AMERICAN PARKINSON DISEASE ASSOCIATION

Strength in optimism. Hope in progress.

Communicating About OFF Episodes and Dyskinesia With Your Doctor

Early in Parkinson's disease (PD), treatment with medications such as levodopa can provide continuous relief from symptoms. As the disease progresses, however, Parkinson's symptoms can come and go throughout the day. Typically, the biggest benefit of medication is felt soon after taking a dose, but when medication levels are low, usually before your next dose, you may experience an "OFF" period, with symptoms of PD returning.

OFF Periods in Parkinson's Disease

- OFF periods occur when a person with PD is no longer experiencing the benefit of the most recent dose of a medication.
- OFF periods are a significant feature of advancing PD.
- OFF periods are a major source of disability when untreated.
- OFF periods may affect you differently from the way they affect someone else.
- OFF symptoms may be different from day to day as well as change over time as PD advances.

The good news is that treatment is available to help people with PD reduce OFF periods and maintain their best quality of life.

This booklet can help explain OFF time to you and your care partner and give you information to communicate with your doctor about what you are experiencing, so you can receive optimal care and maintain your best quality of life.

The information contained in this booklet is solely for the information of the reader. It should not be used for treatment purposes, but rather for discussion with the patient's own physician.

What Causes OFF Periods?

Dopamine is a chemical in the brain that helps control movement and other functions. OFF periods, in which Parkinson's symptoms return during the day, may occur as PD progresses and the brain loses its ability to produce or release dopamine at a steady rate.

- The healthy brain maintains a steady level of dopamine, allowing it to function normally.
- In people with PD, the cells that make dopamine die over time. This results in an inconsistent supply of dopamine in the brain.

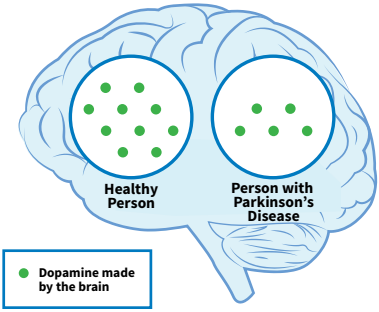


Figure 1. Dopamine in healthy individuals vs. people with Parkinson's disease

- Levodopa is a drug that is taken by mouth and enters the bloodstream via the small intestine. Once it reaches the brain, it is turned into dopamine. Early in PD, the brain is healthier and the effects of levodopa medication last longer. The brain is also still producing some of its own dopamine. At this stage of disease, PD symptoms can be controlled throughout the day.

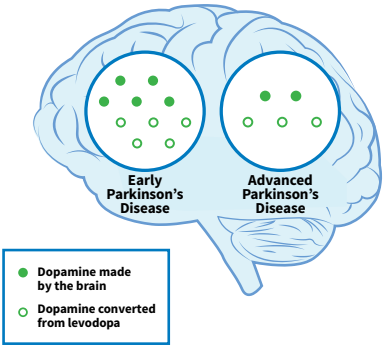


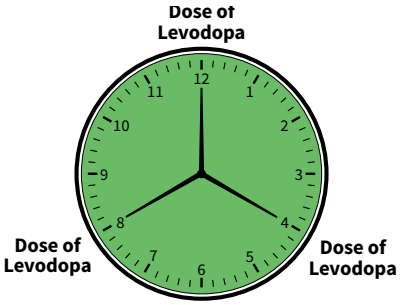
Figure 2. Levodopa treatment in early and advanced Parkinson's disease

- As PD progresses to later-stage disease, the brain is less healthy. There are fewer dopamine-producing cells, and the effects of levodopa doses don't last as long. At this stage in the disease, PD symptoms are not controlled steadily throughout the day. When symptoms return before the next dose of levodopa, this is called an OFF period.

How Will OFF Affect Me as I Go About My Day?

Once you take your dose of levodopa, the dopamine level in your brain rises. The dopamine controls your PD symptoms, and you experience an ON period. As time passes from your last levodopa dose, your dopamine level drops. Low dopamine levels may cause you to experience an OFF period. OFF periods can occur at any time of day, but they are most likely to occur close to when your next dose of medication is due. They also can occur in the morning before you take your first dose of levodopa, since many hours have passed since your last dose. It is important to note that for some people, OFF time can be unpredictable, and not clearly related to timing of medication doses. The image below represents how levodopa levels change over time. Speak with your physician about your specific dosing needs.

