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RESEARCH ARTICLE

Levodopa Response in Patients With Early Parkinson Disease

Further Observations of the LEAP Study

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Abstract

Background and Objectives

The Levodopa in EArly Parkinson's Disease (LEAP) study enabled us to conduct post hoc analyses concerning the effects of levodopa in patients with early Parkinson disease.

Methods

The LEAP study was a double-blind, placebo-controlled, randomized, delayed-start trial in which patients with early Parkinson disease were randomized to receive levodopa/carbidopa 300/75 mg daily for 80 weeks (early-start group) or to placebo for 40 weeks followed by levodopa/carbidopa 300/75 mg daily for 40 weeks (delayed-start group). We analyzed the effect of levodopa with the Unified Parkinson's Disease Rating Scale on bradykinesia, rigidity, and tremor. At week 80, participants answered 3 questions regarding motor response fluctuations.

Results

A total of 222 patients were randomized to the early-start group (mean ± SD age at baseline 64.8 ± 8.7 years; 71% male) and 223 to the delayed-start group (mean ± SD age at baseline 65.5 ± 8.8 years; 69% male). The difference between the early- and delayed-start groups in mean change from baseline to week 4, expressed as Hedges *g* effect size, was −0.33 for bradykinesia, −0.29 for rigidity, and −0.25 for tremor (for all symptoms indicating a small effect in favor of the early-start group); from baseline to week 22, respectively, −0.49, −0.36, and −0.44 (small to medium effect); and from baseline to week 40, respectively, −0.32, −0.19, and −0.27 (small effect). At 80 weeks, fewer patients in the early-start group (46 of 205 patients, 23%) experienced motor response fluctuations than patients in the delayed-start group (81 of 211, 38%; $p < 0.01$).

Discussion

In patients with early Parkinson disease, levodopa improves bradykinesia, rigidity, and tremor to the same order of magnitude. For all 3 symptoms, effects were larger at 22 weeks compared with 4 weeks. At 80 weeks, there were fewer patients with motor response fluctuations in the group that had started levodopa earlier.

Classification of Evidence

This study provides Class II evidence that the effect of levodopa on bradykinesia, rigidity, and tremor is larger after 22 weeks compared with 4 weeks of treatment.

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LEAP Study Group coinvestigators are listed in the appendix at the end of the article.

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Glossary

LEAP = Levodopa in EArly Parkinson's Disease; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Trial Registration Information

ISRCTN30518857, EudraCT number 2011-000678-72.

The treatment of motor symptoms in patients with Parkinson disease consists mainly of dopamine replacement therapy such as levodopa and dopamine agonists. We initiated the Levodopa in Early Parkinson's Disease (LEAP) study, which used a randomized delayed-start design, to investigate whether levodopa has a disease-modifying effect in patients with Parkinson disease.[1] The randomized delayed-start design was used to separate a possible disease-modifying effect from the effect on symptoms. This study design comprises 2 phases.[2] During phase 1, patients receive either the active drug or placebo. A difference between the 2 groups at the end of this phase may be the result of an effect on symptoms, a disease-modifying effect, or a combination of these. During phase 2, both groups receive the active drug, and persistent differences between the groups at the end of this phase are presumed to be explained by a disease-modifying effect because the effects of the drug on symptoms should be the same in both groups. The results of the LEAP study showed that levodopa has no disease-modifying effect over the course of 80 weeks.[1] The clinical implications of the primary outcomes of the LEAP study are not addressed further in the current article because they have been discussed previously.[1]

In 1969, a cohort study suggested that tremor responds as well to levodopa as bradykinesia and rigidity.[3] However, over the years, physicians noted that some patients have a tremor that does not respond well to levodopa.[4] This resulted in the current belief that tremor is less likely to improve with levodopa than bradykinesia and rigidity. However, the effect of levodopa on tremor compared with bradykinesia and rigidity has not been studied in a large randomized, placebo-controlled trial.

The first phase of the LEAP study had a randomized placebo-controlled design, thus offering the opportunity to investigate the effects of low-dose levodopa compared with placebo on separate motor signs in the first months of use in patients with early Parkinson disease. Therefore, we report post hoc analyses of clinical data of the LEAP study that were not included in the main article. This information should be useful both in clinical practice and for future trials investigating possible disease-modifying treatments in patients with early Parkinson disease. The research questions of this study are whether the effects of levodopa on separate motor signs (i.e., bradykinesia, rigidity, and tremor) are in the same order of magnitude, whether levodopa causes improvement of motor signs that are considered to be relatively levodopa unresponsive,[5] to investigate the long-duration response, and to investigate whether earlier vs later initiation of levodopa causes a higher prevalence of early signs of medication-induced motor response fluctuations at 80 weeks.

