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ADVANCING PARKINSON'S TREATMENT WITH

Long-Lasting Levodopa Therapy

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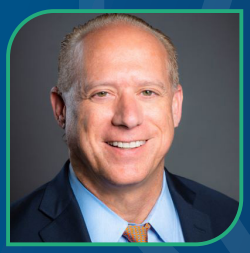

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Levodopa first appeared on the clinical scene in the late 1960s as a potent and highly effective medication for the treatment of Parkinson's disease motor symptoms. Since then, continued efforts have been made to advance levodopa therapy, most notably by extending levodopa's half-life. Here, we explore the history and evolution of levodopa therapy and discuss its clinical use with renowned movement disorder specialists Drs Fiona Gupta and Stuart H. Isaacson.

When levodopa was first synthesized in the early 1900s, its therapeutic potential was not immediately apparent.[1,2] In fact, it would be nearly 5 decades before pharmacologist and future Noble laureate Arvid Carlsson would administer levodopa to reserpine-treated rabbits, highlighting its therapeutic potential.[1] Reserpine was the first selective medication for the treatment of schizophrenia, but it had significant side effects, including the tendency to induce parkinsonian symptoms.[1,3] Carlsson demonstrated that the parkinsonian-like symptoms caused by reserpine in his rabbits were due to the depletion of dopamine and that their symptoms could be reversed by systemically injecting levodopa.[1] Following Carlsson's discovery, Oleh Hornykiewicz examined dopamine levels in the postmortem brains of Parkinson's patients and found that the striatum was deficient in dopamine.[1,3,4] Hornykiewicz would later partner with neurologist Walter Birkmayer, injecting levodopa into advanced Parkinson's patients and demonstrating a significant improvement in their motor function.[1,3,5] Building on Hornykiewicz and Birkmayer's work, neurologist George Cotzias began clinical trials of oral levodopa and published the results of his successful studies in the *New England Journal of Medicine*.[6,7] Shortly after, in 1970, the US Food and Drug Administration (FDA) approved levodopa for the treatment of Parkinson's disease motor symptoms.[1,2]

A short half-life

Over the years, levodopa has evolved into several oral formulations, each with advantages and limitations. In 1975, carbidopa was added to levodopa to increase the amount that reaches the brain.[2] Immediate-release carbidopa/levodopa (IR CD/LD) was the first FDA-approved formulation of CD/LD, and while IR CD/LD provides significant motor symptom control, especially in the early stages of Parkinson's disease, its short half-life (1.5 hours) requires frequent dosing at regular intervals to be effective.[2,8]

"While levodopa therapy is a mainstay in Parkinson's disease treatment, it has a short half-life, which complicates treatment," says Dr Stuart H. Isaacson, movement disorder specialist at the Parkinson's Disease and Movement Disorders Center of Boca Raton. "Because patients must rely on multiple daily doses of levodopa, treating patients with a short-acting levodopa formulation becomes difficult."

Parkinson's disease medications often require multiple daily doses to control motor symptoms, and as a result adherence can be challenging and lead to missed doses that negatively impact motor symptoms. The most effective approaches to improve adherence are those that simplify dosing.[9-11] Dr Fiona Gupta, movement disorder specialist at Mount Sinai Health System and Assistant Professor of Neurology says, "Parkinson's patients who require multiple levodopa doses—4, 5, 6 doses or more per day—have their lives completely consumed by medication, which can be frustrating and burdensome," adding, "Patients do much better when they are taking fewer doses. They feel they have reclaimed some control. They aren't chained to their medications, giving them more flexibility and freedom."

The short half-life of IR CD/LD is also thought to contribute to the development of motor complications such as motor fluctuations and involuntary movements known as dyskinesias.[8] Motor fluctuations are broadly defined as alternating states when motor symptoms are well controlled by levodopa ("on" time), and when motor symptoms reappear ("off" time).[12] Approximately a median of 40% of Parkinson's patients on levodopa therapy develop motor fluctuations within 4 to 6 years of starting treatment, and nearly a median of 70% will experience them after 9 years.[13] As a result, several attempts have been made to extend levodopa's half-life and address the unmet needs of patients on IR CD/LD.

