Should Levodopa Therapy Be Started Early or Late?

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ABSTRACT: Clinical and experimental evidence suggests that, in Parkinson's disease, the late-occurring fluctuations in response to levodopa therapy are due to progression of the disease rather than to the therapy. Therefore, treatment with carbidopa/levodopa should be started early, because postponement does not provide patients with added benefits but deprives them of the most satisfying period of the therapeutic response.

RÉSUMÉ: L'évidence clinique et expérimentale suggère que, dans la maladie de Parkinson, les réponses oscillatoires tardives à la lévodopa sont dues à la progression de la maladie plutôt qu'au traitement. Par conséquent il faut commencer le traitement carbidopa/lévodopa le plus tôt possible, parce qu'un retard ne procure pas les bénéfices escomptés aux patients, mais plutôt les prive de la période de réponse thérapeutique la plus favorable.

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To answer the question "Should levodopa therapy for Parkinson's disease be started early or late?" we require a definition of what is "early" and what is "late." There are three points in the course of Parkinson's disease at which therapeutic decisions become particularly important.

1.) Mild symptoms of the disease have developed; they are causing neither physical nor social disability. 2.) The disease has progressed to the extent that the patient is now aware of mild physical or social disability or both and desires effective treatment; however, the disability is not severe enough to pose a threat to employability, physical independence, or social life. 3.) Disability poses a threat to employability, physical independence, or social life.

It is clear that there is no strong need for treatment with levodopa or any other drug at point 1. It is an accepted view of general medical practice that disease is treated aggressively only if it causes disability or if postponement of treatment exposes the patient to added risk. Neither circumstance applies to the patient with Parkinson's disease at point 1. The diagnosis and prognosis should be discussed with the patient and the family at this point, but pharmacologic treatment is not indicated. It is also clear that levodopa, the most effective treatment of Parkinson's disease available, should be used at point 3 when the patient's disability threatens employability, physical independence, or social life. Generally, there is consensus about treatment at points 1 and 3. The controversial issue is what should be done therapeutically at point 2 and prior to point 3.

Starting levodopa at point 2 would be starting it early; starting levodopa at point 3 would be starting it late. I strongly favor starting levodopa therapy at point 2 — that is, early.

There are two schools of thought. One favors the use of drugs other than levodopa — i.e., bromocriptine, anticholinergics, or amantadine hydrochloride — at point 2 and up to point 3, with levodopa reserved for later use, at point 3 and thereafter. The second view is to start levodopa early, at point 2. The main argument in support of starting levodopa late is that levodopa therapy itself causes the severe fluctuations in the therapeutic response and greater sensitivity to the drug which results in increasing dyskinesias, at a later stage of the disease. If this is so, then levodopa should be started late — that is, at point 3 in order to reserve the patient's potential to obtain a satisfactory response to levodopa for the more severe and disabling phase of the disease. This approach was suggested by Yahr (1976) and supported by Lesser et al. in 1979 on the basis of their data on 131 patients. There has been considerable support for this opinion, presented elsewhere in this volume.

The second view is to start levodopa early. This view is based on the opinion that the later occurrence of fluctuations in the therapeutic response and of dyskinesias is due to progression of the primary disease process rather than to chronic administration of levodopa and that the patient does not gain any benefit from deferring levodopa therapy from "early" to "late" (point 2 to point 3). I propose that this latter view is correct. Supportive arguments come from three areas: longitudinal clinical studies, cross-sectional clinical studies of the effect of starting levodopa in patients with different severities of the disease, and some experimental data.

In 1981, Markham and Diamond published a careful longitudinal clinical study (Figure 1). It compares the results of levodopa therapy in three groups of patients: those started on levodopa between 1 and 3 years after onset of first symptoms of the disease, those started between 4 and 6 years, and those started between 7 and 9 years. All patients were followed for 2 to 6 years. The data indicate that, regardless of when in the course of the disease levodopa is started, the disability in the treated state for any point in the duration of the disease is the same for all groups. In other words, there is no evidence from this study that postponing treatment with levodopa resulted in any benefit to the patient in terms of long-term disability. This study did not address the question of whether clinical fluctuations in later years of therapy are due to treatment with levodopa or progression of the disease. At the recent meeting of the American Neurological Association, Hoehn (1983) presented follow-up data on 160