Methods

LEAP Study Design

The methods of the LEAP study have been published previously.[1] Patients were randomly assigned to the early-start group and received a 2-week dose-escalation schedule of levodopa/carbidopa and thereafter 300/75 mg per day for 78 weeks (i.e., during phase 1 and phase 2) or to the delayed-start group in which patients received placebo for 40 weeks (phase 1) followed by a 2-week dose-escalation schedule of levodopa/carbidopa and thereafter 300/75 mg per day for 38 weeks (phase 2). If during the first phase—that is, the placebo-controlled phase—patients from either arm developed the need for extra medication, the medication was converted to unblinded study medication (levodopa/carbidopa 300/75 mg per day). This meant that the patients from the early-start group continued the same dose, but knew for sure that they were taking levodopa, and that the patients from the delayed-start group switched from placebo to levodopa. In this way, patients and investigators remained blinded regarding the initial randomization.

Patients

Patients were recruited from 50 community hospitals and 7 academic hospitals in the Netherlands. Patients were eligible for enrollment if they had received a diagnosis of Parkinson disease within the previous 2 years based on the standard clinical criteria, if they had insufficient disability to warrant treatment with antiparkinson medication, if they were aged 30 years or older, and if they had a life expectancy of more than 2 years. Patients who had been treated with antiparkinson medication previously were excluded. Patients were also excluded 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.[1]

Standard Protocol Approvals, Registrations, and Patient Consents

The trial protocol of the LEAP study was approved by the ethics committee at the Amsterdam University Medical Centers in the Netherlands. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

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Trial monitoring and data management were performed in accordance with the International Conference on Harmonisation–Good Clinical Practice guidelines. All patients provided written informed consent. The trial was registered at the ISRCTN registry (ISRCTN30518857) and the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) with number 2011-000678-72.[1]

Outcomes

Patients underwent 8 study visits: at baseline (before the start of study medication) and at weeks 4, 22, 40, 44, 56, 68, and 80. The Unified Parkinson's Disease Rating Scale (UPDRS) was administered at every visit,[6] and no distinction was made regarding the ON or OFF state. To investigate the effect of levodopa on separate motor signs, the scores of the UPDRS items corresponding to a specific sign were summed. For bradykinesia, we summed the scores of UPDRS items 23, 24, 25, 26, and 31 (score range 0–36); for rigidity, UPDRS item 22 (score range 0–20); and for tremor, the scores of UPDRS items 20 and 21 (score range 0–28). We also analyzed the sum of the UPDRS part III items that are relatively responsive to levodopa (Levy A score, range 0–80) and the sum of the items that are considered relatively less or nonresponsive to levodopa (Levy B score, range 0–20).[5] The Levy A score consists of the 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 (i.e., items 19, 20, 21, 22, 24, 25, 26, and 31). The Levy B score consists of the UPDRS part III items for speech, arising from chair, posture, gait, and postural stability (i.e., items 18, 27, 28, 29, and 30). Solely at the 80-week visit, the prevalence of early signs of motor response fluctuations was assessed with the following 3 questions that could be answered by the patient with yes or no: Do you notice improvement of symptoms in response to the morning medication? Do the Parkinson symptoms worsen if you skip or forget the medication? Do the Parkinson symptoms worsen before you take the next medication?

Statistical Analysis

We compared the baseline clinical characteristics of the early-start group and the delayed-start group. All variables were normally distributed and were expressed in mean and SDs. Data were analyzed according to the intention-to-treat principle.

The response of bradykinesia, rigidity, and tremor to levodopa was analyzed by a comparison of the mean change sign-specific UPDRS scores (bradykinesia, rigidity, and tremor) between the early- and delayed-start groups. The differences in mean change scores from baseline to week 4, from baseline to week 22, and from baseline to week 40 were expressed in Hedges *g* effect sizes with their 95% confidence intervals (95% CIs). Hedges *g* effect size was calculated as follows: between-group difference in mean change scores from baseline to follow-up divided by the pooled weighted SD of the change scores of the total group (early- and delayed-start groups combined). An effect size of 0.2 refers to a small effect, 0.5 to a medium effect, and 0.8 to a large effect.[7] In addition, we performed a multivariable linear regression model that assessed the effect of treatment group on change in the sign-specific UPDRS score of bradykinesia, rigidity, and tremor between week 4 and week 22 with adjustment for the sign-specific UPDRS score at week 4. With exception of the regression model, the same statistical approach was used to assess the between-group differences in mean change Levy A and Levy B scores from baseline to week 4, from baseline to week 22, and from baseline to week 40.

Because a substantial number of patients proceeded to unblinded study medication before week 40, we additionally performed a per-protocol analysis on motor signs and Levy A and B scores. Patients were excluded from the per-protocol analyses if they were converted to unblinded study medication before week 40.

