Levodopa Remains Foundational—From the Start

Although every person with PD is different, **oral LD remains the cornerstone of treatment, including for those with early PD** first initiating therapy for motor symptoms[9]

Beyond the Basics: Optimizing Therapy With Extended-Release CD/LD

- Extended-release (ER) carbidopa/levodopa (CD/LD) formulations are **designed to provide longer-lasting LD plasma levels with less frequent dosing** than immediate-release (IR) formulations[10]
- ER CD/LD formulations **combine IR components**, which release part of the medication immediately, **and ER components**, which release the remaining medication over an extended period of time[11]
- ER CD/LD therapies are **approved across all stages of PD**, including for patients who are treatment-naïve[12,13]

Learn more about how an ER CD/LD therapy is turning innovation into duration for patients with PD

References: 1. de Bie RMA, Clarke CE, Espay AJ, Fox SH, Lang AE. Initiation of pharmacological therapy in Parkinson's disease: when, why, and how. *Lancet Neurol.* 2020;19(5):452-461. **2.** Fahn S, Oakes D, Shoulson I, Kieburtz K, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med*. 2004;351(24):2498-2508. **3.** Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: Insights into motor complications from sub-Saharan Africa. *Brain.* 2014;137(Pt 10):2731-2742. **4.** Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med*. 2019;380(4):315-324. **5.** Frequin HL, Schouten J, Verschuur CVM, et al. Levodopa response in patients with early Parkinson disease: Further observations of the LEAP study. *Neurol.* 2023;100(4):e367-e376. **6.** Pringsheim T, Day GS, Smith DB, et al. Dopaminergic therapy for motor symptoms in early Parkinson disease practice guideline summary: A report of the AAN Guideline Subcommittee. *Neurol*. 2021;97(20):942-957. **7.** de Bie RMA, Katzenschlager R, Swinnen BEKS, et al. Update on treatments for Parkinson's disease motor fluctuations—an International Parkinson and Movement Disorder Society evidence-based medicine review. *Mov Disord*. 2025;40:776-794. **8.** American Academy of Neurology. Dopaminergic therapy for motor symptoms in early Parkinson disease. Reaffirmed February 8, 2025. Accessed February 2, 2026. https://www.aan.com/Guidelines/home/GuidelineDetail/1043 **9.** Lees A, Tolosa E, Stocchi F, et al. Optimizing levodopa therapy, when and how? Perspectives on the importance of delivery and the potential for an early combination approach. *Expert Rev Neurother.* 2023;23(1):15-24. **10.** LeWitt P, Ellenbogen A, Burdick D, et al. Improving levodopa delivery: IPX203, a novel extended-release carbidopa-levodopa formulation. *Clin Park Relat Disord*. 2023;8:100197. **11.** Power D, Crotty GF. Advances in the pharmacological management of Parkinson's disease. *Curr Treat Options Neurol.* 2025;27(1). **12.** CREXONT [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; 2024. **13.** RYTARY [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; 2019.

Levodopa in Parkinson's Disease:

Clinical Practice Informed by Evidence

This guide summarizes the evidence reinforcing the role of oral levodopa as the cornerstone of Parkinson's disease treatment.

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Misconceptions That Undermine Effective Levodopa Treatment

Clinicians face complex decisions when treating patients with Parkinson's disease (PD), especially around when to start oral levodopa (LD). Even with new therapeutic options, outdated concerns continue to influence practice—but evidence can help clarify the path forward[1]

MYTH #1

"Early initiation of LD accelerates disease progression or increases the risk of dyskinesia."

REALITY

Dyskinesia is associated with disease progression, not early LD use. Delaying LD initiation postpones symptom control without impacting risk of motor fluctuations over time.[2,3]

In a trial comparing early oral LD initiation with placebo, there was **no acceleration of disease progression in patients receiving oral LD**[2*]

- After 40 weeks of treatment and 2 weeks of washout, LD significantly reduced the worsening of PD symptoms versus placebo ($P<0.001$ for trend), as shown by change from baseline in total UPDRS score (placebo: +7.8 points; LD 150 mg/day: +1.9 points; 300 mg/day: +1.9 points; 600 mg/day: –1.4 points)

Naturalistic cohort data show that **LD-induced symptom fluctuation is due to disease duration** rather than treatment duration[3†]

- Motor fluctuations and dyskinesias emerged after similar disease duration for patients in Ghana and Italy (~6–7 years from symptom onset), despite significantly shorter LD exposure in Ghana (median LD duration at onset: motor fluctuations 0.5 vs 2.0 years [$P=0.001$]; dyskinesias 1.0 vs 3.0 years [$P=0.004$], respectively)

*The ELLDOPA study was a double-blind, placebo-controlled trial of 361 patients with early PD assigned to 3 doses of oral immediate-release carbidopa/levodopa or placebo for 40 weeks, followed by a 2-week washout period. The primary outcome was change in total MDS-UPDRS score from baseline to Week 42.[2]

†Cross-sectional, case-controlled analysis of a 4-year, multicenter study in Ghana, where access to oral carbidopa/levodopa is limited. The primary objective was to investigate whether the occurrence of motor complications is primarily related to the duration of LD therapy or to disease-related factors, using multivariate regression analyses to adjust for clinical covariates.[3]

ELLDOPA=Earlier versus Later Levodopa Therapy in Parkinson Disease; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

MYTH #2

"Early use of LD limits its effectiveness later in the disease course."

REALITY

LD remains effective when initiated early in PD. Apparent declines in clinical response over time reflect disease progression rather than pharmacologic tolerance from early use.[4,5]

In a trial comparing early- vs delayed-start oral LD, **early LD provided better early symptom control and led to fewer motor fluctuations after 80 weeks**[4,5*]

- During the placebo-controlled phase (baseline to Week 40), total UPDRS scores improved in the early-start levodopa group and worsened in the delayed-start group (–3.1 vs +2.0 points, respectively)[4]
- Change in total UPDRS scores from baseline to Week 80 did not differ between the early- vs delayed-start LD groups (mean change: –1.0 vs –2.0 points, respectively; $P=0.44$); however, a post-hoc analysis found that fewer patients in the early-start group reported motor response fluctuations at Week 80 (23% [46/205] vs 38% [81/211], respectively; $P<0.01$)[4,5]

MYTH #3

"Dopamine agonists should be considered before oral LD."

REALITY

AAN guidelines recommend initiating oral LD instead of dopamine agonists in early PD with motor symptoms, and MDS Evidence-Based Medicine guidance positions dopamine agonists as adjunctive therapy for motor fluctuations.[6,7]

Based on an analysis of a series of clinical studies, **AAN guidelines**, reaffirmed in 2025, **recommend that oral LD be used before dopamine agonists** for patients with early PD and motor symptoms[6,8]

- These guidelines constitute Level B recommendations, meaning they reflect solid evidence and a high degree of confidence in the benefit-risk profile

The 2025 MDS Evidence-Based Medicine review classifies **dopamine agonists** as efficacious or likely efficacious **for motor fluctuations only as adjunctive treatment to optimized oral LD therapy**[7]

*The double-blind LEAP trial randomized 445 PD patients to early-start oral immediate-release carbidopa/levodopa or placebo for 40 weeks, followed by delayed-start oral immediate-release carbidopa/levodopa for the placebo group or continued carbidopa/levodopa for the next 40 weeks. The primary outcome was change from baseline to Week 80 in total MDS-UPDRS scores. Motor fluctuations at Week 80 was a post-hoc analysis.[4,5]

AAN=American Academy of Neurology; LEAP=Levodopa in Early Parkinson's disease.