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THE IMPORTANCE OF

"Good On" Time and Reducing Dyskinesia

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"Good On" time refers to the sum of "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia, and has become a meaningful clinical indicator of successful motor symptom control as well as an emerging primary endpoint for Parkinson's disease clinical trials. Long-acting carbidopa/levodopa formulations, including oral extended-release carbidopa/levodopa, have been shown to provide significantly more "Good On" time than short-acting, immediate-release carbidopa/levodopa. Here, we detail the importance of "Good On" time with movement disorder specialists and Parkinson's disease experts, Drs Richard B. Dewey Jr and Rajesh Pahwa.

Parkinson's disease is a neurodegenerative disorder marked by a progressive loss of dopaminergic neurons and motor function that will affect an estimated 14 million individuals worldwide by 2040.[1,2] The primary motor symptoms of Parkinson's disease include tremor, rigidity, bradykinesia, and postural instability, though non-motor symptoms are also common.[2,3] Since the 1960s, dopamine replacement therapy has been the mainstay of Parkinson's disease treatment, with levodopa being the most widely used and efficacious treatment option for motor symptoms.[4,5] There are currently several oral formulations of levodopa available, including immediate-release carbidopa/levodopa (IR CD/LD), controlled-release CD/LD (CR CD/LD), carbidopa-levodopa-entacapone (CLE), and extended-release CD/LD (ER CD/LD), all of which aim to replace missing dopamine in the brain and improve motor function.[6-9]

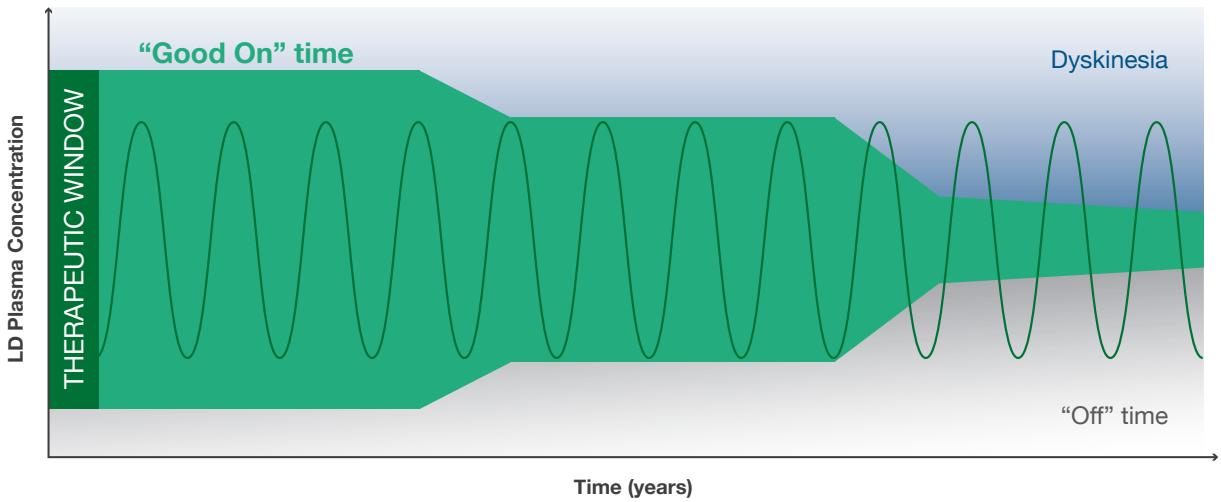
A narrowing therapeutic window

Levodopa therapy is associated with excellent symptom management early in the clinical course, with even short-acting formulations of levodopa providing long-lasting symptom control, also known as "on" time.[10] However, as the disease progresses, the therapeutic window of levodopa narrows, such that previously effective doses of levodopa no longer provide adequate motor symptom control.[10] Patients with a narrow therapeutic window experience motor fluctuations including "off" episodes when Parkinson's

symptoms recur.[10,11] Another consequence of a narrow therapeutic window is dyskinesia, which is characterized by involuntary, erratic, writhing movements of the face, arms, legs, or trunk.[12] Peak-dose dyskinesia is the most common type of dyskinesia and occurs during the “on” phase when levodopa concentrations are at their highest.[10] Indeed, the median percentage of patients with dyskinesia is approximately 40% after 4 to 6 years of levodopa treatment.[13]

“As Parkinson’s disease progresses, ‘on’ time can become compromised by dyskinesia,” says Dr Richard B. Dewey Jr, a movement disorder specialist and Professor of Neurology at the University of Texas Southwestern Medical Center. “We’re attempting to raise dopamine levels with medication, but we end up overshooting, causing a patient to become dyskinetic.”

Achieving “Good On” Time With a Narrowing Therapeutic Window



The therapeutic window narrows as Parkinson’s disease progresses, making it difficult to achieve beneficial levodopa levels. When levodopa levels are too low, patients have “off” episodes during which their Parkinson’s symptoms reoccur. In contrast, patients experience dyskinesia when their levodopa levels are too high. Dyskinesia is classified as either non-troublesome or troublesome, with the former causing little impairment to one’s activities and the latter causing significant disability. “Good On” time is defined as the sum of “on” time without dyskinesia plus “on” time with non-troublesome dyskinesia and is the goal of levodopa therapy.