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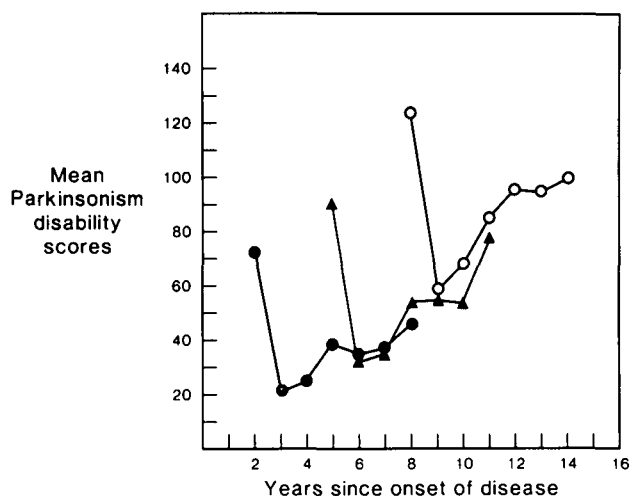Reprint requests to: Dr. Manfred D. Muenter, Dept. of Neurology, Mayo Clinic, Rochester, Minnesota 55905 U.S.A.

Figure 1 — Effect of levodopa therapy begun at different times after onset of Parkinson's disease. ●, 1 to 3 years after onset (n = 19);▲, 4 to 6 years (n = 16); ○, 7 to 9 years (n = 23). (Redrawn from Markham and Diamond (1981). By permission of Modern Medicine Publications.)
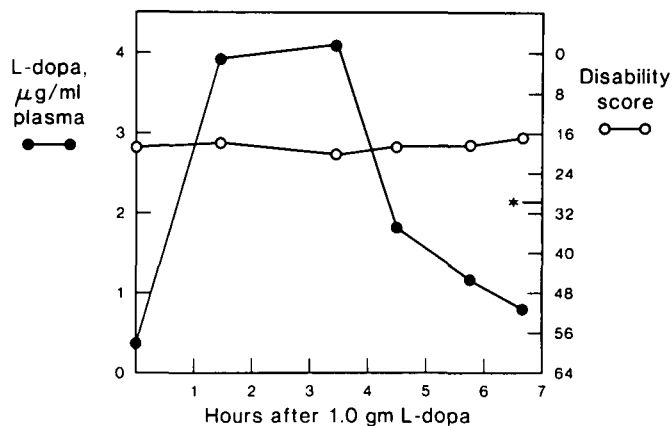

Figure 2 — Moderate long-duration response, indicated by the decrease of fasting disability (first open circle) compared with disability prior to any levodopa therapy (*). There is no short-duration response, indicated by the absence of a significant decrease in disability during the period of observation. (Modified from Muenter and Tyce, 1971. By permission.)
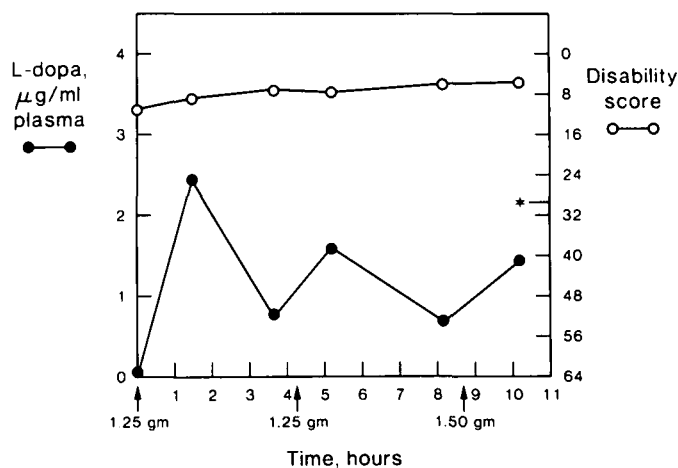

