

# Parkinson Disease, the Effect of Levodopa, and the ELLDOPA Trial

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**T**he introduction of effective doses of levodopa for the treatment of Parkinson disease (PD)<sup>1,2</sup> was a revolutionary step in overcoming symptoms of a progressive neurodegenerative disease. This took place a little more than 30 years ago, and still, today, levodopa remains the most effective drug for the reversal of symptoms of PD.<sup>1,2</sup> If there were no associated adverse effects with long-term use, treatment of PD would be a simple matter. But most of the physician's effort in providing optimum care of patients with PD is in trying to overcome all too common adverse effects of levodopa.

## THE NATURE OF THE PROBLEMS

### Motor Complications With Levodopa Therapy

Motoric adverse effects of dyskinesias and clinical fluctuations ("wearing-off" and "on-off" phenomena) often develop after patients have been treated with levodopa for a period of time. After 5 years of treatment, 75% of patients no longer have a smooth, stable, and effective response.<sup>3</sup> It was not long after the introduction of levodopa that concern about these motor complications led to the suggestion that it might be wise to delay the introduction of levodopa until it was really needed.<sup>4</sup>

### *For editorial comment see page 524*

Since then there have been several debates in public forums<sup>5-9</sup> and within American Academy of Neurology courses at its annual meetings (Charles Markham, MD, vs S.F., 1996 Course on Controversies in Neurology; Roger Duvoisin, MD, vs S.F., 1996 Course on Movement Disorders) and at plenary sessions of International Congresses of Movement Disorders (1996, Vienna, Austria, Gerald Stern, MD, vs Eldad Melamed, MD; 1998, New York, NY, Yves Agid, MD, vs Eldad Melamed, MD), and also reports in the literature<sup>10-13</sup> on the merits and problems of earlier vs later introduction of levodopa.

Younger patients are more likely to develop dyskinesias and motor fluctuations than are older patients,<sup>14-16</sup> with virtually every early-onset patient (onset before age 40 years) ultimately developing these complications.<sup>17</sup> There is uncertainty as to whether the duration and dosage of levodopa is primarily responsible for these motor complications<sup>18,19</sup> or whether they occur simply because of increasing severity of the disease.<sup>10,20,21</sup> It is likely that a combination of both severity of disease and the medication itself are responsible.

When levodopa is introduced in patients with more advanced stages of PD<sup>20,22</sup> or in patients with severe destruction of substantia nigra dopaminergic neurons as with *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism<sup>23-25</sup> or with postencephalitic parkinsonism,<sup>26-29</sup> motor complications occur after a shorter latency following exposure to levodopa, indicating that the quantity of the loss of dopamine terminals is an important factor in the development of these adverse effects. These patients may develop dyskinesias and fluctuations within weeks to months after starting levodopa treatment. On the other hand, treatment of PD with dopamine agonists instead of with le-

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levodopa reduces the likelihood of developing dyskinesias and motor fluctuations.

Both open-label and double-blind, placebo-controlled studies with dopamine agonists as the sole or concomitant therapy report fewer dyskinesias and response fluctuations than seen with levodopa therapy. Rinne<sup>30-32</sup> first proposed that early use of the dopamine agonists can reduce the likelihood of developing motor complications seen with long-term levodopa therapy as the sole therapy. The Rinne reports were based on retrospective analyses, using historical rather than contemporary controls. The result of a large, multicenter, drug company-sponsored, double-blind, placebo-controlled study that evaluated patients with early (mild) PD comparing bromocriptine mesylate alone, bromocriptine with levodopa, and levodopa alone was never published. However, Weiner et al<sup>33</sup> participated in this study, and they published the results obtained from their small component of this larger study; they were not able to confirm Rinne's findings. Since then, however, in other randomized trials there were fairly consistent reports of fewer motor complications in patients who started with bromocriptine<sup>34-37</sup> or cabergoline,<sup>38</sup> to which levodopa was later added to the regimen, than in those subjects treated with levodopa alone. Currently in progress are double-blind trials comparing pergolide mesylate vs levodopa, pramipexole dihydrochloride vs levodopa, and ropinirole hydrochloride vs levodopa in patients with early disease requiring symptomatic therapy. Animal studies in primates with parkinsonism induced by MPTP also show that dopamine agonists induce fewer dyskinesias with equal antiparkinson effect compared with levodopa treatment.<sup>39,40</sup> Because dopamine agonists are the most powerful antiparkinson medications after levodopa, if one desires to use dopa-sparing strategies, one can choose among the dopamine agonists.

