive change scores from baseline to, respectively, 3 or 5 years indicate worsening of symptoms; negative change scores indicate improvement of symptoms. The unadjusted LEDD change scores are expressed as median with interquartile range. The estimated difference between treatment groups in UPDRS score at 3 and 5 years was analyzed using linear regression, taking into account sex, baseline age, baseline total UPDRS scores, and LEDD at the concerning visit. The outcomes were square root transformed due to skewness. An estimate higher than zero indicates a higher score in the early-start group. Figure S1 shows an example of the effect on the original UPDRS. The estimated difference in square root transformed LEDD between the treatment groups at 3 and 5 years was analyzed using linear regression, taking into account sex, baseline age, and baseline total UPDRS scores.
Abbreviations: SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose.

reach statistical significance ($P = 0.06$) (Supporting Information Table S3). The prevalence of wearing off at 5 years did not differ between the early-start (58/160 patients, 36%) and delayed-start group (58/161 patients, 36%) (Supporting Information Table S3). Total SCOPA-AUT and MoCA did not significantly differ between the treatment groups at 5 years (Supporting Information Table S3). More data concerning the medication at 5 years are shown in Supporting Information Table S4. Results of all UPDRS items concerning motor complications are shown in Supporting Information Table S5, and the results of all subscales of the SCOPA-AUT are shown in Supporting Information Table S3.

Discussion

There were no statistically significant differences in UPDRS scores at 3 and 5 years between the early- and delayed-start groups. There also were no statistically significant differences between the groups in prevalence of motor response fluctuations, in symptoms of autonomic dysfunction, in cognition, and in LEDD at the follow-up visits. Altogether, we did not find a difference in disease progression between patients with early PD starting low-dose levodopa 40 weeks earlier versus 40 weeks later over the subsequent 5 years.

Our findings are in line with the results of studies comparing a dopamine agonist with levodopa in early PD,[13-15] with a substudy of the Parkinson's Progression Markers Initiative cohort,[16] and with the PD MED trial.[17] These studies all show no faster worsening of UPDRS or quality of life with levodopa compared with "levodopa sparing treatment" (dopamine agonists or monoamine oxidase type B inhibitors). These studies of levodopa-sparing therapies compared with levodopa in early PD showed inconsistent results regarding motor response fluctuations at long-term follow-up. However, in the studies that showed a higher prevalence of motor complications in the levodopa treatment groups, dyskinesia was usually mild.[14-16,18] A relatively small well-designed case–control study investigated the effect of duration of levodopa treatment on motor response fluctuations. It compared patients who started levodopa relatively late in the disease course because of lack of access to any antiparkinson medication with patients who started levodopa earlier in the disease course.[19] The results showed that motor complications are not associated with the duration of levodopa use, but that they are associated with disease duration and a higher levodopa daily dose. The current results, showing no higher prevalence of motor response fluctuations in the group that started levodopa 40 weeks earlier, confirm the results of the case–control study regarding the absence of a relation between duration of levodopa use and prevalence of motor response fluctuations.

Only 6% of the original study patients did not have PD but another diagnosis 5 years after baseline; this percentage is lower compared with other studies recruiting patients with early PD.[6] A possible explanation for this high clinical diagnostic accuracy could be that neurologists did not refer patients for trial participation if they were unsure about the clinical diagnosis. A confirmation of this explanation is the relatively high number of 104 patients who underwent a dopamine transporter single-photon emission computed tomography scan before trial participation. This probably helped to exclude individuals with essential tremor or dystonic tremor, diagnoses that were indeed rare in this study. Of the 27 patients who did not have PD, 13 patients had multiple system atrophy and 5 patients had progressive supranuclear palsy. This is in line with the results of a large meta-analysis that also found multiple system atrophy to be the disease most frequently misdiagnosed for PD, with progressive supranuclear palsy coming in second.[6] This meta-analysis also found dementia with Lewy bodies and Alzheimer's disease to be frequently misdiagnosed for PD. These diagnoses were not among the misdiagnosed diseases in our cohort because dementia was an exclusion criterion.

A substantial strength of the study is the high proportion of originally randomly assigned patients (77%) who completed the 5-year follow-up, minimizing the risk of bias caused by dropout.

Another strength is that patients and investigators remained blinded to the initial treatment allocation for the whole follow-up period, minimizing the risk of bias. In addition, we considered the high percentage of reassessed diagnoses at 5 years a strength because it allowed us to perform all analyses exclusive of the patients who were confirmed to have a diagnosis other than PD.

A limitation of the current results is that not all eligible patients underwent the 3-year study visit because of a delay in funding. There was no other bias in selection of the patients with a 3-year visit. Another limitation is the absence of a distinction between *on* or *off* drug state (ie, wearing off) while the UPDRS motor score was administrated. However, the prevalence of any wearing off during the waking day at 5 years was 36% for both treatment groups and mainly consisted of patients with 1% to 25% of the time during the waking day spent in *off* drug state. Nevertheless, this could have caused a higher variance and consequently less power. One could argue that if the study had more power, then the trend toward more UPDRS worsening in the

early-start group at 5 years could have passed the threshold for statistical significance. However, the difference in unadjusted between-group total UPDRS change score from baseline to 5 years is below the clinically important difference[20]; therefore, the clinical relevance of a statistically significant difference would be questionable. The last limitation is related to the investigation of cognition. Because of a higher patient burden and funding limitations, we chose to administer the MoCA instead of a full neuropsychological evaluation, which would have resulted in more accurate and detailed information. However, we can still indicate that after 5 years there are no large differences in cognition between the two treatment groups.

In conclusion, we did not find a difference in disease progression or prevalence of levodopa-induced motor complications between patients with early, nondisabling PD starting treatment with a low dose of levodopa 40 weeks earlier versus 40 weeks later over the subsequent 5 years.

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Data Availability Statement

The data set that underlies the results reported in this article is available to researchers conducting academic research. Requests may be directed to the corresponding author.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.