

Impact of OFF Episodes Related to Parkinson's Disease and Treatment Considerations for This Patient Population

NOVEMBER 2020

Overview of Parkinson's disease

Currently, nearly 1 million people in the United States have Parkinson's disease, and the age-related neurodegenerative disorder is associated with an average age of onset of 60 years.^{1,2} Available medications for Parkinson's disease treat symptoms, but there are no cure or disease-modifying therapies available.⁴ Standard maintenance therapy for this condition is oral levodopa/carbidopa.³

However, following long-term use of levodopa, patients can develop motor complications, including motor fluctuations and dyskinesia.⁵ As Parkinson's disease progresses, the duration of levodopa's effect narrows so that motor symptoms may become difficult to control.⁶⁻⁸ These motor fluctuations result in periods of ON and OFF states: ON is the duration of time during which the patient responds to medication and has satisfactory improvement in motor and non-motor symptoms, while OFF episodes are changes in the clinical state of the patient where motor and/or non-motor symptoms reappear or worsen.^{5,9}

Focus on OFF episodes

Conservative estimates suggest that motor fluctuation, including OFF episodes, occurs in nearly 50% of patients within five years of starting levodopa maintenance treatment, although these effects could be seen as soon as two to three years after beginning treatment. After a few years, the benefit from each levodopa dose becomes shorter, more unpredictable, and associated with involuntary movements.^{10,11}

Each patient's experience with OFF episodes is unique, as symptoms and progression vary from one patient to another.² There are four common types of OFF episodes that patients with Parkinson's disease can experience:^{9,12,13}

1. Unpredictable OFF: The patient randomly and abruptly transitions from an ON to an OFF state.
2. Wearing OFF: A predictable recurrence of the patient's motor and/or non-motor symptoms before the next scheduled dose of medication.
3. Morning OFF: The patient wakes in an OFF state prior to taking their first morning dose of medication.
4. Delayed ON: A delay in time during which the patient responds to medication and has satisfactory improvement in motor and/or non-motor symptoms.
 - » Partial ON: The patient has a partial response to medication and has a less than satisfactory improvement in motor and/or non-motor symptoms.

- » No ON: The patient has no response to medication and has no improvement in motor and/or non-motor symptoms.

Impact of OFF episodes

OFF episodes impact a patient's quality of life. In a survey, The Michael J. Fox Foundation assessed the impact of OFF time from the patient perspective. More than 3,000 patients completed the online survey, which asked about time spent in the OFF state (including prevalence and duration), as well as the impact of OFF time on activities of daily living, well-being and quality of life, and disability. The survey found that 64% of patients spend two to more than four hours cumulatively of their day in OFF time. Nearly 32% of patients frequently or always experience pain during OFF time, and more than 30% of patients frequently or always have difficulty walking safely while in an OFF state. The study is limited by its use of patient-reported information, which may introduce bias.¹⁴

In another study, researchers sent a quality of life survey to nearly 5,000 members of the Japan Parkinson's Disease Association and their caregivers regarding their experience with morning OFF time. The patient questions included information on age, gender, work situation, Hoehn and Yahr stage, disease duration from the onset, pharmaceuticals used, quality of life, whether they had experienced morning OFF, frequency of morning OFF, and problems due to morning OFF. Morning OFF was observed in 79.8% of all patients, and 52.4% of patients were at stage I on the Hoehn and Yahr scale. As the level of Hoehn and Yahr scale severity increased, the percentage of patients with morning OFF increased. Among patients with morning OFF, 68.0% report difficulty changing clothes, 44.2% have difficulty using the bathroom, 42.9% are unable to be active in the morning, 35.0% have difficulty with meals, 31.2% fear being a "nuisance" to their family, and 17.3% report waking up with pain. The study is limited in that the treatment regimens of patients was unknown.¹⁵

The combined direct and indirect cost of Parkinson's disease, including treatment, social security payments, and lost income, is estimated to be nearly \$52 billion per year in the United States, with medications costing an average of \$2,500 per person per year.¹ In a study, researchers created a burden of Parkinson's disease model combining information from nationally representative surveys. Estimated prevalence rates and costs were applied to the U.S. Census Bureau's 2010 to 2050 population data to estimate this burden. The study assumed that approximately 630,000 people in the United States had diagnosed Parkinson's disease in 2010, with diagnosed prevalence likely to double by 2040. The national economic burden of Parkinson's disease exceeded \$14.4 billion, with each patient incurring approximately \$22,800 in medical expenses.¹⁶