Figure 3 — Marked long-duration response. Three doses of levodopa given over a period of 11 hours produce peaks of plasma concentration of the drug but no change in clinical state.
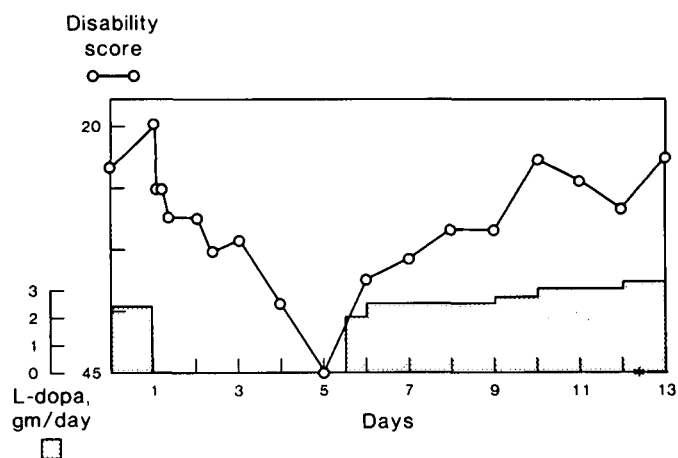

Figure 4 — Long-duration response, indicated by difference between pretreatment disability (score = 45) and fasting disability during long-term levodopa therapy. The pretreatment disability is reached 5 days after discontinuation of levodopa therapy. (Modified from Muenter et al., 1972. By permission.)

patients. They were divided into two groups: one in which levodopa therapy was started within 1 year of the diagnosis and one in which therapy was started more than 1 year after the diagnosis. Her data indicate that, of the patients followed for 10 years or longer, those who were started on levodopa therapy early did better in terms of disability or longevity than those who were started on therapy later.

Another way to address the problem of whether levodopa should be started early or late is to look, in a cross-sectional way, at the clinical response when levodopa is started in patients with different severities of disease.

In order to avoid confusion at this point, it will be necessary to define our terminology clearly. What is the short-duration response? What is the long-duration response? What is the wearing-off effect? What is the on-off effect? What are monophasic and biphasic dyskinesias or IDI and DID response (Muenter and Tyce, 1971; Muenter et al., 1977)? Although these terms seem confusing, they can be defined rather easily.

Levodopa has two different pharmacokinetic actions: one is of long-duration (Figs. 2, 3, and 4), measured in days, and is prevalent early in the disease; the other is of short-duration, measured in hours, and is more prevalent in advanced stages of the disease (Fig. 5). The long-duration effect accounts for the fact that patients placed on a drug holiday do not reach their baseline disability level until about 1 week after levodopa has been stopped.

The "on-off" and "wearing-off" phenomena are part of the short-duration response as are monophasic and diphasic dyskinesias (Figs. 6 and 7). "Short-duration response" and "wearing-off effect" refer to the same pharmacokinetic sequence, but one refers to the positive therapeutic peak effect and the other to the return of lack of effect. I favor the term "short-duration response." Using the term "wearing-off" is like describing the effect of an insulin dose by defining the return of hyperglycemia after the insulin effect disappears rather than hypoglycemic effect of the insulin, which is its real positive property. The term "short-duration response" describes the specific positive levodopa effect in terms of onset, duration,
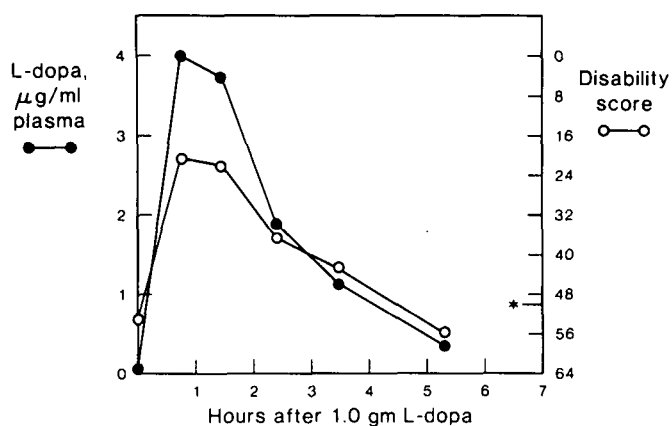
Figure 5 — Short-duration response, indicated by a rapid but transient decrease in disability between examinations 1 and 6 (at hours 0 and 5.3). The absence of long-duration response is indicated by the lack of difference between pretreatment disability (*) and fasting disability (first open circle).
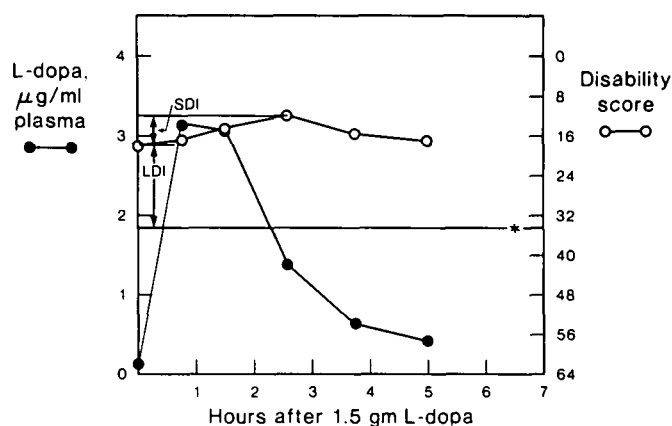