The between-group difference in the proportion of patients with any feature of early signs of motor response fluctuations (i.e., patients who answered yes to at least 1 of the 3 questions) and the between-group difference in the proportion of patients who answered yes to each question on early motor response fluctuations separately at week 80 were analyzed with the Fisher exact test. These analyses were also performed for different age groups: <50 years, 50–59 years, and ≥60 years. In addition, we conducted the same analyses for the group of patients who converted to unblinded study medication before week 40 or were in need of extra medication during the rest of the study and for the group of patients who were not converted to unblinded study medication before week 40 and did not need extra medication. In view of the explorative nature of this study, we did not correct for multiple comparisons; we expressed the results in confidence intervals.[8]

Data Availability

After deidentification, the data set that underlies the results reported in this article is available 2 years following publication to researchers conducting academic research. Requests may be directed to r.m.debie@amsterdamumc.nl.

Results

Patients

Patients were recruited between August 2011 and May 2016. A total of 222 patients were randomized to the early-start group and 223 to the delayed-start group. These patients were included in the intention-to-treat analyses. Because of a need for symptomatic relief, 6 patients in the early-start group and 47 patients in the delayed-start group were converted to unblinded study medication (levodopa/carbidopa 300/75 mg per day) before week 22. An additional 18 patients in the early-start group and 40 patients in the delayed-start group were converted to unblinded study medication between weeks 22 and 40. Thus, 198 patients from the

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Table 1 Baseline Clinical Characteristics[a]

	Intention to treat		Per protocol[b]	
	Early-start group (N = 222)	Delayed-start group (N = 223)	Early-start group (N = 198)	Delayed-start group (N = 136)
Characteristic				
Age—y	64.8 ± 8.7	65.5 ± 8.8	64.9 ± 8.2	65.3 ± 8.5
Male sex—no. (%)	157 (70.7)	154 (69.1)	140 (70.7)	96 (70.5)
UPDRS score[c]				
Total	28.1 ± 11.4	29.3 ± 12.1	27.5 ± 11.4	28.4 ± 12.5
Part I	2.4 ± 1.4	2.3 ± 1.2	2.4 ± 1.3	2.3 ± 1.1
Part II	7.3 ± 3.6	7.4 ± 3.7	7.2 ± 3.6	7.0 ± 3.5
Part III	18.4 ± 8.7	19.5 ± 9.4	17.9 ± 8.7	19.1 ± 10.0
Bradykinesia[d]	8.8 ± 4.9	9.5 ± 5.2	8.6 ± 4.9	9.3 ± 5.7
Rigidity[e]	4.0 ± 3.1	4.2 ± 3.2	3.9 ± 3.1	4.1 ± 3.1
Tremor[f]	2.1 ± 2.1	2.2 ± 2.1	2.0 ± 2.1	2.3 ± 2.2
Levy A[g]	13.7 ± 6.7	14.4 ± 7.2	13.3 ± 6.7	14.3 ± 7.6
Levy B[h]	2.4 ± 1.8	2.6 ± 2.0	2.3 ± 1.8	2.4 ± 2.1

Abbreviation: UPDRS = Unified Parkinson's Disease Rating Scale.
[a] Plus–minus values are mean ± SD.
[b] Patients were excluded from the per-protocol analyses if they were converted to unblinded study medication before week 40.
[c] Scores on the UPDRS range from 0 to 176, with higher scores indicating more severe disease; the scale includes subscales of mental function (Part I), activities of daily living (Part II), and motor function (Part III).
[d] Bradykinesia refers to the mean score of the sum of UPDRS items 23, 24, 25, 26, and 31 (score range 0–36).
[e] Rigidity refers to the mean score of the sum of UPDRS item 22 (score range 0–20).
[f] Tremor refers to the mean of the sum of UPDRS items 20 and 21 (score range 0–28).
[g] Levy A refers to the sum of UPDRS items 19 to 22 and 24 to 26 and 31 (score range 0–80).
[h] Levy B refers to the sum of UPDRS items 18 and 27 to 30 (score range 0–20).

early-start group and 136 patients from the delayed-start group were included in the per-protocol analyses. The baseline characteristics of the patients in the early- and delayed-start groups included in the intention-to-treat analyses and the per-protocol analyses were comparable (Table 1). Dopamine transporter single-photon emission CT imaging was performed in 191 patients because of participation in an ancillary diagnostic accuracy study[9] or as a part of standard clinical care. Of these 191 patients, 4 had a scan without evidence of dopaminergic deficiency.