In addition, OFF episodes may result in higher healthcare resource utilization. This patient population also required approximately 1.9 million hospital inpatient days, which is 801,000 more days than what would be expected for

a population with similar demographics but without Parkinson's disease. The study does not specify if the hospitalizations were directly related to Parkinson's disease. The study is limited because patient disease severity is unknown.¹⁶

Patients experiencing OFF episodes have three- to four-fold more emergency department (ED) visits and hospitalizations compared with those without OFF episodes. These patients also have significantly higher annual rates of hospitalization (mean, 0.15), ED visits (mean, 0.20), total length of stay (mean, 0.68), and intensive care unit (ICU) admissions (mean, 0.01) than patients without OFF episodes ($P < 0.05$ for all). Each incremental OFF episode hour per day is associated with a 60% to 70% greater ICU admission and length of stay.¹⁷ The study does not specify if the hospitalizations and ICU stays were directly related to Parkinson's disease.

Treatment landscape

Therapies to treat Parkinson's disease–related symptoms include SINEMET® (carbidopa and levodopa) tablet, DUOPA® (carbidopa and levodopa) enteral

suspension, NEUPRO® (rotigotine transdermal system) rotigotine patch, extended release, OSMOLEX ER™ (amantadine) extended-release tablets, SYMMETREL® (amantadine hydrochloride) tablets and syrup, and RYTARY® (carbidopa and levodopa) extended-release capsules.¹⁸⁻²³ Several factors can interfere with steady, accurate dose delivery of these agents, so they may also be used in combination with other classes of medications to better address OFF episodes, including dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase B (MAO-B) inhibitors, and anticholinergic agents.^{24,25}

Among these options are scheduled adjunctive therapies that work to extend ON time or shorten OFF time, such as XADAGO® (safinamide) tablets, NOURIANZ™ (istradefylline) tablets, and ONGENTYS® (opicapone) capsules.²⁶⁻²⁸

In addition, on-demand therapies, such as APOKYN® (apomorphine hydrochloride injection) for subcutaneous use, INBRIJA™ (levodopa inhalation powder) for oral inhalation, and KYNMOBI™ (apomorphine HCl) sublingual film, bring patients who are OFF back ON.²⁹⁻³¹



Insights from a neurologist

Fernando L. Pagán, MD, professor and vice chairman for the Department of Neurology at Georgetown University Hospital, discussed the shifting treatment paradigm for Parkinson's disease and the educational gaps that persist in patient–provider communication.

Disclaimer: The views expressed in this interview are Dr. Pagán's personal opinion and clinical experience.

Thinking of your current patients with Parkinson's disease, how often are you discussing OFF episodes with them?

We are seeing a paradigm shift in the treatment of Parkinson's disease in that most of the medicines coming out are targeting OFF. OFF is basically the reemergence of Parkinson's disease symptoms. When the medicines are working, we call that ON; when the medicines aren't working or there's a reemergence of symptoms, that's what we call OFF episodes or time.

I think we're starting to do a better job of trying to define that. There needs to be a lot more education in the clinic to describe what OFF is to patients, because patients use different terminology than neurologists. However, I'm not sure all neurologists and primary care doctors who take care of Parkinson's disease patients really recognize these OFF episodes, if you don't really ask for them. In my clinic, I discuss OFF on a daily basis with my patients. I start to introduce the terms ON and OFF and what they mean. There's still a huge educational unmet need for both clinicians and patients. I think there's a huge opportunity to help our patients understand what ON and OFF mean.

In the course of their disease, when do these patients predominantly seem to experience OFF episodes, and what related symptoms do they report to you?

That is where the education of OFF episodes is so important, because a lot of patients don't recognize what an OFF episode is, and that's why there's such a huge educational need. We can start seeing OFF episodes very early on in

the disease, especially if the patient is not compliant with their medication or is undertreated, etc. If the patient is undertreated and OFF all day, they don't recognize being ON or OFF. If you adequately treat someone, when the medicines do wear off or there's a missed dose, that's when patients start to experience OFF episodes. In general, you start seeing a more predominant emergence of OFF episodes after a few years in a well-treated patient. Half of patients treated with levodopa within five years have OFF episodes and nearly all patients treated with levodopa have OFF episodes within 10 years of treatment.^{10,11}

The hard part is that a lot of people still don't know that OFF episodes can be themed by symptoms of what we call motor symptoms and non-motor symptoms. Motor symptoms are easy to see, like a reemergence of tremor, rigidity, stiffness, or slowness of movement. You might see cramped handwriting, difficulty getting out of the chair, etc. Those are going to all get worse when you have an OFF episode.

