AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Motor Fluctuations in Parkinson's Disease What You Need to Know

Motor fluctuations refer to a decline in the usual benefit from a dose of levodopa. Instead of the smooth, uninterrupted control of Parkinson's disease (PD) symptoms that levodopa offers early in the disease, symptoms return before the next dose is scheduled or are only partially controlled by a given dose. Motor fluctuations usually develop gradually, after several years of successful treatment. Many people with PD will eventually experience motor fluctuations as their disease progresses.

What are Motor Fluctuations?

There are several types of motor fluctuations.

Predictable motor fluctuations:

- **Wearing OFF** is the predictable return of PD symptoms before the next scheduled dose of levodopa. It is the most common form of motor fluctuation.
- **Morning OFF** is the predictable occurrence of PD symptoms first thing in the morning, before the first dose of levodopa takes effect.

Unpredictable motor fluctuations may include:

- **Partial ON** – when there is an incomplete benefit from a dose of levodopa.
- **Delayed ON** – when symptoms persist for a longer time after taking a dose of levodopa.
- **Dose failure** – when there is no benefit from a dose of levodopa.
- **Unpredictable OFF** – when symptoms return unexpectedly and without a clear relationship to dosing schedule.

Motor fluctuations can have a significant impact on quality of life by reducing mobility and interfering with social interaction and activities of daily living.

What Causes Motor Fluctuations?

The brain functions best with a steady amount of dopamine. PD motor symptoms occur when the level of dopamine in the brain falls too low due to loss of dopamine-producing neurons (nerve cells). Levodopa can supply the missing dopamine but, in pill form, this causes peaks and troughs in the level of dopamine in the brain. Early in the disease, the brain can make enough dopamine to smooth out these peaks and troughs. But as the disease progresses, continued loss of dopamine neurons reduces this ability, increasing the risk for motor fluctuations.

Other factors also contribute to that risk. Levodopa is absorbed through the small intestine but, in PD, there may be a reduction in the smooth flow of materials out of the stomach into the intestine (reduced gastric motility). This can slow the absorption of levodopa, and thus slow the rate at which it reaches the brain. High-protein meals can also reduce levodopa absorption because dietary protein can compete with levodopa to cross from the small intestine into the blood.

Additional risk factors for motor fluctuations include younger age at disease onset, longer disease duration, higher levodopa dose, and more severe disease.

How are Motor Fluctuations Treated?

Treatment of motor fluctuations can be complex and is not always entirely successful. Motor fluctuations are best treated by a PD specialist, who will be familiar with the full range of treatment options and strategies. All treatments have side effects, which must be considered when determining the best treatment plan. Treatment strategies include:

- **Dosing changes.** Levodopa may be dosed more frequently in order to reduce periods of low levodopa concentration in the brain. The individual dose may be reduced or may be maintained as is, whichever produces the best symptomatic effect. The dosing schedule may be adjusted to avoid mealtimes, and the diet may be changed to reduce the amount of protein eaten or the timing of when protein is eaten.
- **Long-acting oral formulations of levodopa** (such as carbidopa-levodopa ER, Crexont®, and Rytary®) may offer more sustained ON time.
- **Subcutaneous levodopa** (foscarbidopa-foslevodopa [Vyalev™]) is a soluble form of carbidopa-levodopa that is infused continuously into the subcutaneous tissue via a small pump.
- **Levodopa gel delivered to the small intestine.** Carbidopa-levodopa enteral suspension (Duopa®) is infused continuously directly into the small intestine, where it is absorbed, via a small pump through a surgically placed tube.

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- **An inhaled formulation of levodopa** (Inbrija®) can be used on demand in someone already taking carbidopa-levodopa if medication effects wear off between oral doses.
- **Additional medications.** Drugs that delay the breakdown of dopamine can help reduce Wearing OFF. These include monoamine oxidase B (MAO-B) inhibitors selegiline (Zelapar®, Emsam® patch), rasagiline (Azilect®), and safinamide (Xadago®); and catechol-O-methyl transferase (COMT) inhibitors entacapone (Comtan®), tolcapone (Tasmar®), and opicapone (Ongentys®). A carbidopa-levodopa-entacapone (Stalevo®) combination tablet is also available. Dopamine agonists (pramipexole [Mirapex®, Mirapex ER®], ropinirole [Requip®, Requip XL®], and rotigotine [Neupro®]) mimic the effect of dopamine, providing symptomatic benefit directly. Istradefylline (Nourianz®) inhibits another brain chemical called adenosine, which modulates dopamine signaling. Amantadine, or an extended-release amantadine (Gocovri®), can be used for both the treatment of levodopa-induced dyskinesias and for reduction of OFF time.
- **Apomorphine** is a very fast-acting dopamine agonist. Apokyn® is an apomorphine formulation that is injected subcutaneously (under the skin) to be used as a "rescue" medication if a person with PD experiences an unexpected OFF episode. Onapgo™ is continuously infused into the subcutaneous tissue via a small pump in order to provide more consistent symptom control.
- **Deep brain stimulation (DBS)** is a neurosurgical procedure in which thin electrodes are implanted into selected deep parts of the brain that control movement. By stimulating specific points in the motor control circuits, DBS disrupts abnormal brain signals, thereby restoring more normal movement. A battery-operated pulse generator, much like a cardiac pacemaker, is implanted under the skin of the chest or abdomen.
- **Focused ultrasound** is a technology in which beams of ultrasound waves are focused on a designated target in the brain, thereby concentrating enough energy to create a small lesion. The lesion disrupts abnormal brain signals, restoring more normal movement.

Resources

At the American Parkinson Disease Association (APDA), we provide the support, education, research, and community that helps everyone impacted by PD live life to the fullest. To accomplish this, APDA funds important research and provides education and support to individuals living with PD, their family members, and the community at large. In addition to reading this fact sheet, visit APDA's website at **apdaparkinson.org** for more information. You can find out about your local resources at **apdaparkinson.org/community**.

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