Outcomes

In the intention-to-treat analysis, the differences between the early- and delayed-start groups in mean change from baseline to week 4, expressed as Hedges *g* effect size, was −0.33 (95% CI −0.14 to −0.52) for bradykinesia, −0.29 (95% CI −0.10 to −0.48) for rigidity, and −0.25 (95% CI −0.06 to −0.44) for tremor, all in favor of the early-start group. For the mean changes from baseline to week 22, the differences between the 2 groups were −0.49 (95% CI −0.30 to −0.68) for bradykinesia, −0.36 (95% CI −0.17 to −0.55) for rigidity, and −0.44 (95% CI −0.25 to −0.63) for tremor. The between-group differences for the changes from baseline to week 40 were −0.32 (95% CI −0.13 to −0.52) for bradykinesia, −0.19 (95% CI −0.00 to −0.38) for rigidity, and −0.27 (95% CI −0.08 to −0.46) for tremor (Figure 1A). Additional data concerning these analyses are shown in eTable 1 (links.lww.com/WNL/C422), and the histograms of the distributions of the change scores per symptom per time interval are shown in eFigures 1–3.

The per-protocol analysis of the differences between the early- and delayed-start groups in mean change from baseline was also all in favor of the early-start group: baseline to week 4 bradykinesia −0.32 (95% CI −0.10 to −0.54), rigidity −0.23 (95% CI −0.01 to −045), and tremor −0.24 (95% CI −0.02 to −0.46); baseline to week 22 bradykinesia −0.51 (95% CI −0.28 to −0.74), rigidity −0.34 (95% CI −0.12 to −0.57), and tremor −0.48 (95% CI −0.26 to −0.71); and baseline to week 40 bradykinesia −0.57 (95% CI −0.34 to −0.80), rigidity −0.34 (95% CI −0.12 to −0.57), and tremor −0.44 (95% CI −0.21 to −0.67) (Figure 1B). Additional data concerning these analyses are shown in eTable 2 (links.lww.com/WNL/C422), and the histograms of the distributions of the change scores per symptom per time interval are shown in eFigures 4–6. The multivariable linear regression model showed an effect of treatment group on change of bradykinesia ($\beta = 1.39$, $p < 0.01$), rigidity ($\beta = 0.74$, $p < 0.01$), and tremor ($\beta = 0.43$, $p < 0.01$) from week 4 to week 22 adjusted for the score at week 4.

For the Levy A and Levy B scores, the between-group differences in mean change from baseline to week 4, to week 22,

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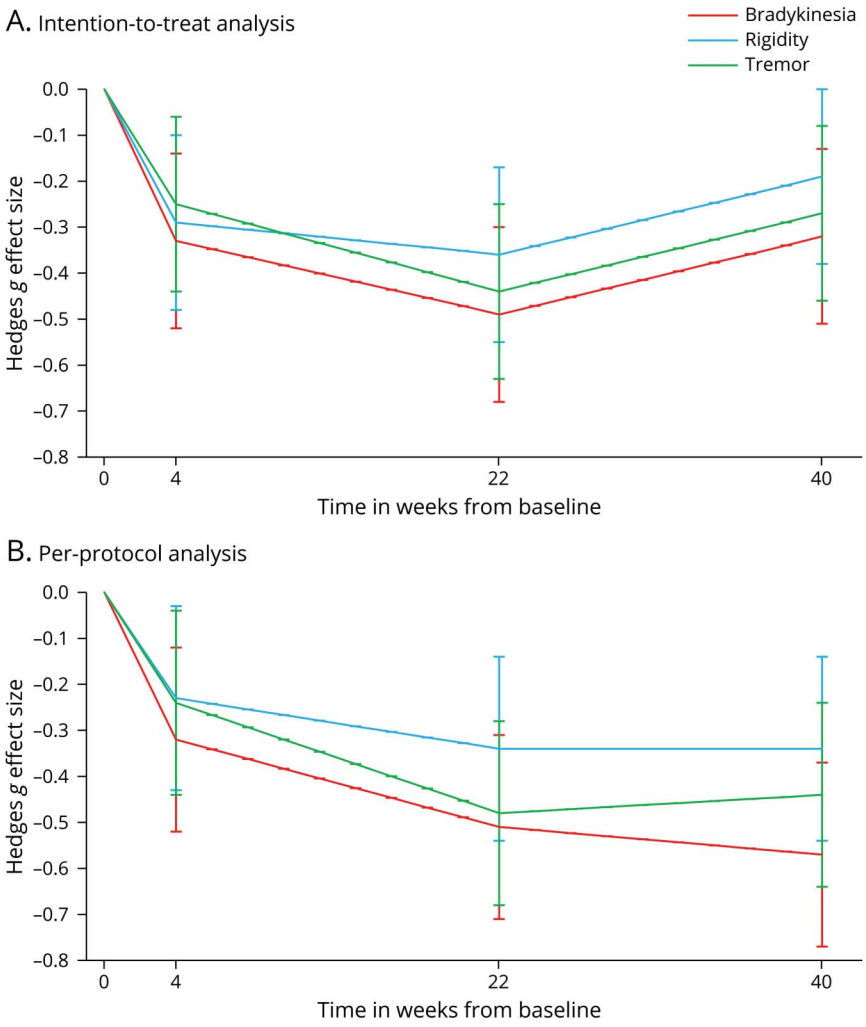
Figure 1 Difference Between the Early- and Delayed-Start Groups in the Mean Change Scores From Baseline to Weeks 4, 22, and 40 on the UPDRS Part III Corresponding to Bradykinesia, Rigidity, and Tremor; Differences Expressed in Hedges *g* Effect Sizes