The mechanism as to how the motor complications develop remains unclear, but that proposed by Chase and colleagues<sup>41,42</sup> is widely regarded. Chase<sup>43</sup> suggests that intermittent (compared with continuous) administration of levodopa is the main contributor to this problem. Dopaminergic neurons from the nigra terminate on dendrites of the  $\gamma$ -aminobutyric acid (GABA)ergic medium spiny neurons in the neostriatum, which in turn project to the globus pallidus externa and interna and to the substantia nigra pars reticulata. Striatal medium spiny neurons also receive other inputs, including cortical glutamatergic efferents, and both extrinsic and intrinsic nerve terminals containing serotonin, adenosine, acetylcholine, and somatostatin. Chase and associates<sup>41,42</sup> propose that intermittent levodopa administration alters the striatal dopaminergic medium spiny neurons and potentiates the glutamate receptors (of the *N*-methyl-D-aspartate [NMDA] subtype) on these GABAergic striatal efferents. The result would be excessive activity of these striatal efferents, which also release a variety of neuropeptides (enkephalin and neurotensin in the D<sub>2</sub> receptor indirect pathway to the globus pallidus externa; dynorphin, neurotensin, and substance P in the D<sub>1</sub> receptor direct pathway to the globus pallidus interna; and substantia nigra pars reticulata). Along with this concept that

these medium spiny neurons, via NMDA receptor activation, are producing the motor complications is the finding from Chase's laboratory that NMDA antagonists can reduce dyskinesias in MPTP-lesioned primates<sup>44</sup> and can reverse the shortened levodopa response time in the 6-hydroxydopamine-lesioned rats, an animal model of PD.<sup>45</sup>

The disabling motor complications that commonly ensue several years after initiation of levodopa greatly limits the overall effectiveness of the drug. Yet, levodopa is superior to all other currently available drugs<sup>46</sup> primarily because it is the most effective agent in reversing symptoms in patients with more advanced stages of PD, and because it takes less time to reach an effective dosage compared with dopamine agonists. In early PD, however, a number of studies report comparable antiparkinson effects from dopamine agonists and levodopa.<sup>31,32,34,47</sup> Thus, in early PD, one has considerable choice in selecting the medication to treat the symptoms.

### The Question of Levodopa Toxicity

In historical terms, the motor complications of long-term levodopa use were the first indication that led to the suggestion that perhaps the introduction of levodopa should be delayed until the drug was needed, ie, when symptoms could not be controlled by other remedies. The concept of this approach is to postpone the development of such adverse effects. More recently, with the awareness that levodopa could increase oxidant stress in dopaminergic neurons, concern has arisen whether such stress can lead to more rapid progression of the disease itself, ie, enhance further neurodegeneration of dopaminergic neurons. This concern has evolved because oxidant stress has been and continues to increasingly be a widely suspected mechanism causing or contributing to neurodegeneration, particularly in the monoaminergic neurons, the cells that are predominantly lost in patients with PD.<sup>48-77</sup>

There is considerable evidence from in vitro studies indicating that levodopa is toxic to neurons in culture<sup>78-92</sup>; and see also review by Fahn<sup>93</sup> for earlier reports. The concentration of levodopa used in these in vitro studies are typically much greater than would be expected in brain tissue in patients treated with levodopa. Moreover, recent in vitro studies show levodopa is not toxic if glial cells are present in the tissue culture,<sup>94,95</sup> and that the mechanism by which astrocytes offer protection may be by increasing synthesis of reduced glutathione.<sup>96</sup>