Dr Rajesh Pahwa, a movement disorder specialist and Professor of Neurology at the University of Kansas Medical Center, says patients often confuse dyskinesia with their Parkinson’s symptoms. He uses the following analogy when discussing the relationship between levodopa therapy and dyskinesia with patients: “I like to explain that levodopa is like gas for your car, and dyskinesia occurs when we press too hard on the gas pedal. Your car is working, and you have gas; however, you are speeding, and we need to slow it down. This is not as easy as slowing a car, not enough levodopa causes ‘off’ time and with a narrow therapeutic window even low doses of levodopa can result in dyskinesia.”

Because Parkinson’s disease is progressive, patients on levodopa therapy commonly encounter dyskinesias at some point during their treatment. The median percentage of patients with dyskinesia increases over time, from approximately 40% after 4 to 6 years of levodopa treatment to approximately

90% after 9 to 15 years of levodopa treatment.[13,14] However, dyskinesia exists on a spectrum and is classified as non-troublesome or troublesome, with the former not causing any detriment to one's activities and the latter causing considerable disability and discomfort.[11,15,16] Even so, Dr Pahwa notes, "Troublesome dyskinesia differs depending on the patient. What one patient finds troublesome, another patient may not. It all comes down to educating the patient about dyskinesia so that they can recognize how dyskinesia affects their life."

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Establishing the treatment goal of more "Good On" time

"Good On" time is defined as the sum of "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia, and has emerged as a powerful clinical indicator of successful motor symptom control.[17] Clinical studies have shown that patients consider "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia as "good" time, and "off" time as well as "on" time with troublesome dyskinesia as "bad" time.[11,15] Clinical data also show that "Good On" time more strongly correlates with patients' perceived duration of a good response throughout the day than "on" time alone.[17]

Dr Dewey explains, "'Good On' time allows my patients to initiate movement easily, their tremor is minimal, they are less rigid, and walk well. Their medication dose is not so high that they become dyskinetic. It's like threading a needle to achieve the ideal balance of dopaminergic stimulation. That is the goal of treatment."

"Every Parkinson's patient requires a different amount of levodopa to achieve a 'Good On'," notes Dr Pahwa. "However, if a patient on levodopa tells me they can do tasks with less effort–for example, they can walk better, roll in bed easier, or exit the car with less effort–in my experience, I consider the patient to have achieved 'Good On'."

"Good On" time is also becoming an increasingly common primary endpoint for emerging Parkinson's disease therapies.[18-20] Every one-hour increase in "Good On" time is associated with a 19% higher likelihood of performing activities of daily living independently.[21] More "Good On" time is also associated with fewer falls, lower likelihood of uncontrolled motor/non-motor symptoms, and decreased emergency room visits and lower likelihood of hospitalization.[21]

While Dr Dewey hopes that clinical trials for Parkinson’s disease will continue to measure “off” time, he emphasizes the importance of medications providing quality “on” time, highlighting that, “We can reduce ‘off’ time at the expense of troublesome dyskinesia, so ‘Good On’ time is a helpful shift in perspective.”

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The “Good On” time benefits of oral extended-release levodopa

Though the specific mechanisms underlying dyskinesia are unknown, studies suggest that pulsatile stimulation of dopamine receptors caused by levodopa’s short half-life is likely one of the contributing factors.[10] “When levodopa preparations were first developed, they [formulations] had a very short half-life, which resulted in the pulsatile stimulation of dopamine receptors,” explains Dr Dewey. “Pulsatile stimulation of dopamine receptors is now known to be harmful because it abnormally activates downstream neural networks in ways that promote dyskinesia.” Accordingly, newer levodopa preparations have focused on providing smooth, longer-lasting levodopa levels.[22,23]

ER CD/LD formulations were developed with the goal of providing improved pharmacokinetics over earlier, short-acting levodopa preparations.[22,23] In clinical trials, ER CD/LD formulations have been shown to increase “Good On” time more than short-acting IR CD/LD.[24,25] ER CD/LD formulations have also been shown to provide more “Good On” time per dose compared to IR CD/LD.[26,27]

Common adverse events associated with oral CD/LD, including long-acting preparations, are nausea, dizziness, headache, and somnolence, which can occur suddenly and without warning.[28] The most common side effects in elderly patients on levodopa can include confusion, hallucinations, delusions, psychosis, and agitation.[28] Levodopa is also contraindicated with the concurrent use of monoamine oxidase inhibitors (MAOIs) as hypertension can occur when these medications are used together.[28] “Levodopa is highly effective and has relatively few side effects,” says Dr Pahwa, “so it is generally considered a safe medication.”

"I favor starting Parkinson's disease treatment with levodopa therapy. As longer-acting formulations of levodopa become available, the primary limitations of the original levodopa preparations are addressed," says Dr Dewey. "I've been following the new developments in extended-release levodopa formulations with great interest and excitement. If we could give a pill that would provide more continuous dopaminergic stimulation, it might mitigate several of the problems associated with levodopa therapy."

Advice for neurologists on providing patients with more "Good On" time

"Good On" time has become an increasingly common endpoint for Parkinson's disease clinical trials.[18-20] Indeed, "Good On" time is more strongly correlated with a patient's perception of a good response during the day compared to "on" time alone.[17] Emerging levodopa therapies, including ER CD/LD formulations, aim to provide more "Good On" time than short-acting IR CD/LD formulations, making them an effective tool for helping patients achieve more "Good On" time.[18-20]

Dr Pahwa offers this advice to neurologists wanting to improve their patients' "on" time: "Spend as much time as possible speaking to your patients. Ask them what happens when they take their levodopa medication, as this can help determine whether the patient has too much 'off' time or dyskinesia." He notes, "If you educate your patients early on, they will be able to tell you how well their medication is working."

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