Should Levodopa Therapy for Parkinsonism be Started Early or Late? Evidence Against Early Treatment

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ABSTRACT: We define the meaning of early and late treatments and present arguments opposed to early treatment with levodopa. These are based on the development of complications with long-term Sinemet which include clinical fluctuations, loss of efficacy, and painful dystonic cramps. By delaying the onset of levodopa therapy until the symptoms require this most potent of antiparkinsonian agents, we can delay the onset of these disabling problems. Also, using as low a dosage as possible should reduce the risk of any long-term complication related to accumulative dose.

We also present the serial evaluations of 26 patients followed for as long as 7.5 years before levodopa therapy was initiated. Three scoring scales on these patients are compared. Arguments are presented which suggest that the Columbia University and the ADL scales are superior to the UCLA scale, and more closely approximate the curve of the progressive clinical disability of the disease as assessed by global evaluation. We conclude that the ultimate answer to any clinical debate must come from well-designed, controlled studies to assess the differences between two treatment modalities.

RÉSUMÉ: Nous définissons le sens qu’il faut accorder à un traitement “précoce” et à un traitement “tardif” et présentons nos arguments s’opposant à un traitement précoce avec le levodopa. Ces arguments se basent sur les complications à long terme avec le levodopa. Ces complications comprennent les fluctuations cliniques, la perte d’efficacité, et les crampes dystoniques douloureuses. En retardant le début de la thérapie au levodopajusqu’à ce que les symptômes le requièrent nous pouvons espérer retarder le début de ces complications, de même en utilisant une dose aussi basse que possible.

Nous présentons également l’évaluation sériée de 26 patients suivis pendant 7,5 ans avant le début du levodopa. Nous comparons 3 échelles d’évaluation chez ces patients. Nous croyons que les échelles Columbia et ADL sont supérieures à l’échelle UCLA et reflètent mieux la courbe progressive de la maladie telle qu’évaluée globalement. La réponse finale de ce débat clinique réside dans la préparation de protocoles bien pensés pour étudier les différences entre les modes de traitement.

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Fahn and Calne (1978) proposed delaying the onset of levodopa therapy for Parkinson’s disease until the symptoms are manifest enough to threaten to compromise social, occupational, or psychological well-being. Controversy over this suggestion arose after Markham and Diamond (1981) concluded from their studies that levodopa therapy should be started earlier, rather than later. We will analyze the evidence for both points of view.

First, we need to define what we mean by “early” and “late” treatment. By early treatment, we mean that levodopa (given with carbidopa) is started as soon as the diagnosis of parkinsonism has been made with a reasonable degree of certainty. By late treatment, we mean that this medication is not started until there are symptoms of parkinsonism that are beginning to interfere with the patient’s psychological well-being, social life, or occupational efforts, and after anticholinergics or amantadine have been found to be ineffective for these situations or their usage is considered contraindicated by the physician. For example, anticholinergics are usually contraindicated in elderly or demented patients since these drugs can produce memory loss, confusion, and psychosis in such individuals. A corollary of late treatment is to use levodopa at a low dosage when it is needed, rather than high dosage (Fahn and Calne, 1978). In other words, use the lowest effective dose to keep a patient functioning independently. Naturally, the dosage varies with each patient.

Essential in the consideration as to whether levodopa should be initiated early or late in the course of parkinsonism is the realization that this form of therapy is purely symptomatic and is not curative or preventative of further worsening. When levodopa was first introduced, it was not known whether this treatment would be more than just symptomatic therapy. In fact, one of us (SF) began to utilize levodopa as soon as the diagnosis of parkinsonism was established in the hope that this form of therapy might prevent further loss of the dopaminergic nigrostriatal neurons, and thereby prevent progression of parkinsonism. After observing that patients continued to show worsening of parkinsonism symptoms, and also developed new adverse effects (particularly clinical fluctuations) with long-term usage of levodopa, the therapeutic strategy was changed from early treatment to late treatment.