Studies of giving levodopa to healthy animals<sup>96-100</sup> and to nonparkinsonian humans<sup>101,102</sup> have failed to find any loss of dopaminergic neurons in the substantia nigra. Studies in rodent models of PD have provided mixed results. Two studies<sup>103,104</sup> demonstrated loss of nigral neurons in animals following levodopa treatment; both used rodents in which the dopaminergic neurons had been compromised, trying to mimic the condition in PD. However, in a more recent study in the rodent model, Murer et al<sup>105</sup> found that long-term treatment with levodopa is not toxic for the remaining dopaminergic neurons, but instead promotes their recovery. Thus, there is genuine uncertainty what effect on dopaminergic neurons levodopa therapy in patients with PD will actually have.<sup>106,107</sup>

**Table 1. Delay of Levodopa Treatment in Younger and Older Patients\***

Responses	How Often Do You Delay Starting Levodopa in Patients?	
	<60 y	≥60 y
Always	40.0	20.8
Most of the time	45.8	54.2
Seldom	12.5	20.8
Never	1.2	4.2

\*Results of survey of 120 neurologists, given as percentage.

**Table 2. Reasons for Delaying Levodopa Treatment\***

Responses	How Likely Is It That Levodopa	
	Enhances Progression of PD?	Is Responsible for Motor Fluctuations?
Extremely likely	1.7	13.5
Very likely	3.4	28.6
<b>Likely</b>	<b>16.8</b>	<b>26.1</b>
<b>Equally Likely/Unlikely</b>	<b>25.2</b>	<b>16.0</b>
<b>Unlikely</b>	<b>32.0</b>	<b>10.1</b>
Very unlikely	13.5	4.2
Extremely unlikely	7.6	1.7

\*Results of survey of 120 neurologists, given as percentage. Boldface rows represent cluster of responses indicating uncertainty (clinical equipoise) about likelihood of levodopa enhancing progression of Parkinson disease (PD).

## HOW DO NEUROLOGISTS DEAL WITH THE ABOVE PROBLEMS?

To collect data on current patterns of treatment of PD by neurologists, a questionnaire was prepared by the Parkinson Study Group and distributed to the neurologists attending the symposium on the "Etiology, Prevention and Treatment of Parkinson's Disease" held on October 22, 1995, just prior to the annual meeting of the American Neurological Association in Washington, DC. To ensure 100% response, the symposium was delayed prior to the last speaker to allow the 120 attendees sufficient time to complete the questionnaire. The results were initially presented at the same-titled symposium 1 year later, of which an abstract was published.<sup>108</sup> The results of the survey are presented in **Table 1** through **Table 4**.

The survey found (Table 1) that 85.8% and 75.0% of surveyed neurologists delay starting levodopa treatment in younger and older patients, respectively, either all the time (40.0% and 20.8%, respectively) or most of the time (45.8% and 54.2%, respectively). Only 12.5% and 20.8%, respectively, seldom delay starting levodopa therapy, and only 1.2% and 4.2%, respectively, never delay starting levodopa therapy.

The reasons for delaying levodopa are shown in Table 2; 68.2% of the respondents believe that levodopa is likely (to extremely likely) to be responsible for motor fluctuations, while 16.0% believe that it is unlikely (to extremely unlikely) to cause fluctuations;

**Table 3. Indications for Controlled Clinical Trial\***

Responses	Is a Controlled Clinical Trial Warranted	
	To Assess If Levodopa Hastens Progression?	To Assess If Levodopa Causes Fluctuations?
Urgent	37.0	31.4
Moderately urgent	41.2	44.9
Slightly urgent	6.7	14.4
Uncertain	5.0	0.9
Slightly unwarranted	3.4	3.4
Moderately unwarranted	5.0	2.5
Definitely unwarranted	1.7	2.5

\*Results of survey of 120 neurologists, given as percentage.