Figure 8 — Method used to measure long-duration and short-duration responses (LDI and SDI) in a patient who experiences both. See text. "I" represents the old term "improvement" which has been replaced with "response".
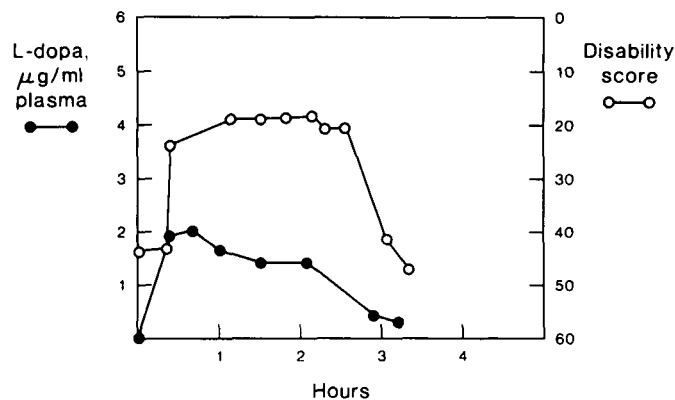
and end, and it includes the wearing-off effect. The latter can occur rapidly, over a period of a minute or less.

Many patients, particularly those in moderate stages of the disease, experience a combination of the long- and short-duration responses (Fig. 8). One can measure these in the same patient as long as the baseline pretreatment disability is known. The long-duration response is the difference between pretreatment and fasting disabilities because prior to the first dose in the morning the clinical state is not contaminated by the short-duration response. The change in disability after the first dose of the morning then is the short-duration response. It is very important to adhere to these criteria. Confusion is created if the crucial pretreatment disability is omitted in defining long- and short-duration responses (Fahn, 1982). Many studies reporting results of levodopa therapy do not indicate when the clinical data were obtained in relation to administration of a levodopa dose, which makes it difficult to assess what type and how much improvement has occurred.

A brief discussion of the controversial "on-off" phenomenon as an entity distinctly different from the wearing-off effect is appropriate at this point. The on-off phenomenon has been defined as an unexpected, temporary, sudden return of a parkinsonian state while the patient presumably has a full therapeutic response to a dose of levodopa and a therapeutically adequate plasma concentration of levodopa. In 87 patients in whom we studied the clinical response profile and plasma levodopa concentration, we have never seen such a phenomenon (Muenter et al., 1977). Hoehn (1983) thinks that the phenomenon is either very rare or nonexistent. Markham and Diamond (1981) saw it in 5 of their 58 patients, and many other investigators have mentioned it.

Figure 6 — Monophasic dyskinesias ( ), occurring during the peak of clinical improvement, in a patient on chronic levodopa therapy with a short-duration response after a dose of carbidopa/levodopa given at time 0. (From Muenter et al., 1977. By permission.)

There is a possible explanation, related to the design of our studies, of why our experience might differ from that of others. All of our profile studies were done after the individual dosage of levodopa had been adjusted upward until a slightly supraoptimal clinical response was obtained — that is, until mild but detectable levodopa-induced dyskinesias occurred. Also, we strictly avoided overlapping doses and we studied only responses to single doses in patients on chronic levodopa therapy. All profiles were determined after the patient had taken a levodopa dose on an empty stomach, in order to avoid the interference with gastrointestinal absorption caused by meals. Our observations
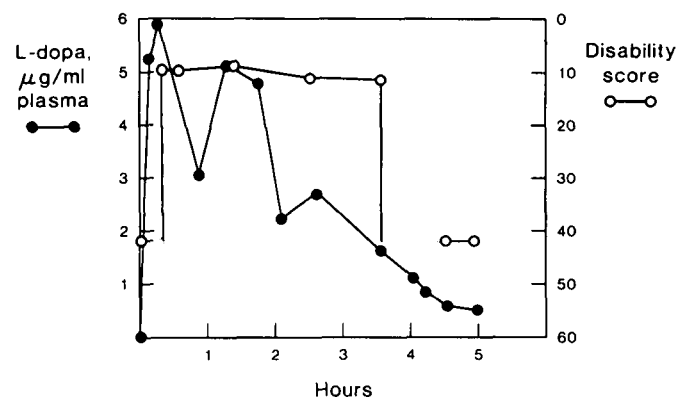