Non-motor symptoms are what don't often get communicated enough between the physician and patient—in addition to the motor symptoms, sometimes these OFF episodes are associated with anxiety, feelings of depression, or mood irritability. Some people have a feeling of impending doom or anxiety. They can have pain, sweating episodes, shortness of breath, etc. It's probably not until things get really severe that people start to pay more attention to them. We as physicians have to teach our patients what ON and OFF is and what these OFF episodes entail.

How do your patients experiencing OFF episodes describe how it impacts their daily life?

It's very different from patient to patient, and these OFF episodes can be quite disabling for some. I've had some patients describe an OFF episode as, "I felt like I was dying. I couldn't breathe. I was anxious. I just had this feeling of impending doom, like I was going to die." Other patients describe severe pain. It's quite variable. Normally, a patient is not going to say, "I was OFF," because they haven't learned that terminology, but they're going to tell you they had periods throughout the day where they just sat there for

one, two, or three hours waiting for the medicine to work again.

OFF episodes can be really impactful to their activities of daily living—they can't function or they're in pain; they feel foggy brain. This is why it's so important to get the patient and physician talking the same language of what these OFF episodes are and the symptoms associated.

Have any of your patients with Parkinson's disease gone to an ED or were admitted to a hospital due to an OFF episode or Parkinson's disease-related complications?

Absolutely. A lot of times our patients with Parkinson's disease, when they were OFF, can have shortness of breath, increased sweating, pain, etc. Sometimes it's almost like chest pain or dystonia of the diaphragm. We've had patients show up thinking they're having a heart attack, and they get the entire cardiac workup, and everything comes back negative; all they needed was for the medicine to start working again. I had patients show up almost like in a hypertensive crisis because they're no longer getting their carbidopa/levodopa and have almost a neuroleptic malignant syndrome kind of effect. They're diaphoretic, hypertensive, and just feeling horrible. We've had other patients freeze up, and they've been diagnosed with having a transient ischemic attack (TIA). It turns out, they were just having an OFF episode.

If you evaluate a patient in distress, short of breath, pain, hypertensive, and diaphoretic, healthcare providers are going to rule out hypertensive crisis, TIA, or a cardiac event when all the workup comes out negative; they finally get their medication and return back to normal. Some OFF episodes can be so severe that patients do show up in the ED. I've been called by ED physicians. Everything's negative; they look terrible. I tell them we have to give them more carbidopa/levodopa. Sometimes they've been in the ED for hours without their medicine.

Again, the language our patients use is not "I'm OFF" or "I'm ON." They just describe their symptoms, but I think there's still a huge educational gap for the medical community to understand what Parkinson's disease patients look like throughout the day—how they fluctuate in terms of their medicine being ON and OFF.

What are some of the bigger challenges in managing the treatment of your patients who experience OFF episodes associated with Parkinson's disease?

One of biggest challenges is that most of our medicines require absorption through the gastrointestinal (GI) system, and our patients have a lot of GI issues that can delay the absorption of these medications: gastroparesis, constipation, or other absorption problems. We see a lot of missed-dose effect or delayed ON effect with these oral medicines. The go-to is always to pop an extra pill of the carbidopa/levodopa, and that can sometimes take hours to take effect. Patients don't feel better. I think that leads our patients to go into the ED saying, "I took the medicine; I'm not better, so there's probably something wrong."

How do you currently manage symptoms of motor fluctuations? Do you adjust the patient's carbidopa/levodopa regimen or add an adjunctive therapy, or both, depending on the patient?

It depends on the patient, and we can do both: adjust the maintenance carbidopa/levodopa and add an adjunctive. We definitely use longer-acting carbidopa/levodopa medicine. Sometimes we switch from an immediate-release to a longer-acting one or extended release, but we definitely

use adjunctive medication, which could be a MAO-B inhibitor, dopamine agonist, COMT inhibitor, or the A2A antagonist. All of these can decrease OFF time and improve ON time.

Most patients in clinical studies are having OFF time somewhere between 2.5 hours to up to six or more hours a day. No matter what we do, we're not going to completely eliminate OFF episodes. Often, our patients wake up in the OFF state and have morning akinesia because it has been so long since they took their last carbidopa/levodopa.

There has been a shift in the paradigm, in my belief, in treating these OFF episodes. It's always good to have the maintenance drug of carbidopa/levodopa and adjunctive medication, but as soon as you start seeing patients go through their motor fluctuations, you should really think about using some of these on-demand therapies to treat OFF episodes when they really impact patients' daily lives.

What is typically the clinical rationale or signs of progression that precipitate adding an additional therapy for OFF episodes?