**Table 4. Treatment Strategy Changes Based on Results of Controlled Clinical Trial\***

Responses	Would You Change Your Strategy			
	If Levodopa Hastens Progression?		If Levodopa Is Responsible for Fluctuations?	
	Younger Patients	Older Patients	Younger Patients	Older Patients
<b>Those Who Would Not Delay Levodopa (Seldom or Never in Table 1)</b>				
No change	5.3	3.2	26.3	21.9
Delay longer	94.7	90.3	63.2	68.8
Other	0.0	6.5	10.5	9.4
<b>Those Who Would Delay Levodopa (Always or Most of the Time in Table 1)</b>				
No change	59.5	57.3	44.3	42.2
Start earlier	39.7	41.7	50.4	52.0
Other	0.8	0.9	5.2	5.9

\*Results of survey of 120 neurologists, given as percentage. The survey asked if neurologists would change their current treatment pattern based on the results of a controlled clinical trial.

16.0% were equally uncertain. Fewer neurologists believe that levodopa enhances progression of PD (21.9%); in fact, most (53.1%) believed this to be unlikely (to extremely unlikely) and 25.2% were equally uncertain. Another way to view the results presented in Table 2 is to look at the results from the middle 3 rows (boldface print), hovering around the answer of "likely/unlikely"; from this perspective, 74.0% of the neurologists have considerable uncertainty (clinical equipoise) about the likelihood of levodopa enhancing the progression of PD. There was much more "certainty" in the response to the question as to whether levodopa is the likely cause of motor fluctuations, 42.1% responding very likely to extremely likely, but still 52.2% expressing uncertainty or clinical equipoise about this question (data from middle 3 rows).

The survey then questioned the neurologists as to whether a controlled clinical trial is indicated to determine levodopa's role in motor response fluctuations and in progression of PD (Table 3). These results indicate that 84.9% and 90.7% of neurologists surveyed believe that a controlled clinical trial is urgent, moder-

ately urgent, or slightly urgent to determine whether levodopa hastens progression or is responsible for fluctuations, respectively. This response probably reflects the great deal of uncertainty of the effects of levodopa on the underlying disease and its relation to motor complications.

The survey also asked if neurologists would change their current treatment pattern based on the results of a controlled clinical trial. Their responses (Table 4) show that more than 90% of neurologists who currently do not delay the introduction of levodopa would delay such treatment if it were shown that levodopa hastens progression of PD (Table 4, top). For those who currently delay levodopa therapy, only about 40% to 50% of the neurologists would start levodopa earlier if it were shown that the drug does not hasten the progression of PD or if it were not responsible for motor fluctuations (Table 4, bottom).

#### A CONTROLLED CLINICAL TRIAL TO DETERMINE IF LEVODOPA ALTERS THE NATURAL HISTORY OF PD: THE ELLDOPA TRIAL

The Parkinson Study Group has been awarded a grant (NS34796) from the National Institutes of Health to conduct a controlled clinical trial in patients with newly diagnosed PD to determine whether levodopa slows or hastens the progression of PD. This Earlier vs Later L-DOPA (ELLDOPA) study is a placebo-controlled, randomized, double-blind clinical trial.

The *primary objective* will be achieved by comparing the rates of progression of PD as measured by the change in the Unified Parkinson's Disease Rating Scale (UPDRS) in untreated subjects with early PD receiving placebo or levodopa. Three dosages of carbidopa-levodopa will be used, namely, 32.5/150 mg/d, 75/300 mg/d, and 150/600 mg/d, to obtain a dose-response curve. The rate of progression for each subject will be measured by comparing the differences in UPDRS scores between baseline and the final evaluation after 40 weeks' exposure to levodopa or placebo. Both evaluations will be performed in a drug-free state, the final one after 14 days' washout of levodopa (therefore, 42 weeks after baseline). These UPDRS assessments will be carried out by the same blinded primary rater, who will otherwise not have been involved in the clinical follow-up or medication adjustments during the trial. Another blinded investigator, the site's treating investigator, will regularly observe the subject during the trial to document the occurrence of adverse effects (eg, motor fluctuations and dyskinesias), to adjust medication if necessary, and to help reinforce for each subject the importance of completing the trial.