Figure 7 — Biphasic dyskinesias ( ), occurring prior to and after clinical improvement, in a patient on chronic levodopa therapy with a short-duration response after a 1,500 mg dose of levodopa taken at time 0 on an empty stomach. (From Muenter et al., 1977. By permission.)

are only valid for these experimental conditions. If doses smaller than we used are tested or if the effect of a meal interferes with absorption or if small singly subtherapeutic doses are given in an overlapping fashion, the levodopa level will be lower, the clinical response becomes much less predictable, and an on-off phenomenon well may occur.

It appears that the range of plasma concentrations of levodopa below which the patient becomes parkinsonian and above which there is improvement is very narrow. If a dose causes a plasma concentration of levodopa clearly above that narrow range and a slightly more than optimal clinical response, true on-off phenomena will not occur. However, if the plasma concentration stays in that narrow range between response and no response for the reasons described above, on-off events may occur because of minor fluctuations of the level of cerebrally effective levodopa. Also, if a patient with biphasic dyskinesias takes a subtherapeutic dose of levodopa, the clinical state may repeatedly fluctuate back and forth between a parkinsonian state and dyskinesias, causing on-off phenomena (Fig. 9). These disappear, however, with higher blood levels (Fig. 7).

In regard to the on-off effect, it is of interest that there have now been three studies, by Shoulson et al. (1975), Nutt et al. (1983), and Quinn et al. (1983), of the response to intravenous administration of levodopa in patients who fluctuated severely on oral levodopa therapy. All of these authors reported a stable response to intravenous levodopa therapy and none mentioned the occurrence of on-off events during a stable intravenous regimen. One would expect that, if there were true on-off phenomena unrelated to plasma levels, they would have been seen in these studies.

Clinical fluctuations in response to levodopa therapy are very significant in terms of the question of whether the therapy should be started early or late. In this discussion, fluctuations mean the short-duration response with the wearing-off phase, monophasic or biphasic dyskinesias, and the on-off phenomena. If it is chronic levodopa therapy rather than severity of the disease that brings on the fluctuations of the response, one would expect that no patient, regardless of whether the disease

is mild or severe, should experience these phenomena if treatment with levodopa has been started recently. The phenomena should develop only after prolonged therapy. But there is no published objective evidence to support this view. The main and only argument in its favor has been that the occurrence of clinical fluctuations increases with duration of therapy. Although this fact is undisputed, it can be equally interpreted as being due to progression of the disease which causes alteration of the response of the cerebral dopamine receptor population. If the severity of the disease were responsible, clinical fluctuations should become apparent early during levodopa therapy if the state of the disease were advanced. There is considerable objective evidence from several sources to support this view.