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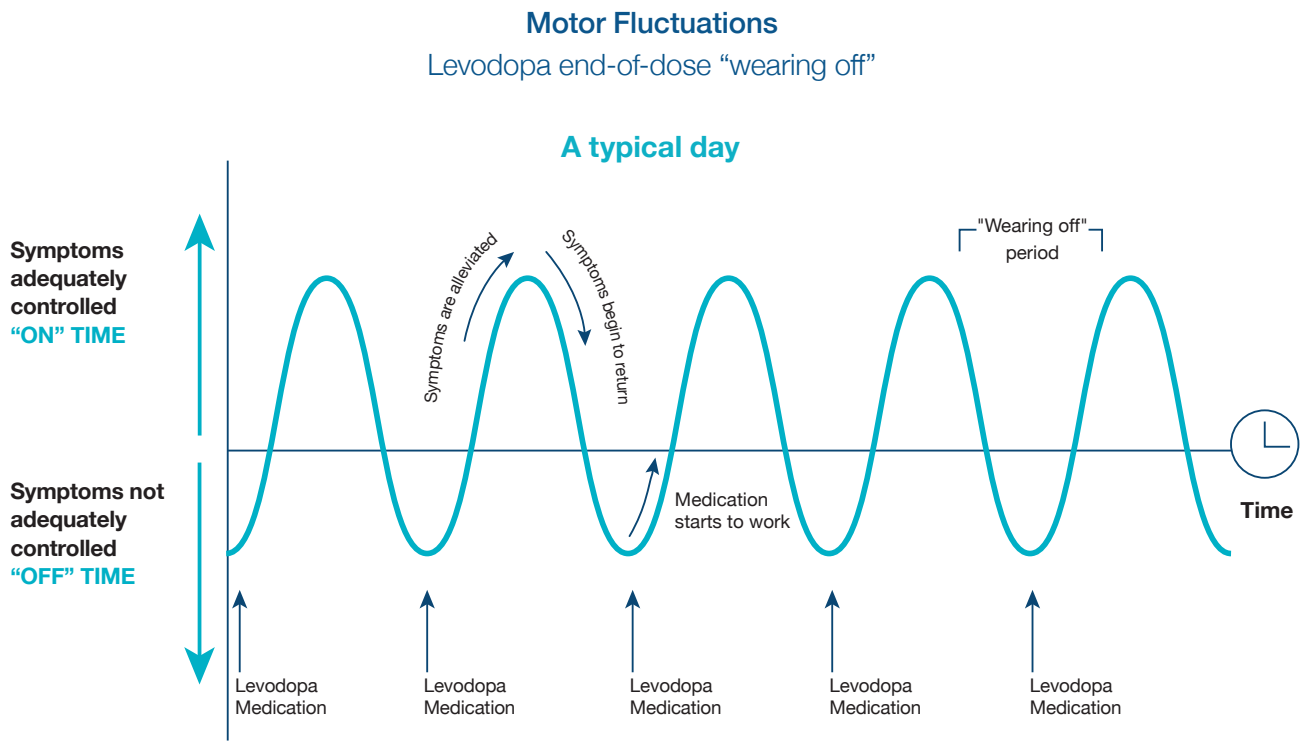
Fine-tuning levodopa

Under normal conditions, dopamine receptors in the brain are exposed to relatively continuous levels of dopamine.[12] In Parkinson's disease, however, continuous dopaminergic stimulation is lost due to the progressive degeneration of dopamine neurons.[14] Early in the disease, levodopa can replace the missing dopamine, and the brain can supply the rest.[12] But as the disease progresses, dopamine levels become increasingly dependent on oral levodopa, causing the benefits of each dose to wear off more quickly.[12] With IR CD/LD, the therapeutic benefit of levodopa can wear off as soon as 60 to 90 minutes after administration.[12] Additionally, pulsatile stimulation of dopamine receptors by short-acting levodopa formulations is thought to contribute to the narrowing of levodopa's therapeutic window, further exacerbating motor fluctuations.[12,14] As a result, continuous dopaminergic stimulation has emerged as a treatment strategy for limiting motor complications, laying the groundwork for the development of several long-acting levodopa formulations.



As Parkinson's disease progresses, brain dopamine levels become increasingly dependent on oral levodopa. As a result, the therapeutic benefits of each levodopa dose begin to wear off more quickly.