When I see a patient who has an impact on their quality of life—if there's pain or disruption of their daily life, they can't do anything during these episodes, they're waiting hours for the medicine to kick in. You really see the impact in the lifestyle at the individual and sometimes caregiver level, especially if in addition to the reemergence of motor symptoms there's anxiety, impending doom, pain, difficulty with thinking, or freezing. If you just add an adjunctive therapy to their routine maintenance drugs, that may not be enough.

Have you experienced pushback from insurance plans when trying to prescribe an adjunctive therapy for OFF episodes?

This has become more of a problem dealing with insurance companies. I don't think insurance companies understand how severe these motor fluctuations can be in Parkinson's disease. We try to add medicines to decrease the OFF times, but again, that's not going to completely get rid of the OFF episodes, so it makes sense to add an adjunctive therapy. Sometimes we're using more than one adjunctive therapy along with carbidopa/levodopa to treat these motor fluctuation and Parkinson's disease.

The on-demand therapies are also hard to get approved by the insurance companies; these include treatments like the injectable apomorphine, inhaled levodopa, or sublingual apomorphine. [Editor's note: sublingual apomorphine was recently approved by the U.S. Food and Drug Administration.] These treatments can be extremely important for patients. That's what the insurance companies don't really get—that we are trying to reduce OFF time with modulation of carbidopa/levodopa and adding adjuncts; our patients may still require an on-demand therapy.

I think there has been a paradigm shift in movement disorders and Parkinson's disease that we need our maintenance medications and sometimes a cocktail approach of adjunctive medicines and carbidopa/levodopa to have more ON time and less OFF time. We call this "rationale polypharmacy." I think it's really important to think about having an on-demand therapy for a patient, especially if it bypasses the GI system and gets our patients moving and feeling better quicker.

Do you believe currently available pharmacotherapies are adequate to fully manage a patient who experiences OFF episodes associated with Parkinson's disease?

Even with the best adjunctive treatment, I don't think we completely eliminate

all OFF periods. We try our best, and I think we definitely can improve the quality of life. Some of our adjunctive treatments can reduce the OFF time to one to three hours. When things get really bad, I think it's important to have an on-demand therapy. It's good to have two ways to help our patients, not only decreasing the overall OFF time, but when they have these OFF episodes, we have a treatment for when they need that.

Have recent product developments regarding OFF episodes had any impact on your Parkinson's disease treatment patterns?

Absolutely. With the emergence of newer on-demand therapies, I've taken a step back and taken a second look. We've had some excellent adjunctive therapies that reduced OFF time. Now we have on-demand therapy for when those baseline treatments aren't working.

One reason why it has made a difference is they're more accessible and maybe a bit easier to deliver. I think the delivery of these systems has really improved. We have an injectable, an inhaled, and a sublingual formulation. As neurologists who take care of Parkinson's disease patients, we have to take a look at these agents and offer them to our patients who are being impacted by these OFF episodes.

What role do you see adjunctive and on-demand therapies for OFF episodes playing in the future of Parkinson's disease treatment?

Both adjunctive and on-demand therapies need to play a role in treating OFF episodes for Parkinson's patients. In the past, we did one or the other, but I think we should be doing both for our patients. We should be using adjunctive therapies to help reduce the overall OFF time, but also remember that no matter how aggressive we are with these therapies, our patients are still going to have OFF episodes, and they should also have an

on-demand therapy available.

The most important thing is to look at each individual patient, evaluate the different types of on-demand therapies available, and identify which is going to be the most effective and easiest to use for a patient. But the success of these therapies will rely on us, as neurologists, explaining to our patients the difference between an ON and OFF episode, why we want to treat these OFF episodes, and reminding patients that there is something they can do. A lot of patients don't know there is something that can be done when they are acutely in an OFF episode. They will just sit there sometimes for two or three hours, not doing anything—immobile, feeling horrible, waiting for the medicine to kick in. There's a huge educational gap that still exists out there in the community—both on the medical and patient side. We have to continue educating so we can ultimately improve the quality of life of our patients who suffer from Parkinson's disease and their caregivers.

Dr. Pagán is professor and vice chairman in the Department of Neurology at Georgetown University Hospital (GUH). He is the director of the Movement Disorders Program and the medical director of the GUH National Parkinson Foundation Center of Excellence. He is the fellowship director for the clinical research fellowship in movement disorders at GUH. Dr. Pagán is the medical director of the Translational Neurotherapeutics Program at Georgetown University Medical Center. He has been the primary investigator of numerous clinical trials and is currently the primary investigator of 15 clinical research trials aimed at discovering new drugs or approaches to improving the quality of life of patients with movement and neurodegenerative disorders.

Dr. Pagán received compensation from Sunovion Pharmaceuticals Inc., for his contribution to this initiative.

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