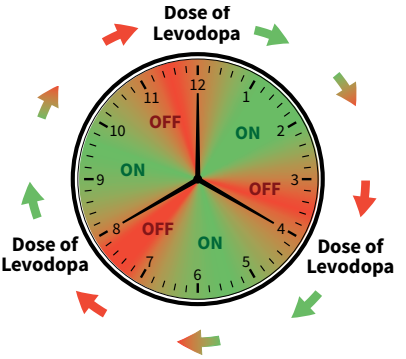
Levodopa Treatment and OFF Cycles



Steady dopamine levels

Early Disease

Steady dopamine levels and consistent symptom control



Decreasing dopamine levels

Later Disease

Decreased dopamine levels between doses lead to "OFF" periods

What Symptoms Am I Likely to Have During OFF?

The symptoms you experience during OFF periods include those you are probably already familiar with as part of your PD. But it is important to realize that you may also experience new or unfamiliar symptoms during OFF periods. Recognizing the wide variety of possible symptoms will help you get the best treatment.

Most people with PD are familiar with motor symptoms. Uncontrolled motor symptoms may reduce your ability to perform many activities of daily living, like getting dressed, preparing food, working, or taking part in community events.

Motor Symptoms of OFF

- Tremor
- Slow or uncoordinated movement
- Stiffness
- Poor balance and increased risk of falling

Non-motor symptoms of Parkinson's disease are very common and can be more troubling than motor symptoms. Some people experience specific non-motor symptoms during OFF periods.

Non-motor Symptoms of OFF

- Anxiety or nervousness
- Irritability or impatience
- Apathy or lack of interest
- Mood changes
- Depression
- Cloudy mind or slowed thinking
- Fatigue or tiredness
- Pain

OFF Periods Can Reduce Quality of Life

When people with PD describe OFF periods, they usually report the return of both motor and non-motor symptoms that affect many different parts of their daily lives. OFF symptoms may reduce your ability to take care of yourself or prevent you from taking part in normal daily activities. Often, OFF time is predictable and occurs prior to the next dose of medication. For some however, OFF time can be unpredictable and can vary in its length and intensity. Unexpected OFF time can be very challenging.

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

Your doctor can help you minimize OFF time and improve your quality of life. Your doctor needs to hear from you and your care partner about all the ways your OFF symptoms affect you. This will help your doctor make the best treatment plan.

Your doctor may ask about symptoms you never considered to be part of your PD, including depression, anxiety, and pain. Your doctor may also ask you to keep a symptom diary to track the timing and pattern of your symptoms. Your care partner can provide important information that may not be as obvious to you, so the doctor may also want to talk with him or her. 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

There are many options for reducing OFF time. Improving drug therapy is the most common strategy. Medication strategies to reduce OFF time tend to fall into two major categories—those that smooth out medication delivery, and those that introduce additional medication only when needed. Most patients with PD take levodopa to manage their symptoms, and adjusting the dose is usually a key strategy for decreasing OFF. Unfortunately, increasing levodopa also increases the risk for developing side effects, such as dyskinesias (uncontrolled, fragmented, or jerky movements). Some people with PD find that dyskinesias are more tolerable than OFF periods. Medications for dyskinesias can be added if necessary as well.

Surgery is another important option for many people with PD. Surgery and other procedures are discussed more on page 6.

Smoothing Out Medication to Reduce OFF Time:

Adjusting levodopa

Levodopa is the most common drug that is prescribed to treat people with PD. Levodopa is almost always combined with carbidopa, a drug that slows levodopa breakdown. As your needs change, your doctor may change the way you take your levodopa. Your doctor could change the strength of your dose or change the timing of your doses. Your doctor might change the type of levodopa that you take. For example, levodopa is available in controlled-release and extended-release formulations (Rytary®), which spread out its absorption in the intestine over time.

Your doctor may also recommend that you change your diet or the timing of your levodopa dose with your meals. High-protein meals can interfere with the way your body absorbs levodopa. Reducing protein in the diet or timing your doses to be on an emptier stomach can improve levodopa activity.