Controlled-release carbidopa/levodopa (CR CD/LD) was developed to provide sustained release of levodopa through the use of a biodegradable polymer matrix.[8] However, subsequent studies found that the CR formulation delayed the absorption of CD/LD by approximately 4 to 6 hours, and that fluctuating Parkinson's patients who were given CR CD/LD did not experience a significant reduction in 'off' time when compared to patients who were given IR CD/LD.[8]

In another attempt to extend the half-life of levodopa, entacapone, a catechol-O-methyltransferase (COMT) inhibitor, was added to IR CD/LD to inhibit the peripheral metabolism of levodopa, allowing more to reach the brain.[8] While CD/LD/entacapone (CLE) extends levodopa's half-life to 2.4 hours and increases its exposure by 35% to 40% compared to IR CD/LD, it also causes large fluctuations in levodopa levels, limiting its therapeutic potential.[8] Furthermore, the STRIDE-PD study found that patients taking CLE had a shorter time to onset and a higher frequency of dyskinesia compared to patients taking IR CD/LD.[15]

More recently, extended-release carbidopa/levodopa (ER CD/LD) was developed to address the limitations of existing levodopa preparations. ER CD/LD capsules contain CD/LD microbeads that dissolve at various rates, providing a rapid and sustained release of levodopa.[8,16] Pharmacokinetic studies have shown that with ER CD/LD, levodopa plasma levels increase rapidly, reaching an initial steady-state approximately 1 hour after administration.[16] Moreover, ER CD/LD maintains plasma levodopa levels for 1.9 to 2.5 hours longer than other existing oral levodopa formulations including IR CD/LD, CR CD/LD, and CLE.[16] ER CD/LD has also been shown to have a smaller fluctuation index than IR CD/LD, meaning the magnitude of the rise and fall of levodopa concentrations remains smoother compared with IR CD/LD.[17] ER CD/LD is generally well tolerated with the most common adverse events being nausea, dizziness, headache, sleeplessness, abnormal dreams, dry mouth, abnormal involuntary movements, anxiety, constipation, vomiting, and low blood pressure upon rising.[18] Importantly, clinical results demonstrate that ER CD/LD significantly reduces "off" time compared to IR CD/LD while also limiting the frequency of dosing.[19]

> ***"Patients frequently report that extended-release levodopa takes them off the roller coaster of ups and downs with multiple daily doses, they begin to reclaim some control of their lives."***
>
> - Dr Fiona Gupta
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> *Movement Disorder Specialist at Mount Sinai Health System and Assistant Professor of Neurology*

ER CD/LD as foundational therapy

ER CD/LD can also provide a strong foundation for additional Parkinson's medications to be added as the disease progresses. COMT inhibitors, dopamine agonists, and on-demand therapy, such as inhaled levodopa or sublingual apomorphine, are examples of such medications.[20,21] However, Dr Gupta says, "Each patient is unique, but before adding adjunctive therapy, I believe in optimizing a patient's levodopa as much as possible."

> ***"When considering adjunctive therapies, we must consider these medications as add-ons to an already optimized levodopa regimen. We will often choose to add these medications to extended-release levodopa rather than immediate-release because of its longer benefit of duration."***
>
> - Dr Stuart H. Isaacson
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> *Movement Disorder Specialist at the Parkinson's Disease and Movement Disorders Center of Boca Raton*

A promising future for longer-lasting levodopa therapy

Levodopa therapy is the most widely used and effective treatment for Parkinson's disease motor symptoms.[22,23] However, because of levodopa's short half-life, treating Parkinson's patients with short-acting formulations can be difficult.[8] As a result, efforts to extend the half-life of levodopa have been made, with ER CD/LD representing a significant achievement. ER CD/LD provides smoother and more sustained plasma levodopa levels, as well as a significant reduction in "off" time when compared to IR CD/LD.[16,17,19] Furthermore, the long-term symptom control from ER CD/LD can provide a solid foundation for the addition of adjunctive medications if necessary.

When asked about the future of levodopa therapy, Dr Isaacson says, "We're investigating several methods for delivering levodopa more consistently. As extended-release formulations become more widely available, I believe they will become the mainstay of levodopa therapy. Newer formulations with longer durations of action will continue to replace each other until, hopefully, once-daily levodopa becomes a reality."

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