The *secondary objectives* of ELLDOPA are to determine (1) when the long-duration response to levodopa is lost; (2) if the dosage of levodopa is a factor in the loss of the long-duration response; (3) how common fatigue is in patients with early disease and how severe it is; and (4) how early initiation or the dosage of levodopa affects signs and symptoms of PD, the quality of life, and fatigue. Although a long duration of exposure to levodopa or placebo would be desirable to increase the

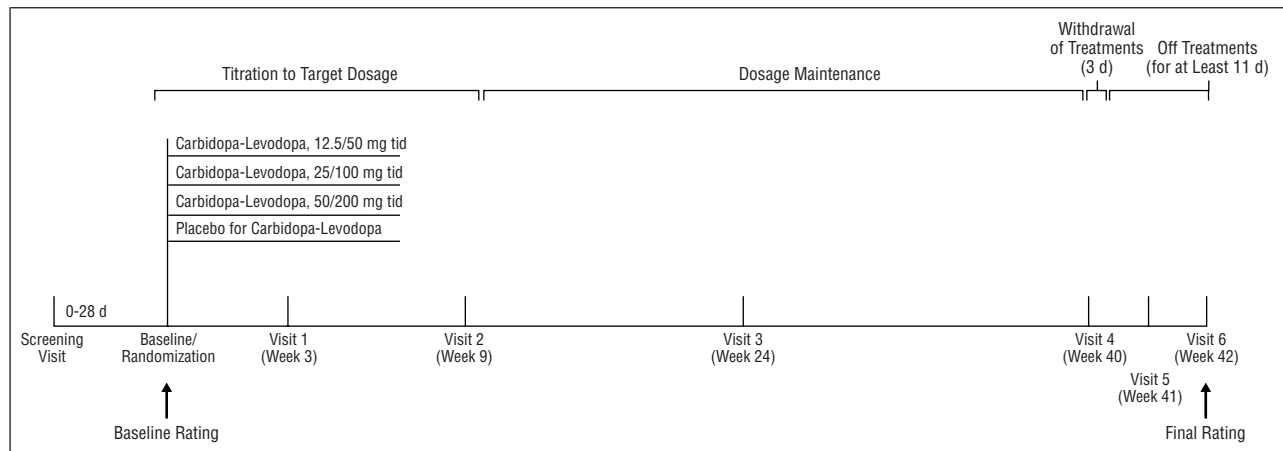
power of the study, we have limited the trial to 40 weeks (9 months) to keep all subjects in the study and minimize premature terminations from the trial, which could occur if parkinsonian symptoms worsen to the point where symptomatic treatment is necessary. No other anti-PD medication will be allowed in the trial to avoid the possible confounding influence of other drugs on the natural history of PD.

Eligibility is restricted to patients with PD who have had no prior exposure to levodopa (to avoid any possible priming effect) or to a dopamine agonist (to avoid any possible proposed neuroprotective effect or altered dopamine receptors). Prior exposure to selegiline hydrochloride, amantadine hydrochloride, or anticholinergics are allowed, but these drugs must be withdrawn prior to entry into the study (up to 4 months for selegiline). Duration of PD must be less than 2 years since diagnosis to avoid bias of purposefully enrolling patients with more slowly progressing PD. A short duration of symptoms plus no knowledge of levodopa responsiveness allows for the potential enrollment of patients who will eventually be diagnosed as having a Parkinson-plus syndrome, such as multiple-system atrophy or progressive supranuclear palsy, and it is anticipated in the power calculations that approximately 15% of enrolled subjects will eventually have 1 of these atypical parkinsonian syndromes, but distributed throughout the 4 treatment arms. Parkinsonian patients who already have signs or symptoms suggestive of a Parkinson-plus syndrome are to be excluded.