Evidence against early treatment

There are now three concerns that argue against early treatment, and all three are related to long-term administration of levodopa: clinical fluctuations occur primarily with continued treatment with levodopa and rarely in the initial stage of treatment; loss of
The efficacy of levodopa after continued usage is common; and painful dystonic cramps (during “off” periods) has been reported as a late complication. One other factor needs to be mentioned as a potential concern: since the pathogenesis of Parkinson’s disease is unknown, could continued levodopa administration hasten the progression of the illness? For example, could the increasing incidence of accompanying dementia seen in patients with Parkinson’s disease be due to the administration of levodopa? It is more likely that dementia is part of the illness itself, and its manifestation is because patients with Parkinson’s disease are living longer, hence are now likely to develop this feature. Since there is no evidence to support the concept of increased progression of parkinsonism due to levodopa, this possibility will not be considered further.

Dystonias, although a common complication of levodopa therapy, are not considered a factor in determining when to start levodopa, since these can develop early in the treatment period, and are not a particular feature of the duration of therapy.

Clinical Fluctuations: The two major types of clinical fluctuations are the wearing-off phenomenon and the randomized on-off phenomenon (Marsden et al., 1982; Fahn, 1982). It is important to distinguish between these types of fluctuations, which are clearly a problem of chronic levodopa usage, and other types of fluctuations that relate to the disease itself. The latter category includes the freezing phenomenon (sudden transient freezing and start-hesitation).

Although dystonias were recognized early in the course of levodopa therapy, clinical fluctuations were not. Of the 29 patients with this problem analyzed by McDowell and Sweet (1976), 14% had the onset after less than 12 months of treatment, 24% had the onset between 13 and 24 months of treatment, 38% between 25 and 36 months, and 24% after 37 months of treatment. These authors also showed that the prevalence of fluctuations increased with duration of therapy, and found that almost 50% of patients treated for five years had this problem (Fig. 1). Barbeau (1980) analyzed his data for a longer duration and found that as many as 87% of patients treated with levodopa for 10 years developed fluctuations. It is widely believed that if the dosage of levodopa is kept low, there is less chance of developing fluctuations. However, in our experience, the wearing-off phenomenon has occurred in some of our patients in which every effort was made to keep the dosage of levodopa low, including some patients who were placed on alternate day levodopa therapy.

Despite the use of dopamine agonists, correction of the problem of clinical fluctuations is not always possible, especially for the random on-off phenomena. In some patients, particularly those with a young age at onset (<40 years) who are particularly likely to develop fluctuations, the fluctuations can be severe enough to prevent them from working. Since the problem of fluctuations tends to increase with duration of levodopa therapy, avoiding early treatment can delay this problem.

Loss of Efficacy: While it is generally appreciated that Parkinson’s disease progresses with time and that this factor accounts for at least some of the loss of effectiveness of levodopa, another factor to be considered is that prolonged treatment with levodopa could also be responsible, in part, for this unfavorable development. A number of studies demonstrated that the degree of benefit from levodopa therapy lessens with time (Hunter et al., 1973; Ludin and Bass-Verrey, 1976; Yahr, 1976; Marsden and Parkes, 1977). The question is how much of this loss of efficacy is due to the dosage and duration of treatment. Yahr (1976) evaluated the response of patients according to severity of disease at the onset of treatment and found that patients in all categories can respond and that all categories showed decline in efficacy beginning after about three years of treatment with levodopa (Fig. 2). The same time pattern for loss of efficacy in patients regardless of severity of disease strongly supports the concept that duration of therapy plays some role in this loss. In a retrospective analysis in which patients were evaluated during a fixed period of time, Lesser et al. (1979) found that the duration of treatment was a more important factor than duration of disease in determining the eventual status of many patients. They found that when patients were matched for the same duration of disease, those treated for a longer period of time had an average parkinsonian score that was worse than those treated for a shorter period.

