AMERICAN PARKINSON DISEASE ASSOCIATION

Strength in optimism. Hope in progress.

Communicating About **OFF** Episodes With Your Doctor

Early in Parkinson's disease (PD), treatment with levodopa and other anti-PD drugs provides continuous benefit. As the disease progresses, however, symptom control waxes and wanes, with the biggest effect felt shortly after taking a dose of medication, and a decline or "wearing OFF" before the next dose. An "OFF" period is a period when the person with PD is no longer experiencing the benefit of the most recent dose of an anti-PD medication (e.g., levodopa). OFF periods are a significant feature of advancing PD, and a major source of disability when untreated. The good news is that treatment is available to help people with PD reduce OFF periods and maintain their best quality of life.

How OFF periods affect you may be different from the way they affect someone else. Their effects may also change over the course of the disease, and even from day to day. That variability and unpredictability is a hallmark of living with PD. Understanding the wide range of potential OFF symptoms may improve your ability to effectively cope with OFF periods, and to better understand the potential and limitations of treatments to reduce OFF periods.

What Causes OFF Periods?

OFF periods occur because, as PD progresses, the brain loses its ability to store and release dopamine to maintain a steady level. When brain dopamine goes down, it may result in an OFF period.

Dopamine is a naturally occurring brain chemical that helps control movements and other functions. The healthy brain maintains a steady level of dopamine, allowing it to function normally. In people with PD, the cells that make dopamine die off over time. The drug levodopa is converted into dopamine and, early in the disease, the brain can use this alternative source to store and steadily release dopamine. Even though you are only taking your medication a few times a day, levodopa can provide continuous control of PD symptoms.

However, as the disease progresses, the storage capacity of the remaining brain cells declines. When that occurs, the level of dopamine begins to fluctuate, rising just after taking a dose of levodopa then falling over time. Declining dopamine levels allow symptoms to reemerge before the next scheduled levodopa dose, creating an OFF period.

OFF periods can occur at any time of day, but are likely to occur in the morning before you take your first dose of levodopa, since many hours have passed since your last dose.

What Symptoms Am I Likely to Have During OFF Periods?

The symptoms you experience during OFF periods include those you are familiar with as part of your PD including motor (movement-related) and non-motor (non-movement) symptoms. But, it's important to realize that you may also experience new or unfamiliar symptoms during OFF periods, both motor and non-motor. Recognizing the wide variety of possible symptoms will help you get the best treatment for them.

Most people with PD are familiar with the motor symptoms including tremor, slowed movements (bradykinesia), stiffness, postural instability (increased risk of falling), and reduced dexterity. Uncontrolled motor symptoms may reduce your ability to perform many activities of daily living like getting dressed, preparing food, and working or taking part in community activities.

Non-motor symptoms are no less common and no less important than motor symptoms. In fact, non-motor symptoms often have an even greater impact on quality of life than motor symptoms. Some people experience emergence of specific non-motor symptoms during OFF time. The box below lists these symptoms.

- Anxiety
- Irritability
- Apathy
- Mood changes
- Depression
- Cloudy mind or slowed thinking
- Fatigue
- Pain

OFF Periods Can Reduce Quality of Life

When people with PD describe the impact of OFF periods, they usually report the return of both motor and non-motor symptoms and indicate that their symptoms affect many different aspects of their daily lives. Research has demonstrated measurable impacts of decreasing OFF periods on health-related quality of life. Motor and non-motor symptoms may reduce or prevent taking part in community activities or self-care, and may affect one's self, family members, and colleagues. Anxiety is a commonly reported non-motor symptom that may have a pervasive effect on interpersonal relationships, self-image, and ability or desire to engage in work or leisure activities. OFF periods may be unpredictable in their onset, duration, severity, and degree of symptom exacerbation, and people with PD report that this unpredictability may be one of the most debilitating aspects of OFF periods.

Reducing OFF Time Begins With Sharing the Complete Picture With Your Doctor

Physicians who specialize in treating PD have learned a lot about how to minimize OFF time and improve quality of life in those with advancing PD. Medication adjustment is the foundation of this stage of treatment. For maximum effectiveness, your doctor needs to hear from you and your care partner about all the ways your PD symptoms, both motor and non-motor, affect you.