A total of 360 subjects with early, mild PD, not yet requiring symptomatic treatment are to be enrolled in a total of 35 clinical sites in North America. Subjects will be randomly assigned to 1 of 4 treatment groups, with 90 subjects in each treatment arm: (1) placebo; (2) carbidopa-levodopa, 12.5/50 mg 3 times a day; (3) carbidopa-levodopa, 25/100 mg 3 times a day; and (4) carbidopa-levodopa, 50/200 mg 3 times a day. The plateau dose of levodopa is to be reached after a gradual increase in dosage to avoid induction of adverse effects.

At baseline, the severity of PD (measured clinically by the UPDRS) will be assessed for each subject by the site's primary rater who remains "blinded" as to treatment assignment throughout the duration of the study and who never sees the subject again until after a 2-week washout of all experimental treatments, which are withdrawn 40 weeks after the baseline examination. Furthermore, the primary rater is not to be exposed to any discussions regarding subjects in the trial. The method of performing the UPDRS by the primary rater has been altered so that the motor examination (part 3) is performed first, prior to any direct questioning of the subject to obtain the results of the behavioral (part 1) and activities of daily living (part 2) scores. These steps are taken to ensure lack of any bias as to concept of the assigned treatment arm or of the clinical severity of the disease.

The treating investigator and nurse coordinator monitor the severity of PD and any adverse effects from medications during the study. If necessary, the treating investigator can adjust the frequency and timing of treatment medications to minimize adverse effects. However, the total daily dosage on tablets is to be main-



*Earlier vs Later L-DOPA (ELLDOPA) study design. Following a screening visit to confirm eligibility and obtain consent, 360 research subjects will be randomized at baseline to 1 of 4 treatment groups (90 in each group). The primary analysis of treatment effects will be the Unified Parkinson's Disease Rating Scale scores by the blinded independent rater, comparing the baseline rating (off treatment) with the rating 42 weeks later (off treatment). See text for details. tid indicates 3 times a day.*

tained if at all possible. Preplanned steps for modifying the dosage should adverse effects be encountered are to be implemented. Only if dosage adjustments are unsatisfactory are certain medications allowed to overcome the adverse effects, such as benzodiazepines, antidepressants, domperidone, carbidopa, and clozapine. No anti-PD drug is allowed at any time. If a subject must receive symptomatic treatment prior to the completion of 42 weeks in the study, he or she will need to drop out of the study. The study design and clinic visits are shown in the **Figure**.

After 40 weeks of treatment, a step-down 3-day washout of investigation medications occurs. The subject returns 7 and 14 days after all medications have been eliminated to assess changes in UPDRS scores at these time points. Because the washout phase is the most crucial part of the study, support and encouragement by the treating investigator and nurse coordinator are anticipated. If any subject is not able to complete 14 days off all medications, he or she is to return sooner for the final UPDRS assessment.

The statistical analysis will compare the rate of progression of PD for each of the 4 treatment groups and determine if there is a trend for a greater or slower rate of progression as a function of the dose of levodopa used (the primary outcome variable), with the null hypothesis being there is no difference from placebo. The secondary outcome variables will also be analyzed. These are (1) quality of life, (2) status of long-duration benefit, (3) severity of fatigue, (4) change in depressive symptoms, (5) the occurrence of levodopa-related complications, and (6) the development of any adverse effects.

Whether levodopa does or does not aggravate underlying PD is extremely important, both as a scientific issue and as a clinical one, since levodopa is the major drug used to treat the symptoms of PD. We ask support for this study from the neurologic community by referring suitable patients with PD for the ELLDOPA Study. The names and locations of the ELLDOPA sites can be found in the Parkinson Study Group Web page ([www.parkinson-study-group.org](http://www.parkinson-study-group.org)). There is no cost to

the patient who participates in the trial. Drugs, examinations, and baseline laboratory tests (complete blood cell count, urinalysis, serum chemistry studies, and electrocardiogram) are free. Some funds for travel costs are also available. After the 42 weeks of the trial, the subject's PD can be treated by the referring physician.

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Teva Pharmaceuticals (Netanya, Israel) has generously provided the carbidopa-levodopa and matching placebo tablets for this study.

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