The mechanism for this loss of efficacy can be explained by down regulation of dopamine receptors after prolonged exposure to levodopa therapy. Lee et al. (1978) found that in brains of parkinsonian subjects not treated with levodopa the dopamine receptors were supersensitive, but in those treated with levodopa this supersensitivity was lost. Rinne et al. (1980) measured spiperone binding in brains of parkinsonian patients as a method for evaluating dopamine receptors. In patients who had not been treated with levodopa, they found that the majority had increased spiperone binding, indicating supersensitivity of dopamine receptors, but a minority had reduced binding. It is possible that those with a reduced binding did not actually have Parkinson’s disease, but rather some form of Parkinsonism Plus syndrome (Fahn, 1977) which tends not to respond favorably to levodopa treatment. In patients who had been treated with levodopa, Rinne et al. (1980) found a loss of dopamine receptor supersensitivity. Again, treated patients could be divided into two groups; those with a reduced number of receptors and those with a normal number. When correlated with the clinical response, patients with preserved normal receptors had dyskinesias and clinical fluctuations. Those with a decrease in receptors had greater parkinsonian disability and loss of levodopa responsiveness.
A "levodopa holiday" has been reported to provide temporary restoration of efficacy after levodopa therapy is resumed (Direnfeld et al., 1980; Weiner et al., 1980). In fact, a lower dosage of levodopa becomes effective after the holiday is terminated. This temporary improvement in clinical response following withdrawal of levodopa and then reinstitution of it at a lower dosage can best be explained on the basis of desensitization of the dopamine receptors due to chronic levodopa therapy. After levodopa withdrawal, receptor desensitization is reversed so that the receptors are once again supersensitive and now can respond to lower dosages of levodopa. Unfortunately, this approach as a therapeutic remedy is dangerous and the benefit is only short-lived. In a few months, the patient again becomes less responsive and requires greater dosages of levodopa.

The notion that chronic levodopa therapy can cause receptor desensitization in humans is supported by laboratory work in rats (Jiang et al., in press; Reches et al., in press). In these studies, long-term treatment with levodopa or the dopamine agonist, pergolide, produced down regulation of the dopamine receptors, as measured by behavioral effects and by spiperone binding. Thus, sufficient evidence has now been accumulated to make a strong case to support the notion that loss of efficacy of levodopa is, in part, related to chronic levodopa therapy. By delaying the introduction of this medication (and probably directly acting dopamine agonists), and by keeping the dosage relatively low, one might be able to delay the occurrence of this problem.

**Painful Dystonic Cramps:** Although painful dystonic cramps of the feet in patients with parkinsonism have been described before the introduction of levodopa therapy (Stewart, 1898; Gortvai, 1963; Duvoisin et al., 1972), these problems also occur as a complication of levodopa therapy. They occur at times during the day when levodopa is not effective ("off" periods), and they can be ameliorated by a dose of levodopa. Melamed (1979) labeled this condition as early morning dystonia. Because we see this problem also at other times of the day when the "off" effect has occurred, we have referred to it as "off" period dystonia. It should not be confused with peak dose dyskinesia or dophasic dyskinesia (Marsden et al., 1982; Fahn, 1982). The four patients reported by Melamed (1979) developed this problem 2, 4, 4.5 and 6 years after starting levodopa therapy. In our observations of seven patients with painful "off" period dystonic cramps, the average time of onset after initiating levodopa therapy was 18 months, with a range of 8 to 30 months (Ilson et al., 1983). None of the patients had painful dystonic cramps prior to levodopa therapy. These painful dystonic contractions have been difficult to prevent and treat. Recently, we have seen some benefit using dopamine agonists (Ilson et al., 1983), but even with this approach, not everyone improved.

**Evidence for early treatment**

The major argument for early treatment has been advanced by Markham and Diamond (1981). They argue that the increased symptoms following introduction of levodopa therapy parallels the worsening of parkinsonism that would have occurred without such treatment. They concluded that this increase of symptoms was, therefore, representative of progression of the disease and not due to a loss of efficacy of levodopa. We object to this conclusion for the following reasons.

The scoring scale that these investigators utilized (called by them the UCLA Scoring Scale) is one that multiplies the severity score (0 to 2) for each symptom and sign by a number (1 to 10) in order to yield a relatively greater score for those problems that tend to give more disability. The severity score of 0 represents no symptom or sign, 1 indicates it is present, and 2 indicates that it is severe. As noted below, this paucity of scores makes the UCLA scale insensitive to slight to moderate changes. The multiplication of the scores makes the UCLA scale a weighted scale.

