ELLDOPA trial: Earlier versus Later Levodopa Therapy in Parkinson Disease (NEJM 2004)

Fahn S, et.al. Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004 Dec 9;351(24):2498-508. doi: 10.1056/NEJMoa033447.

Background: Levodopa is the most effective drug in ameliorating the parkinsonian symptoms in Parkinson's disease (PD). However, long-term treatment with levodopa results in motor fluctuations in terms of dyskinesia and wearing-off. As denervation hypersensitivity was thought to be one of the mechanisms of this dyskinesia, it was presumed that levodopa hastens neurodegeneration by increasing oxidative stress. The ELLDOPA trail was designed to study the effect of levodopa on the rate of progression of PD.

Methods: This multicenter, randomized, double-blind, placebo-controlled trial was conducted in USA (33 centers) and Canada (5 centers) over a period of 3 years (Sept 1998 to August 2001). It was sponsored by NIH/NINDS.

Inclusion criteria: PD diagnosed in the last 2 years, age >30 years, H&Y stage <3, considered not likely to require treatment within 9 months from the enrollment period (because of mild symptoms).

Exclusion criteria: Patients actively on anti-parkinsonian medications, secondary parkinsonism, tremor severity >3 for any of the limbs in UPDRS, freezing of gait, postural instability, dementia, depression.

The patients were randomized to receive either placebo or Levodopa-carbidopa (L+C). Patients received levodopa in 3 different dosages (150 mg/d, 300 mg/d, and 600 mg/d). 70 patients received placebo, 78 patients received 150 mg/d of levodopa, 82 patients received 300 mg/d of levodopa, and 81 patients received 600 mg/d of levodopa. Placebo or Levodopa was given for a total of 40-weeks, followed by complete discontinuation for 2-weeks (wash-out period). The primary outcome measure was the change in the UPDRS scores from the baseline compared to that at 42nd week (40-weeks on treatment + 2-weeks of washout). A subset of the subjects had undergone dopamine transporter scan (DAT-SPECT) as the investigators got funding for it several months after the initial recruitment.

Results: Of the 361 subjects enrolled in the study, 317 (88 %) took the study medication for 40 weeks, and 311 (86 %) completed the 2 weeks of washout. Levodopa was NOT associated with worsening of UPDRS at the end of 42-weeks. As mentioned above, 70 patients received placebo, 78 patients received 150 mg/d, 82 patients received 300 mg/d, and 81 patients received 600 mg/d of levodopa. The total UPDRS score changed by a mean 7.8 ± 9.0 points in the placebo group whereas the change in the 150 mg/d, 300 mg/d, and 600 mg/d were 1.9 ± 6.0, 1.9 ± 6.9, and -1.4 ± 7.7, respectively. The UPDRS-motor score changed by 5.2 ± 6.4 in placebo group, whereas the change in the 150 mg/d, 300 mg/d, and 600 mg/d were 1.4 ± 5.5, 1.4 ± 5.3, and -1.4 ± 5.9, respectively. There was a significant difference between the change in the UPDRS in the placebo group and levodopa groups.

Regarding the DAT-SPECT scan data, the percent decrease in striatal [^{123}I] Beta-CIT uptake in the SPECT scan over the 40 weeks of the study treatment was greater among subjects in the levodopa groups than in the placebo group, but this difference was not statistically significant. However, the reason was unclear, and the authors speculated that the long-term treatment with levodopa could have some effect on DAT density (such as downregulation of dopamine transporters due to chronic levodopa therapy).

Conclusions: From a clinical perspective, the study did not show that levodopa hastens the progression of PD. High doses of levodopa were associated with a greater frequency of adverse events such as dyskinesia. The authors recommended customizing the dose of levodopa to the needs of the individual patient based on the clinical response and the profile of adverse events.

ADDDITIONAL STUDY OF INTEREST:

A recent study (NEJM 2019) explored if Levodopa has any neuroprotective effect. The idea was to treat one group of PD patients early and treat another group late in the course of the disease and to see if the outcome (in terms of UPDRS) differed. In this study, one group received levodopa (100mg TID) early in the course of the disease for a total of 80 weeks, the other group (delayed-start group) received placebo for the first 40-weeks, followed by 40 weeks of levodopa (100mg TID). UPDRS at baseline and after 80-weeks was compared, and no significant differences were found. The rate of dyskinesias was similar between these two groups as well. The authors concluded that, among patients with early PD who were evaluated over the course of 80 weeks, treatment with levodopa in combination with carbidopa had no disease-modifying effect.

Verschuur CVM, et. al; LEAP Study Group. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. N Engl J Med. 2019 Jan 24;380(4):315-324. doi: 10.1056/NEJMoa1809983. PMID: 30673543.