Bradykinesia refers to the mean score of the sum of UPDRS items 23, 24, 25, 26, and 31 (score range 0–36). Rigidity refers to the mean score of the sum of UPDRS item 22 (score range 0–20). Tremor refers to the mean score of the sum of UPDRS items 20 and 21 (score range 0–28). The Hedges *g* effect size is calculated by dividing the between-group difference in mean change scores from baseline to follow-up by the weighted pooled SD of the change scores of the total group (early- and delayed-start groups combined). Upper and lower bars denote 95% CI interval. A negative Hedges *g* effect size indicates a lower UPDRS score in the early-start group, which implies less parkinsonism. Figure 1 shows the intention-to-treat analysis (Figure 1A) and the per-protocol analysis (Figure 1B) of the difference between the early- and delayed-start group in the mean change scores from baseline to weeks 4, 22, and 40 on the UPDRS part III corresponding to bradykinesia, rigidity, and tremor; differences expressed in Hedges *g* effect sizes. Note that the effect sizes display the between-group difference in context of disease progression. The UPDRS scores per group per visit are listed in eTables 1 and 2 (links.lww.com/WNL/C422). UPDRS = Unified Parkinson's Disease Rating Scale.

and to week 40, expressed as Hedges *g* effect size, were all in favor of the early-start group (Figure 2). The differences between the 2 groups for baseline to week 4 were −0.49 (95% CI −0.30 to −0.69) for the Levy A score and −0.16 (95% CI 0.03 to −0.34) for the Levy B score; for baseline to week 22 −0.62 (95% CI −0.43 to −0.82) for the Levy A score and −0.39 (95% CI -0.20 to −0.58) for the Levy B score; and for baseline to week 40 −0.38 (95% CI −0.19 to −0.58) for the Levy A score and −0.19 (95% CI 0.00 to −0.38) for the Levy B score. Additional data of the intention-to-treat analyses are shown in eTable 3 and eTable 4 (links.lww.com/WNL/C422), and the figure and additional data of the per-protocol analyses are shown in eFigure 7, eTable 5, and eTable 6.

There were fewer patients in the early-start group (46 of 205 patients, 23%) who experienced any early signs of motor response fluctuations compared with the delayed-start group (81 of 211 patients, 38%) at week 80 ($p < 0.01$). Table 2 shows the results of the separate questions and also for the different patient groups. eTable 7 (links.lww.com/WNL/C422) shows the results for the different age groups (<50 years, 50–59 years, and ≥60 years). The number of patients in the lower age groups (i.e., younger than 50 years and from 50 to 59 years) was relatively small, which prevents firm conclusions.

Classification of Evidence

This study provides Class II evidence that the effect of levodopa on bradykinesia, rigidity, and tremor is larger after 22 weeks compared with 4 weeks of treatment.

Discussion

The first phase of the LEAP study had a randomized placebo-controlled trial design that we used to investigate the effect of levodopa on separate motor signs up to 40 weeks. With a

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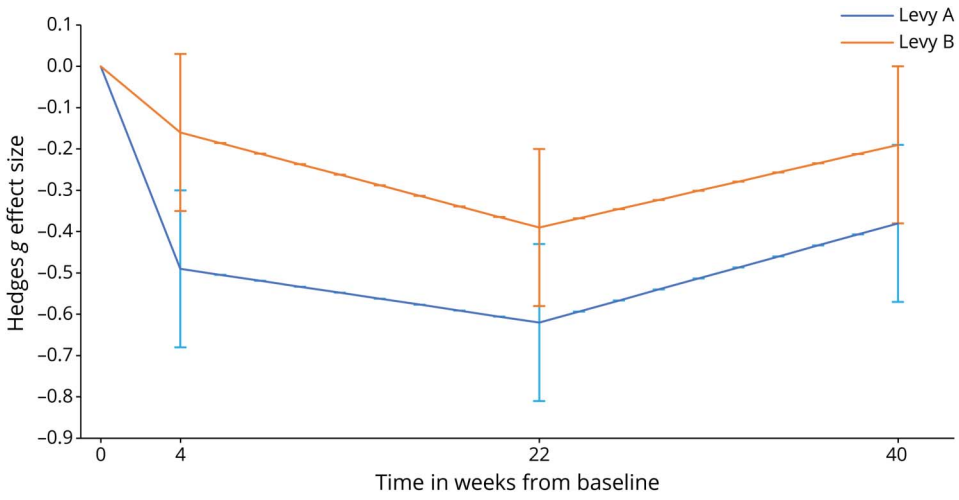
Figure 2 Difference Between the Early- and Delayed-Start Groups in Mean Change Scores From Baseline to Weeks 4, 22, and 40 in Levy A and Levy B; Differences Expressed as Hedges *g* Effect Sizes