There is evidence that the scale is not truly linear with disability because of this weighting. The lowest numbers cannot be linearly compared with larger numbers. In fact, there may be other regions within the scale (from 0 to 220) that are not linear with other regions of the scale. If one extends the upper progression line of the natural worsening of the disease back to the time the disease first begins, we see that Markham and Diamond would obtain a score of approximately 55. The ideal scale should start at zero at the onset of the disease. If one draws a line at zero on the ordinate (time zero of the disease) to the first point of 72.6 obtained by the investigators for year 2, this line would have a much steeper slope than the subsequent line from 2 to 8 years. Therefore, the points on the scale below 72.6 cannot be linear to the points between 72.6 and 126 (the highest value that was obtained by Markham and Diamond). The lack of linear progression on the UCLA scale is illustrated in the diagram below.
of linearity, therefore, makes it inaccurate to compare the relative disability of the upper and lower curves (pretreatment and treatment phases, respectively) obtained by these investigators. Thus, we really do not know that these two curves parallel each other, as claimed by Markham and Diamond. We do not know whether a small change in the bottom curve represents a smaller or a bigger change compared to the same size change in the upper curve.

Another concern in evaluating the scores obtained during the treatment phase is the very low incidence of clinical fluctuations observed by Markham and Diamond. They detected clinical fluctuations in only 5 of 58 patients (8.6%), far less than observed by other clinicians. If fluctuations were present but undetected by the investigators, the resulting scores would be artefactually low. In the study by Lesser et al. (1979), patients with fluctuations were scored while "on" and while "off", and then the average score was used to calculate disability. It is not clear how Markham and Diamond determined the disability score in the five patients they detected with fluctuations.

Finally, if one accepted the conclusions of Markham and Diamond that loss of efficacy represents only progression of the disease and has nothing to do with levodopa, then one would predict that patients should not show any enhanced efficacy after a levodopa holiday. The fact that such improvement is encountered fits best with loss of efficacy of levodopa due to down regulation of the dopamine receptor as discussed below.

Comparison of Columbia University Scale, UCLA Scale and ADL Scale, in an Evaluation of Patients with Parkinsonism maintained off Sinemet

The original Columbia University Parkinson Disease Rating Scale (Duvoisin, 1971) has been modified by us three times. In its most recent version (Fahn, in press), the maximum score possible (most severe parkinsonism) is 128. This scale is based upon assigning a score of 0 to 4 for many signs and symptoms of parkinsonism. The ADL Scale that we use is a slight modification of that developed by Schwab and England (1969). It rates the patient on a scale of 0 to 100% in steps of 5%. The scale is so easy to use that the patient is rated not only by the examiner, but also by family members and the patient himself. Scores are readily assessed for both "on" periods and "off" periods even if the examiner sees the patient in only one of these two periods during the office visit.

For our comparison of the above scales with the UCLA Scale and also to observe the progression in patients with parkinsonism untreated with levodopa, we analyzed the data we had accumulated on patients who met the following criteria. The patient must not have been treated with levodopa; anticholinergics and amantadine are allowed at the time the patient was first seen or at any other time while being followed. The onset of parkinsonism could not be longer than two years before the time the patient was first examined by us. This requirement was set in order not to bias the data toward patients who had an unusually benign form of parkinsonism. The patient must have been seen by us on 2 visits at least 6 months apart, without receiving levodopa. This requirement is to allow us to have at least two examinations free of levodopa in order to determine the rate of progression. Patients were followed approximately every six months. Some patients in the early stages were seen at yearly intervals. We were able to accumulate these patients because we followed the principle of avoiding levodopa therapy unless the symptoms were sufficient to warrant its use and only after trials of amantadine or anticholinergics had been conducted, as stated by Fahn and Calne (1978) and in the introduction above. If levodopa was introduced, we continued to follow and evaluate the patient, but that patient's scores on levodopa were not considered in assessing the natural history of the disease. There are too few patients (a total of eight) who began levodopa and they have not been followed long enough for us to compare our results with those of Markham and Diamond (1981) in terms of response to levodopa treatment.