Lang et al. (1982) described the occurrence of a short duration response within weeks after levodopa therapy was started in two children with a severe secondary parkinsonian syndrome. One child had recurrent obstructive hydrocephalus; the other had a postencephalitic syndrome. Burns, R.S. (personal communication, 1983) has seen a short-duration response to levodopa approximately 1½ hours in duration in patients with severe N-methyl-4-phenyltetrahydropyridine-induced parkinsonism as soon as effective Sinemet therapy was instituted; those with milder disease showed the long-duration rather than the short-duration response. Goldstein et al. (1973) presented data on experimentally induced parkinsonism in monkeys. In acute experiments not involving chronic levodopa therapy, the parkinsonian signs subsided for a period of 2 hours after a dose of levodopa, clearly indicative of a short-duration response. Our own early data show that occurrence of the short-duration response is not related to the duration of therapy but rather to the severity of the disease. We found (Muenter and Tyce, 1971) a statistically significant correlation (P < 0.01) between severity of the disease (as indicated by the pretreatment disability score) and intensity of the short-duration response in patients who had been on levodopa therapy for only 1 to 14 months (Fig. 10). The
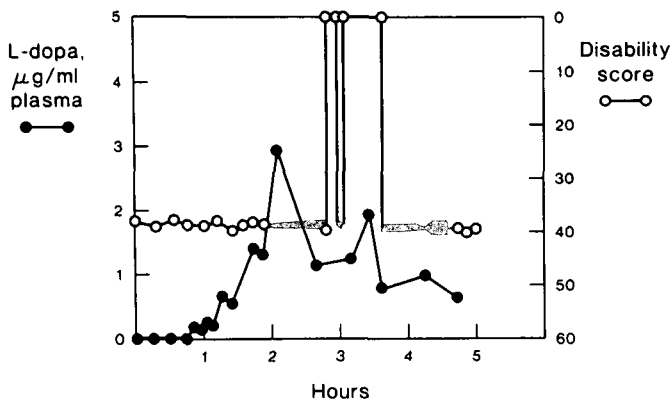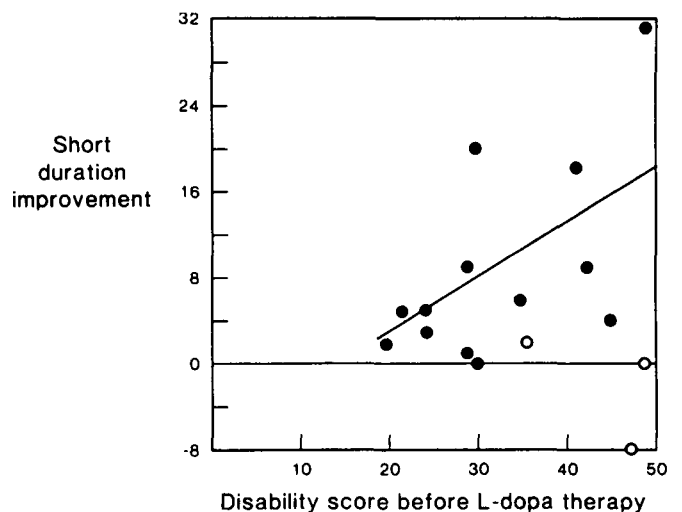

Figure 9 — Patient with short-duration response and biphasic dyskinesias. Unpredictable rapid fluctuations and on-off phenomena can occur when the plasma levodopa concentration is borderline after a 1,500-mg dose of levodopa taken with a protein-rich meal. The unpredictable fluctuations disappear when the plasma level is higher as shown in Figure 7 for the same patient but the same dose was taken on an empty stomach. (From Muenter et al., 1977. By permission.)

Figure 10 — Positive correlation between pretreatment disability and short-duration response (P < 0.01) in 16 patients on chronic levodopa therapy for only 1 to 14 months. Open circles, treatment failures. The correlation was even higher (P < 0.001) between fasting disability during chronic levodopa therapy and short-duration response. (From Muenter and Tyce, 1971. By permission.)

correlation was even higher (P < 0.001) between fasting disability during chronic levodopa therapy and short-duration response.

Of great interest are experimental observations by Spencer and Wooten (1983) who studied the metabolism of levodopa in the brain of rats with extensive unilateral lesions of the substantia nigra, the correlate of a severe parkinsonian state. They found that the more severe the loss of nigrostriatal neurons, the shorter the period of levodopa-induced increase in cerebral dopamine and the faster the metabolic destruction of any dopamine found. This finding fits the clinical observation that the duration of the short-duration response diminishes with the duration of the disease.

One question frequently raised is why were short-duration responses or clinical fluctuations not observed by all investigators 15 years ago when levodopa was first used extensively? There are several reasons why they may have gone largely unnoticed. It was not a matter of routine clinical practice at that time to examine patients every 15 to 30 minutes for hours at a time after a dose of levodopa, which is necessary if one wants to observe the clinical fluctuations. Also, the dosage of levodopa used was more conservative in some countries and institutions than in others, and short-duration responses become identifiable only when relatively high doses are administered. In addition, because many patients had a satisfactory long-duration improvement in addition to fluctuations, the latter may have received less attention.

In summary, there is considerable evidence to suggest that fluctuations of the response of Parkinson's disease to therapy with levodopa and decreased tolerance of levodopa are related to the severity of the disease rather than to the levodopa therapy, and consequently there is no reason to postpone therapy from point 2 to point 3 — that is, levodopa therapy should be started early unless equally effective other therapy is available. Starting it late would mean that the patient is deprived of the benefits of levodopa therapy during that period of the disease during which his response would be the most satisfying.

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