

# When and How to Start Levodopa in the Treatment of Parkinson Disease



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## Abstract

Long term levodopa therapy in Parkinson disease is associated with motor complications. We review ideas and evidence on reducing the risk of levodopa associated motor complications.

**Keywords:** Parkinson disease; Levodopa; Less pulsatile levodopa therapy; Levodopa induced motor complications; Motor fluctuations; Levodopa-induced dyskinesia

**Abbreviations:** LID: Levodopa-Induced Dyskinesia; COM: Catechol-O-Methyltransferase; MAO-B: Monoamine Oxidase B

## Introduction

Levodopa has been used in the treatment of Parkinson disease for half a century. It has been the most effective medical therapy for reducing the cardinal motor symptoms of resting tremor, bradykinesia and rigidity. However, long term use of levodopa can be complicated by dyskinesia and motor fluctuations. Levodopa Induced Dyskinesia (LID) afflicts as many as 40% of patients being treated for Parkinson disease [1]. Over the last 30 years, neuroscientists and neurologists have investigated the pathophysiology and management of levodopa induced motor complications. These researchers have developed novel medications such as dopamine agonists, Catechol-O-Methyltransferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors, and several different preparations of levodopa. Treatment strategies for management of motor fluctuations and LID include switching from an immediate release levodopa to a longer acting oral levodopa, adding adjunctive inhaled preparations of levodopa, and combining levodopa with a long acting dopamine agonist with or without COMT or MAO-B inhibitors. If motor complications remain severe, treatment can be enhanced by continuous infusion of levodopa gel into the jejunum or invasive treatments such as deep brain stimulation [1-3]. All of these methods focus on the management of levodopa induced motor complications. None of the aforementioned approaches is aimed at reducing the emergence of these motor complications in the first place. Here we review the latter topic, prevention of levodopa induced motor fluctuations and LID.

## Should we delay starting treatment with levodopa?

Due to the frequency of long-term levodopa induced motor complications, there has been concern that the medicine is neurotoxic. As a result, in the 1980s and 1990s, it was common practice to delay usage of levodopa (levodopa sparing strategy) by starting treatment with a MAO-B inhibitor or a dopamine agonist. To address the concern about neurodegeneration and progression of Parkinson disease during levodopa therapy, the ELLDOPA trial (Earlier versus Later Levodopa Therapy in Parkinson Disease) was conducted [4]. There were 3 levodopa treatment groups (daily total levodopa doses of 150mg, 300mg and 600mg). Unexpectedly, all three groups showed improved UPDRS total scores (the Unified Parkinson Disease Rating Scale) compared to placebo after 42 weeks of observation. The greatest improvement occurred in the patients who received the highest doses. This trial suggested that levodopa may have slowed clinical progression of Parkinson disease. In contrast to this clinical benefit, striatal dopamine transporter imaging data from the same study demonstrated dose related loss of dopamine transporter signal, a sign of accelerated neuron loss [2,4]. The clinical improvement was not consistent with the apparent neuronal loss.

The LEAP trial (Levodopa in Early Parkinson's Disease) was conducted to investigate these contradictory findings, [5]. Using a daily dose of levodopa 300mg over an extended period (80 weeks) of treatment and observation, a controlled study was

performed. In an early start group, patients received 80 weeks of levodopa treatment. In the delayed start group, patients received treatment for the final 40 weeks of observation. In the end, for the two groups there was no difference in UPDRS scores and a quality of life measure, PDQ-39 (the Parkinson's Disease Questionnaire-39). The results of the ELLDOPA and LEAP studies suggest that levodopa neither slowed nor hastened clinical progression of Parkinson disease. Since there is no evidence that delaying levodopa therapy is beneficial, the neurologist should feel free to prescribe it in early Parkinson disease. However, we should not forget the ELLDOPA trial data, showing that levodopa taken three times per day for 40 weeks, resulted in reduced dopamine transporter signal. This finding could mean that there was increased dopaminergic neuron loss. Further study is needed to determine whether the pulsatile administration of levodopa causes loss of neurons.

### Is there a practical way to reduce the risk of motor complications?

Levodopa induced motor fluctuations and LID are believed to be related to pulsatile dosing of, longer exposure to and higher doses of levodopa [1,4,6-8]. Giving levodopa three times daily is the most popular method of treatment currently. This dosing is pulsatile because the half-life (T<sub>1/2</sub>, 90 minutes) of orally administered levodopa/carbidopa is very short, resulting in rising and falling blood levels of levodopa.

#### There are three approaches to mitigate the problem of the short T<sub>1/2</sub>:

- a. Developing a longer lasting levodopa,
- b. Changing the delivery system or
- c. Giving levodopa in a less pulsatile way, using multiple small doses a day.

Sustained release or extended release preparations of levodopa have been available since the 1990s, but they have failed to reduce motor complications. Addition of entacapone to levodopa/carbidopa has been shown to extend the T<sub>1/2</sub> [9-11]. However, this combination, given 4 times per day, failed to reduce risk of LID compared to traditional levodopa/carbidopa therapy in the STRIDE-PD study [6]. Recently, higher doses of carbidopa combined with levodopa and entacapone have been shown to improve motor fluctuations which had emerged during treatment [12]. Whether this novel formulation of levodopa/carbidopa/entacapone will reduce the development of motor complications in early Parkinson disease has not been tested.

Methods that provide a continuous stable dose of levodopa have been successful in decreasing motor complications. Continuous intravenous levodopa and continuous intraduodenal infusion have successfully reduced motor fluctuations and LID in advanced Parkinson disease [13,14]. However, these invasive approaches are difficult to justify as strategies to prevent levodopa induced motor complications for patients

with early Parkinson disease. Another less pulsatile levodopa delivery method is transdermal. This investigational approach uses a novel liquid formulation of levodopa/carbidopa providing continuous administration via a mini-pump.

A simple alternative method to avoid pulsatile drug levels uses currently available levodopa formulations in frequent small doses. This has been a successful strategy for avoiding motor complications. Recently, we have published the first retrospective cohort study using this approach. Development of LID was rare not only in naïve patients initiated on levodopa treatment every 3 hours (6 doses per day), but also in those patients converted from traditional therapy to 6 daily doses [8]. Because there has been no controlled study or other retrospective evidence supporting this approach, this inconvenient method has not been widely adapted. Currently, there is no consensus among movement specialists about how to start levodopa. In our institute, most movement disorder specialists prescribe levodopa 4-5 times per day (personal communication). We hope that a prospective, randomized clinical trial will compare the incidence of motor fluctuations and LID in patients treated with traditional 3 times daily dosing to patients receiving 6 times daily dosing.

### Conclusion

Because levodopa has a short half-life, the administration of the medicine 3 or 4 times daily results in pulsatile dopaminergic stimulation, a known risk factor for motor fluctuations and LID. Many novel medications have been used to try to help patients with these complications. However, there has been little attention to preventing levodopa induced motor complications. For many years we have treated patients with less pulsatile levodopa therapy (6 doses daily). Those patients, who have been willing to follow this inconvenient regimen, have rarely developed LID or motor fluctuations. Someday, improved levodopa formulations may eliminate the need for frequent dosing. At present, the less pulsatile method of treatment deserves further use and study.

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