Each patient has been evaluated by both the Columbia University Parkinson Disease Rating Scale Version 4 (CU Scale) and the ADL Scale. The 0 to 4 scores from the CU scale were converted to the 0 to 2 scores of the UCLA Scale by the following method. Zero was the same on both scales; a CU score of 2 or less was equivalent to a UCLA score of 1; a CU score greater than 2 was given a UCLA score of 2. The UCLA score obtained was then multiplied by the appropriate weighting factors (Markham and Diamond, 1981). A total of 26 patients (16 men and 10 women) met the above criteria, and their data were analyzed. The age at onset of first symptom ranged from 38 to 77 years, with a mean of 54.3 years (SEM = 2.1) (Fig. 3). Severity as assessed by all three scores was plotted using mean scores at each 6-month interval from time of onset of disease (Fig. 4). The ordinate for each of the rating scales ranged from zero to the maximum scores obtained, which occurred for the only patient seen at 7.5 years of duration, such that the score on each rating scale at this time point was placed along the ordinate so that all three scores were fairly close to each other on the graph. This technique was selected in order not to bias the curves by an arbitrary ordinate for each of the scoring scales.

The number of patients examined at each time point in the duration of illness is given along the bottom of the graph. The SEM for each mean score is presented by the vertical lines. Each asterisk along the abscissa indicates that a patient started levodopa at that particular time point. Their scores were no longer included in the analysis after that time point. If they had not started Sinemet and were allowed to become increasingly disabled, the results of the analysis would be a truer indication of the progression of Parkinson's disease. The curves for each scale would undoubtedly climb at a rate that would be steeper than presented in Fig. 4. Seven patients started Sinemet because they were becoming disabled by parkinsonism. Another patient...
started Sinemet at time point 4 years while still functioning at 100% ADL. He had mainly tremor, which was suppressed with a combination of ethopropazine and amantadine. However, he was not allowed to fly his private airplane if he was taking an anticholinergic medication. Withdrawal of ethopropazine was accompanied by a return of the tremor, and he was placed on Sinemet with slightly less benefit. The administration of Sinemet does not restrict one from flying an aircraft, and he is now flying again.

For the seven patients who were becoming disabled and required Sinemet, we analyzed some possible factors to better understand the criteria for starting Sinemet in our patients (Table 1). These patients had parkinsonism for 2 to 7.5 years (mean 4.7 years) before requiring Sinemet. The table is arranged in order of severity based on ADL disability. Patients were begun on Sinemet when the ADL score was between 60% and 80% of normal, with an average of 71%. The patients who started Sinemet with an ADL score of 70% or higher were the four youngest of the seven, indicating that this amount of disability was enough to slow them sufficiently at work so that they required Sinemet. To compare these seven patients at the time they required Sinemet, we analyzed some possible factors to better understand the criteria for starting Sinemet in our patients (Table 1). These patients had parkinsonism for 2 to 7.5 years (mean 4.7 years) before requiring Sinemet. The table is arranged in order of severity based on ADL disability. Patients were begun on Sinemet when the ADL score was between 60% and 80% of normal, with an average of 71%. The patients who started Sinemet with an ADL score of 70% or higher were the four youngest of the seven, indicating that this amount of disability was enough to slow them sufficiently at work so that they required Sinemet. To compare these seven patients at the time they started Sinemet with their cohorts at the same duration, but not yet requiring this medication, we show the mean score obtained for the number of patients at each assessment point, which is presented along the bottom of the future. Each point represents the mean score obtained for the number of patients at each assessment point, which is presented along the bottom of the figure. Each asterisk represents individual patients who started on Sinemet immediately after the assessment at the time point the asterisk is located. Once Sinemet was started, subsequent scores obtained on that patient are no longer entered into the analysis. The vertical lines represent the standard errors of the means.