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 refers to a sum of UPDRS part III items for speech, arising from chair, posture, gait, and postural stability (range 0–20 points). The Hedges *g* effect size is calculated by dividing the between-group difference in mean change scores from baseline to follow-up by the weighted pooled SD of the change scores of the total group (early- and delayed-start groups combined). Upper and lower bars denote 95% CI interval. A negative Hedges *g* effect size for the Levy A or Levy B score indicates a lower Levy A or Levy B score in the early-start group, which implies less parkinsonism. Note that the effect sizes display the between-group difference in context of disease progression. The Levy A and Levy B scores per group per visit are listed in eTables 3 and 4 (links.lww.com/WNL/C422). UPDRS = Unified Parkinson's Disease Rating Scale.

relatively low daily dose of levodopa in patients with early Parkinson disease, we found a small effect after 4 weeks, a small to medium effect after 22 weeks, and a small effect after 40 weeks in the intention-to-treat analysis on bradykinesia, rigidity, and tremor. At 40 weeks, the effects were larger in the per-protocol compared with the intention-to-treat analysis and in the same order of magnitude as the effects at 22 weeks. The effects measured at 40 weeks in the intention-to-treat analysis are probably smaller because almost 40% of the patients allocated to the delayed-start group already used levodopa instead of placebo. The patients allocated to the delayed-start group who converted to unblinded levodopa before week 40 are likely to have been the patients with more severe disease because they were in need of symptomatic treatment, whereas other patients in the delayed-start group were not. In the early-start group, only 10% of the patients converted to unblinded levodopa before week 40. Consequently, in the per-protocol analysis, there may have been proportionately fewer patients with more severe disease in the delayed-start group compared with the early-start group. This difference could have resulted in an underestimation of the levodopa effect at week 40 in the per-protocol analysis.

The effect sizes of all 3 motor signs suggested that the effect of levodopa was larger after 22 weeks compared with 4 weeks of use (including a 2-week dose-escalation schedule), which was confirmed by the regression model. This finding is in line with the so-called long-duration response, which is levodopa's prolonged effect that builds up over weeks by repeated regular levodopa dosages and takes place in addition to the short-duration response, which is more closely related to levodopa plasma levels.[10–13] The symptomatic effect of levodopa did not increase after 22 weeks. Therefore, we hypothesize that the long-duration response of 300 mg levodopa per day reaches a maximum between 4 and 22 weeks, which is in line with previous cohort studies that suggested the maximum effect to be reached after weeks to months.[3,12] The ELLDOPA trial had a randomized, placebo-controlled design and aimed to investigate whether levodopa had a disease-modifying effect in patients with early Parkinson disease.[14] The doses were increased to the full amount over a period of 9 weeks in a blinded fashion. Although the long-duration response was not specifically evaluated in the ELLDOPA trial, the figure showing the main outcome suggested that the maximum effect on the total UPDRS was reached within 24 weeks after randomization. The current results, since also derived from a randomized, placebo-controlled study setting, broaden the knowledge of the long-duration response of separate motor symptoms. The mechanism underlying the long-duration response is not exactly known. One hypothesis postulates the occurrence of postsynaptic changes in striatal neurons in response to exogenous levodopa and another that the long-duration response is associated with motor learning by which motor improvement is gained.[12] Despite the unknown underlying mechanism, for clinical practice, the notion of the long-duration response is relevant, for instance in timing the evaluation of levodopa's effect as well as in OFF-ON scoring. For future studies of symptomatic add-on medication and for clinical practice, it would be useful to gain more exact information about the time to reach the maximum effect of levodopa's long-duration response.