To understand the full picture, your doctor may ask about symptoms you never considered part of your PD including depression, anxiety, and pain. Your doctor may ask you to keep a symptom diary to track the timing and pattern of your symptoms—when they occur, how they change, and which ones are the most troubling. Your care partner can provide critical information here that may not be as apparent to you, so it may be valuable to get input from him or her as well. With the complete picture in view, your doctor can work with you to develop a treatment plan to reduce the frequency, duration, and severity of your OFF periods.

The Wide Range of Treatment Options for Reducing OFF Time and Motor Complications

PD experts know there are a wide range of options for reducing OFF time. Optimizing drug therapy is the major strategy. This may include changing the dose or timing of your existing medications, adding new medications, or both. Levodopa is the mainstay of PD treatment, and adjusting your levodopa dose is usually a key strategy for decreasing OFF time. Unfortunately, increasing levodopa increases the risk for developing side effects, such as worsening dyskinesias (unwanted movements). However, many people with PD find that an increase in their dyskinesia is more tolerable than OFF periods. In addition, medications for dyskinesias can be added to a patient's regimen, if dyskinesias become problematic.

Other treatment options include non-medical therapies to maximize function. These include physical therapy, voice therapy, and changes in sleep habits, all of which can help improve your abilities in the face of worsening PD. And, as discussed further below, surgery is an important option for many people with PD.

Medication strategies to reduce OFF time tend to fall in two major categories—those that smooth out medication delivery and those that introduce a "rescue" dose only when needed.

Smoothing Out Medication Delivery

Adjusting levodopa. Your physician may recommend increasing the dose or the number of daily doses of levodopa (levodopa is always combined with carbidopa, a drug that slows levodopa breakdown). This can reduce the amount of OFF time. You may also be advised to change your diet or the timing of your levodopa dose in relation to your meals. Levodopa must be absorbed by the gut, and high-protein meals can interfere with this uptake. Reducing protein, or waiting for a certain amount of time after a dose before you eat, can improve your uptake of levodopa. Levodopa is also available in controlled-release and extended-release formulations, which

spread out its absorption over time. The extended-release formulation has been shown to reduce OFF time compared to standard immediate-release formulations.

Adding a dopamine agonist. Dopamine agonists act like dopamine and are less likely to induce dyskinesias than levodopa. Therefore, they are often used as a "levodopa-sparing" option to reduce OFF time, instead of increasing the levodopa dose. These drugs are not as effective as levodopa and the side effects may be troubling. These include drowsiness, dry mouth, dizziness, leg swelling, falling asleep without warning, and impulse control disorders (e.g., development or worsening of compulsive gambling, shopping, or sexuality). Dopamine agonists available in the United States are ropinirole, pramipexole, and rotigotine (delivered through a skin patch). Ropinirole and pramipexole are also available in long-acting versions that are taken orally once daily. Another dopamine agonist, apomorphine, is discussed on page 7.

Adding a Catechol-O-methyltransferase (COMT) inhibitor. COMT inhibitors slow the breakdown of levodopa, extending the duration of benefit from a single dose, and thereby reducing OFF time. Side effects may include drowsiness, hallucinations, and dyskinesias. Two agents are available in the United States; tolcapone and entacapone. Tolcapone may increase the risk for liver toxicity in some people with PD, requiring regular liver monitoring. Entacapone is available either by itself or in a pill combined with levodopa/carbidopa.

Adding an Monoamine oxidase B (MAO-B) inhibitor. MAO-B inhibitors slow the breakdown of levodopa as well, thereby decreasing OFF time. The most common side effects of MAO-B inhibitors include nausea, headache, and dyskinesia. MAO-B inhibitors approved for use in people with PD are rasagiline, safinamide, and selegiline. Safinamide is the most recently approved of the three and may have other beneficial actions in the brain besides its MAO-B inhibiting effect.