The occasional downward dips in the three curves represent improvement in the mean scores because of the addition of amantadine and anticholinergics at various points in the course of treatment, and also represent the improved mean scores as the more disabled patients were removed from the analysis by the addition of Sinemet for treatment (note the asterisks along the bottom of Fig. 4). In comparing the three curves representing the results of the scoring scales (Fig. 4), we see that the ADL and CU scales tend to show increasing slopes with longer duration of illness. This matches what we have long observed by global assessment, namely that the disability from the disease appears to progress slowly initially, and then more rapidly later. The fact that the ADL and CU scales tend to have this type of curve suggests that these two rating scales give a reasonable assessment of functional severity. The UCLA scores are linear in the early parts of the illness and then seem to level off later. This may reflect the multiplication factor that is utilized to derive the UCLA score. The development of new symptoms in the early stage that are not particularly troublesome are multiplied to give a larger number, so the slope is steeper here as new symptoms are added. Later, after the disease has established itself and most of the symptoms have developed, there is little to indicate a steady worsening because the 0 to 2 scores are insensitive and cannot reflect slight worsening of existing symptoms and signs. Thus, we see a levelling of the curve after year 6, when the disease is still mild to moderate. These conclusions are only tentative since there are too few subjects in the later years to be certain of these trends.

Using the UCLA scale, we can compare the results on our 26 patients with the 58 patients reported by Markham and Diamond (1981) (Table 2). We can compare only Markham’s Groups 1 and 2, since we had only one patient in their group 3 (mean duration 7-9 years without Sinemet). Markham’s patients seemed more severely affected than ours (Table 2), a phenomenon which was also seen by Markham and Diamond when they compared their patients with those of Lesser et al. (1979) and those of Sweet and McDowell (1975). However, if their disability curve on nontreated patients is allowed to intersect the ordinate, it would produce a score of approximately 55, while the results on our patients would intersect the ordinate at approximately 20. The reasons for this difference are not apparent. It is of interest to note that the ADL curve intersects the
Table 2: Differences between our results and those of Markham and Diamond*

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<tr>
<th>A. Mean UCLA scores:</th>
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<tbody>
<tr>
<td>Groups</td>
<td>Years of Disease</td>
<td>Our Study</td>
</tr>
<tr>
<td>1</td>
<td>1 - 3</td>
<td>41.5</td>
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<tr>
<td>2</td>
<td>4 - 6</td>
<td>68.9</td>
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<tr>
<td>3</td>
<td>7 - 9</td>
<td>not enough patients</td>
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<th>B. Intersection of ordinate (time zero):</th>
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<tbody>
<tr>
<td></td>
<td>Our Study</td>
<td>Markham’s Study</td>
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<tr>
<td></td>
<td>20</td>
<td>55</td>
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ordinate at the zero point (100% of ADL), and the Columbia University curve intersects at a score of 3. Thus, there is a lot of “dead space” in the UCLA scores, and results within this dead space should not be linearly compared with those above it. Therefore, a change in score from 20 to 40 does not represent the same degree of disability change as that from 100 to 120. Unfortunately, Markham and Diamond did compare such scores, those obtained before and those obtained after Sinemet. We feel this type of linear comparison is unjustified, and no valid conclusion can be drawn from such a comparison. Thus, there is no valid argument to support the claim recommending early treatment. Our own results indicate that many patients are able to be followed for five years or longer without requiring Sinemet and without much disability or inconvenience.

All of the studies are uncontrolled. The ideal study to determine whether Sinemet should be started early or late is one in which all patients are randomly assigned to these two treatment groups and see how they compare after a number of years. Only this type of controlled study will produce a result that should satisfy any existing concerns about what is the best possible therapeutic approach.

As a concluding remark, let us point out that there is actually less disagreement between Markham’s position and ours than there seems to be. Despite Markham’s conclusions, he does not begin Sinemet therapy as soon as is possible for parkinsonism is made (personal communication). In fact, by an informal poll, we were unable to find one neurologist who recommended treating patients with mild parkinsonism with Sinemet as soon as the diagnosis was made.

Our goal in treating patients is to keep them functioning independently as long as possible. We recommend delaying the introduction of levodopa until symptoms are pronounced enough to justify its use. We also recommend keeping the dosage of levodopa as low as possible, enough to keep the patient functioning independently but below that producing dyskinesias. We urge physicians to treat the patient when the patient needs treatment, not just because a drug is available.

REFERENCES