The current belief that bradykinesia and rigidity respond better to levodopa than tremor could have resulted from the

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Table 2 Three Questions Regarding Symptoms of Early Motor Response Fluctuations at 80 Weeks

	Patients who were converted to unblinded study medication or needed extra medication during the study		Patients who did not convert to unblinded study medication and did not need any extra medication during the study		All patients intention-to-treat	
	Early (N = 57)	Delayed (N = 102)	Early (N = 148)	Delayed (N = 109)	Early (N = 205)	Delayed (N = 211)
Any of the below 3 questions answered with yes (i.e., by means of these 3 questions any symptoms of motor response fluctuations) or all 3 questions answered with no						
Yes % (n)	37 (21)	49 (50)	17 (25)	29 (32)	22 (46)	39 (82)
No % (n)	63 (36)	51 (52)	83 (123)	71 (77)[c]	78 (159)	61 (129)[a]
Improvement due to medication in morning?						
Yes % (n)	25 (14)	30 (31)	11 (16)	18 (20)	15 (30)	24 (51)
No % (n)	75 (43)	70 (71)	89 (133)	82 (89)	85 (176)	76 (160)[b]
Complains Parkinson symptoms worsen in case medication forgotten?						
Yes % (n)	21 (12)	24 (24)	8 (12)	15 (16)	12 (24)	19 (40)
No % (n)	79 (45)	76 (78)	92 (137)	85 (93)	88 (182)	81 (171) [d]
Complains Parkinson symptoms worsen before intake of next medication?						
Yes % (n)	23 (13)	25 (26)	9 (14)	16 (17)	13 (27)	20 (43)
No % (n)	77 (44)	75 (76)	91 (134)	84 (92)	87 (178)	80 (168)[e]

Early refers to the early-start group. Delayed refers to the delayed-start group.
The *p* values resulted from the comparison of the number of patients who answered yes and the number of patients who answered no to each question with the Fisher exact test.
[a] $p < 0.01$.
[b] $p = 0.01$.
[c] $p = 0.02$.
[d] $p = 0.04$.
[e] $p = 0.07$.

finding that there are patients with a largely levodopa-resistant tremor.[4] However, in clinical practice, in a substantial proportion of these patients, tremor tends to be controlled with higher-than-average levodopa doses. Data from a cohort study in 1969, however, already suggested that levodopa's effect on tremor is as large as the effect on bradykinesia and rigidity.[3] However, these findings were never followed by data of a larger randomized, placebo-controlled trial. Note that patients were not included in the LEAP study if their most prominent symptom was tremor, such as a severe resting tremor that was present almost continuously or resulted in disability. However, patients who experienced disability due to other symptoms (e.g., bradykinesia) were also excluded. Nevertheless, our findings are in line with the cohort study from 1969[3] and with the findings of a more recent study,[15] which found that patients in whom levodopa was increased had significant improvements in rest tremor, rigidity, bradykinesia, posture, and gait compared with those with no treatment change. Taking previous literature and the current study results into account, although there are indeed patients with a tremor who does not improve with a low to normal dosage of levodopa, overall, in a large group of early untreated patients with mild symptoms, levodopa improves tremor in the same order of magnitude as rigidity and bradykinesia.

A distinction was made between items of the UPDRS part III (motor function) that were considered relatively responsive to levodopa (Levy A score) and relatively nonresponsive to levodopa (Levy B score).[5] The validity of this dichotomy of the UPDRS part III has never been formally assessed. We found that both the Levy A and Levy B scores improved with low-dose levodopa compared with placebo, although the magnitude of the effect was less for Levy B than Levy A, suggesting that Levy B scores can also be considered to be at least partially levodopa responsive in patients with early Parkinson disease. This is in line with findings of 2 recent studies in which the Levy B scores improved after the start of dopamine replacement therapy in patients with longer disease duration or increase of dopamine replacement therapy in patients with relatively short disease duration.[10,15] This finding emphasizes that the pathophysiology of various so-called axial motor symptoms including impairment of speech, gait, and posture stability also includes a dopaminergic component. For clinicians in daily practice, this justifies judicious but

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concerted attempts to further increase levodopa in patients experiencing disability arising from axial motor symptoms, particularly in early stages of Parkinson disease, but presumably also in later disease stages.