Switching to carbidopa/levodopa gel infusion. For people with PD whose fluctuations between ON and OFF periods are not well-controlled, one alternative is to switch to a form of carbidopa/levodopa that is infused directly into the gut rather than being taken in pill form. This allows levodopa to be delivered continuously, smoothing out its level in the blood and promoting a steadier level in the brain as well. The gel infusion, called Duopa™ (carbidopa/levodopa), is stored in a wearable pump, which can fit in a vest or fanny pack. It is delivered via a tube surgically placed through the abdominal wall into the intestine. Side effects include redness and infection at the abdominal site. Additionally, the tube may clog, kink, or become dislodged.

Deep brain stimulation (DBS). DBS surgery is an important option for people with significant motor complications. Those who benefit the most from DBS are those who retain a good response to levodopa, but who have significant amounts of fluctuation between ON and OFF time, coupled with dyskinesias. Successful DBS treatment allows such people to lower their levodopa dose, which reduces dyskinesias without increasing OFF time.

DBS requires implanting electrodes (thin metal rods) into the brain, most often in the area called the subthalamic nucleus. The electrodes receive pulses of electricity delivered by a very thin wire, which in turn is connected to a pulse generator. The pulse generator is implanted under the skin near the collar-bone, and the wire runs under the skin and across the scalp to the electrodes. Risks include surgical complications, wire breakage, and infection.

Rescue Doses

Despite the best medical management, OFF periods and other motor complications tend to increase over time. In addition to predictable OFF periods, patients may experience OFF periods unrelated to levodopa dosing.

When OFF time becomes unpredictable despite attempts to smooth out medication delivery, introducing rescue doses of medication could be an effective strategy. An inhaled formulation of levodopa, Inbrija™, is now available and can be used to rapidly provide a boost in levodopa to overcome OFF time. It is available by prescription from your physician.

An orally disintegrating tablet form of levodopa/carbidopa is also available. An alternative is apomorphine, a very fast-acting dopamine agonist that is available in an autoinjector syringe.

The wide range of treatments for OFF periods and motor complications present many options to the physician and the person with PD for a personalized treatment approach. Working with your physician and the rest of your care team can help you maintain your best quality of life as you live with PD.

Experimental Approaches to Reducing OFF Time

Research into better treatments for PD continues. Promising new approaches are being developed to provide more continuous levodopa delivery or to provide rescue medication options. These include:

- **Apomorphine sublingual film** – Delivers apomorphine via a quickly dissolving film placed under the tongue, for rapid treatment of OFF periods.
- **Continuous subcutaneous delivery of a liquid form of levodopa** – Smooths out the fluctuations in levodopa levels that can worsen OFF periods.
- **A novel, extended-release form of levodopa** – Releases the drug for up to 12 hours, providing a more continuous supply and reducing the number of individual doses that must be taken.

Resources

APDA is here to help you live with PD. The APDA network provides information and referrals, education and support programs, health and wellness activities, and events to facilitate a better quality of life for the PD community. Search the APDA website by state to connect to an Information & Referral (I&R) Center or APDA Chapter in your community at: **apdaparkinson.org/community/** or **(800) 223-2732**.

APDA provides free online publications on a variety of topics at: **apdaparkinson.org/resources-support/download-publications/**

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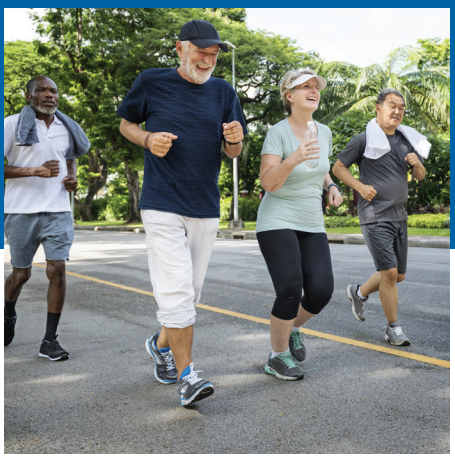
APDA Healthcare Communication Graph

By using the APDA Healthcare Communication Graph you will be able to consistently track important PD symptoms. This tool will allow you to identify any changes in symptoms and make visits with your healthcare professionals focused and productive.

TO ACCESS THE HEALTHCARE COMMUNICATION GRAPH TOOL, VISIT APDAPARKINSON.ORG/HEALTHGRAPH



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