Adding additional drugs to your routine

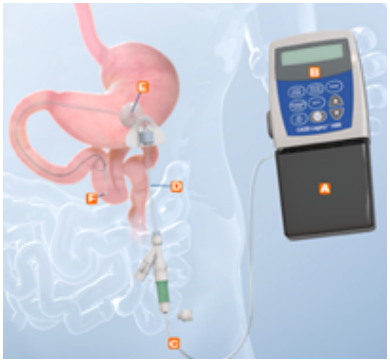
After adjusting and optimizing your levodopa dose, your doctor may choose to add another medication to help reduce OFF. Common additional drugs include the following:

- Amantadine
- Amantadine ER (Gocovri®, Osmolex ER®)
- Entacapone (Comtan®)
- Istradefylline (Nourianz®)
- Opicapone (Ongentys®)
- Pramipexole (Mirapex®, Mirapex ER®)
- Rasagiline (Azilect®)
- Ropinirole (Requip®, Requip XL®)
- Rotigotine (Neupro®)
- Safinamide (Xadago)
- Selegiline (Eldepryl®, Zelapar®)
- Tolcapone (Tasmar®)

See the *APDA Parkinson's Disease Handbook* for more information about these drugs.

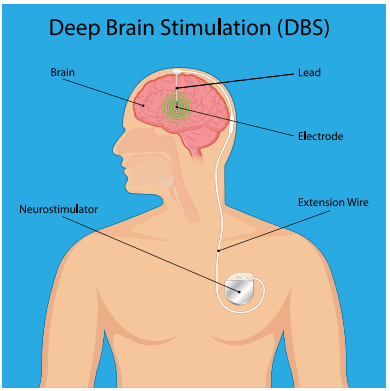
Other options to smooth out medication delivery and dopamine levels

Switching to carbidopa/levodopa enteral suspension. For people with PD whose fluctuations between ON and OFF periods are not well controlled, one alternative is switching to a form of carbidopa/levodopa that is infused directly into the gut through a surgically placed tube. This allows levodopa to be delivered continuously, smoothing out its level in the blood and promoting a steadier level of dopamine in the brain as well.



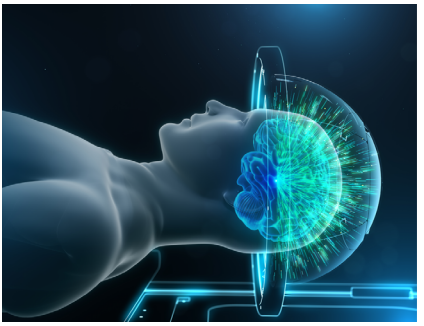
This levodopa suspension, called Duopa™, is stored in a cartridge that is attached to a wearable pump. The pump can fit in a vest or fanny pack. Because this medication device requires a minor surgery to insert the tube into the small intestine, side effects include redness and infection at the body wall site. Additionally, the tube may clog, kink, or become dislodged. Ask your doctor if this treatment could be right for you.

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 have considerable amounts of fluctuation between ON and OFF time. Successful DBS may improve symptom control throughout the day, increasing ON time. DBS requires implanting electrodes (thin metal rods) into the brain. The electrodes receive pulses of electricity through a very thin wire, which 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. This surgery carries a small chance of a serious complication such as bleeding or infection. Ask your doctor if this treatment might be right for you.



Focused ultrasound has been approved for the treatment of PD tremor. During focused ultrasound treatment, beams of ultrasound waves are focused on a target inside the brain. This

concentrated energy creates a small lesion in the brain tissue. Focused ultrasound for PD targets the thalamus, a deep brain



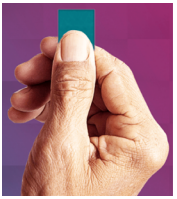
structure, where it disrupts the abnormal brain pathway that causes tremors. Focused ultrasound to treat the slowness and stiffness of PD is being developed. Ask your doctor if this treatment or any ongoing experimental trials may be right for you.

As-needed Medication Dosing to Reduce OFF time:

Despite the best medical management, OFF periods and motor complications tend to increase over time. In addition to predictable OFF periods, patients may experience OFF periods that are not predictable. When this occurs despite attempts to smooth out medication delivery, your doctor may prescribe fast-acting medications to use as needed for symptoms of OFF. These drugs are used in addition to your regular treatment to boost your dopamine levels.

Fast-acting drugs for OFF (used as needed)

Inhaled levodopa	(Inbrija®)	
orally disintegrating carbidopa/levodopa	(Parcopa®)* Generic forms are available	

Injectable dopamine agonist	(Apokyn®) Auto-injectable apomorphine	
Sublingual (under the tongue) dopamine agonist	(Kynmobi®) Sublingual apomorphine film	

*Parcopa (levodopa/carbidopa) is no longer manufactured in brand form.