Multiple parameters need to be taken into account when considering the right moment to start pharmacologic therapy in patients with Parkinson disease, such as current disability, quality of life, and the risk of developing motor response fluctuations.[16] Motor response fluctuations are a well-known complication of levodopa use. Higher levodopa dosages and a longer disease duration are associated with the occurrence of motor response fluctuations.[14,17] The results published in the original LEAP publication and the current results concern the timing of initiation of levodopa and the possible relation with motor response fluctuations. In the original LEAP publication, we reported that patients in the early-start group did not experience more dyskinesia or OFF time at 80 weeks.[1] These analyses were based on the specific UPDRS items covering these features, which inquired whether dyskinesia or OFF time was present. However, despite that dyskinesia and OFF periods can occur early in the disease course, they usually occur later. Because we anticipated that this method may be less sensitive for picking-up subtle signs, we have added the 3 questions concerning early signs of motor response fluctuations (i.e., wearing-off) to the protocol before the start of the study. We did not present the results of these questions in the original LEAP publication because these questions had not been subjected to a rigorous validation process and because of space limitations. And interestingly, these results showed that fewer patients allocated to 80 weeks of treatment with levodopa (i.e., early-start group) experienced early signs of motor response fluctuations at 80 weeks compared with the patients randomized to initially receive placebo followed by 40 weeks levodopa (i.e., delayed-start group). Note that the delayed-start group had a nonsignificant 1.2 higher total UPDRS score at baseline, which is also well below the clinically significant difference. However, we cannot rule out that this may have influenced the results.[18] Patients who converted to unblinded study medication or required extra medication during the study more often had wearing-off at 80 weeks compared with the patients who followed the study protocol. This is likely due to more severe disease in combination with a higher dose of levodopa in this group. In the delayed-start group, more patients converted to unblinded study medication than in the early-start group, which may have caused a bias toward less progressive disease overall in the delayed-start group in the per-protocol analysis. Among the patients who did follow the study protocol, however, the early-start group less often had wearing-off compared with the delayed-start group. These observations suggest 2 related conclusions: (1) patients who need medication sooner, implying more severe disease, more often have signs of wearing-off, and (2) patients with evidence for less severe disease who start levodopa earlier less often develop wearing-off compared with patients who start levodopa later. Motor response fluctuations including dyskinesia appear due to continuous degeneration of functional dopaminergic neurons, in combination with a variety of changes in postsynaptic striatal medium spiny neurons. However, based on these analyses, we cannot plainly deduce that there is less disease progression in patients who started levodopa earlier. That is because the questions were not rigorously validated and the levodopa dose might have been too low for patients with more severe disease to experience actual benefit and consequently wearing-off. This also would be in contrast with our primary analysis of the LEAP study, where we concluded that there was no disease-modifying effect following an earlier start of levodopa. Alternatively, the later introduction of levodopa in the delayed-start group occurred at a time when patients had become more symptomatic, which may have attuned them sooner to its short-duration response. It is also theoretically possible that the earlier use of levodopa, at a time when the presynaptic storage and release of dopamine may be more physiologic, could result in less postsynaptic pharmacodynamic changes in response to the pulsatile stimulation of dopamine receptors that might occur faster with later treatment. Our findings are not in keeping with a previous case-control study,[17] who found no difference in response fluctuations between patients with longer disease duration who started treatment later in the disease course (due to lack of access to medication) and patients who started treatment earlier. Those results suggest that earlier start of levodopa neither worsens nor protects against the development of response fluctuations. However, because of its case-control design, there is more risk of bias compared with the current results. Taken together, our finding of fewer response fluctuations following an early start of levodopa is interesting but also unexpected and deserves further study.

A limitation of the current results concerning motor symptoms is that they are derived from post hoc analyses. Yet, we only focus on intuitive, clinically relevant outcomes. Another limitation of the data presented here is the short follow-up time. Longer follow-up in the previously mentioned case-control study did not demonstrate a relation between motor response fluctuations and the duration of levodopa use, but it did with disease duration and higher levodopa dosage.[17] Trials that compared the occurrence of dyskinesia and motor response fluctuations between patients who started with levodopa compared with patients who received a levodopa sparing strategy treatment showed inconsistent results.[19-21] We are conducting an open-label follow-up of the LEAP study, 3 and 5 years after baseline.

We conclude that the use of a low dose of levodopa in patients with early Parkinson disease improves bradykinesia, rigidity, and tremor to the same order of magnitude. In these patients, our results suggest that the effect of levodopa on bradykinesia, rigidity, and tremor was larger after 22 weeks compared with 4 weeks of treatment, proposing that the full extent of the long-duration response to levodopa takes between 4 and 22 weeks to develop. Levodopa also improved axial symptoms in patients with early Parkinson disease, for example, gait and postural stability, although to a lesser extent. We did not find more motor

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response fluctuations in the group that started levodopa earlier, in fact preliminary evidence suggested that these were less frequent in this group, however follow-up time was short.

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Disclosure

H.L. Frequin, J. Schouten, C.V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, J.M. Dijk, G. Deuschl, A.E. Lang, M.G. Dijkgraaf, and R. J. de Haan report no disclosures relevant to the manuscript. R.M.A de Bie reports grants from the Parkinson Vereniging (Dutch patient organization), Stichting ParkinsonFonds (Dutch funding organization for Parkinson disease research), Stichting Parkinson Nederland (Dutch funding organization for Parkinson disease research), and the Netherlands Organization for Health Research and Development (Dutch governmental fund for health research, project number 0-82310-97-11031). These organizations did not have a role in the study design, data collection, and analysis, the interpretation of data, writing the report, or the decision to submit the paper for publication. Go to Neurology.org/N for full disclosures.

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Continued

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Appendix 1 *(continued)*

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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/C421.

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