Experimental Approaches to Reducing OFF Time

There is ongoing research for improved PD treatments. Promising new approaches are being developed to provide more continuous levodopa delivery and to provide as-needed medication options. Here are a few of the new treatments that are currently in clinical trials:

- Continuous subcutaneous (under the skin) delivery of liquid levodopa. This treatment could smooth out the changes in levodopa levels and decrease OFF periods.
- Longer-acting extended-release forms of levodopa. These medications would release levodopa over an even longer period than currently available medications, providing a more continuous supply of dopamine and reducing OFF periods.
- New formulations of already available dopamine agonists as well as new dopamine agonist medications.
- Ask your doctor if there are any new or ongoing clinical trials that might be right for you.

Levodopa-induced Dyskinesias

Having ON and OFF time over the course of the day is one complication of levodopa treatment. Another is the development of dyskinesias.

- Dyskinesias are involuntary movements that tend to occur at the time of peak brain dopamine levels or when brain dopamine levels are changing.
- Dyskinesias may not be troublesome, and some people with PD report they prefer some dyskinesia with good motor symptom control to no dyskinesia with less complete symptom control.
- Sometimes, however, dyskinesias can be socially distressing and/or disabling. Development of significant dyskinesias is often the point at which DBS surgery is considered.

Similar to OFF time, dyskinesias may be treated by altering levodopa dosages to make dopamine levels smoother throughout the day. If this is not sufficient to control dyskinesias, amantadine formulations may be prescribed.

- Amantadine is available in immediate release and in two extended-release formulations, Gocovri® and Osmolex ER™.
- Gocovri® is taken once daily at night and is used for both the treatment of levodopa-induced dyskinesias and for reduction of OFF time. It is the only medication specifically approved for the treatment of levodopa-induced dyskinesias.

Speak with your doctor about your individual treatment needs

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

Resources

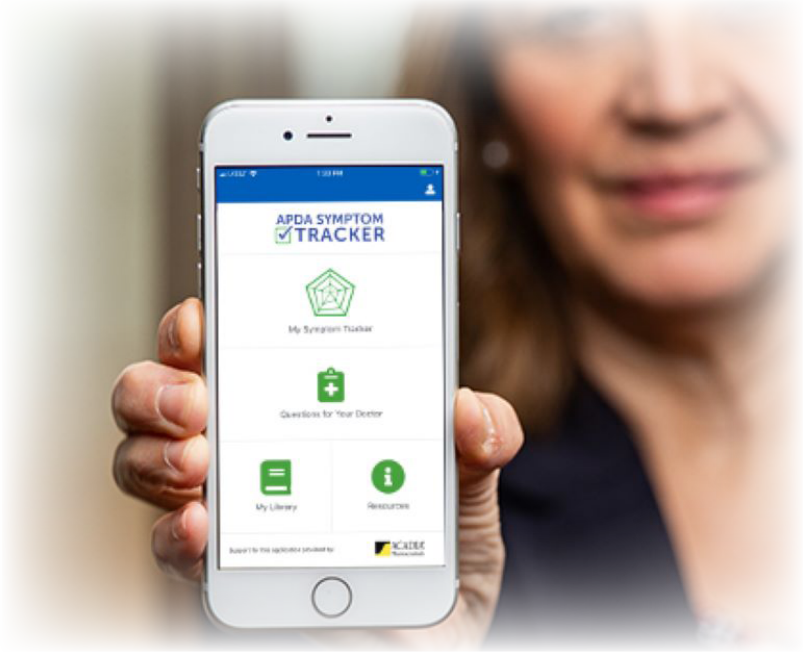
APDA is here to help you live your best life with PD. The APDA network provides information and referrals, education and support programs, health and wellness activities, and events to facilitate a better quality of life for the PD community. Search the APDA website by state to connect to an Information & 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/**

A Closer Look Blog, by Dr. Rebecca Gilbert, APDA Vice President and Chief Scientific Officer, aims to address both timely and timeless topics related to PD. In addition, the blog focuses on practical, take-home tips that can be gleaned from the information discussed. **apdaparkinson.org/doctor-blogs/a-closer-look/**

Notes

APDA SYMPTOM TRACKER



APDA has released updates to our Symptom Tracker Mobile App with expanded features.

Our user-friendly app helps people with Parkinson's disease track their symptoms and medications to help communicate with your healthcare team for better care.

Available in Spanish!

GET IT ON Google Play

Download on the App Store

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