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 symptoms of Parkinson's disease (PD) 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. Most 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 also occur, including:

- **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 social interaction, and interfering with 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 weighed in the balance 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 change when protein is eaten.
- **Additional medications.** Drugs that delay the breakdown of dopamine can help reduce wearing off. These include catechol-O-methyl transferase (COMT) inhibitors (entacapone [Comtan®], tolcapone [Tasmar®], opicapone [Ongentys®]) and monoamine oxidase B (MAO-B) inhibitors (selegiline [Emsam®, Zelapar®], rasagiline [Azilect®], safinamide [Xadago®]). Dopamine agonists (pramipexole [Mirapex®, Mirapex ER®], ropinirole [Requip®, Requip XL®], rotigotine [Neupro®]) mimic the effect of dopamine, providing symptomatic benefit directly. Istradefylline (Nourianz®) inhibits another brain chemical called adenosine that 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.

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- **Other formulations of levodopa.** Longer-acting formulations of levodopa (such as carbidopa/levodopa ER, Sinemet® CR, and Rytary®) may offer more sustained ON time.
- **Levodopa gel delivered to the small intestine (Duopa®).** By delivering levodopa through a tube directly to the small intestine, a smooth and continuous dose of levodopa can be provided without the problem of delayed emptying of the stomach.
- **Deep brain stimulation (DBS).** DBS is a surgical procedure in which electrodes are implanted in the movement centers of the brain. Electrical stimulation is provided by an implanted battery. The stimulation reduces the intensity of symptoms and reduces the need for additional medications.
- **Apomorphine** is a very fast-acting dopamine agonist. Apokyn® is an apomorphine formulation that is injected subcutaneously to be used as a "rescue" medication if a person with PD experiences an unexpected OFF episode.
- **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.
- **Focused ultrasound** has been approved for the treatment of Parkinson's disease tremor as well as for the treatment of bradykinesia (slowness), rigidity (stiffness), and dyskinesias. Focused ultrasound is a technology in which beams of ultrasound waves are focused on a designated target thereby concentrating enough energy to create a small lesion. When a lesion is created in the thalamus, a deep brain structure, it can disrupt the abnormal Parkinson's circuitry that causes tremor. Focused ultrasound of other areas of the brain to treat the slowness and stiffness of Parkinson's disease is currently in clinical trials.
- **Experimental treatments under development.** Among these is a subcutaneous delivery system for levodopa.

## Can Motor Fluctuations be Avoided?

Researchers have suggested that motor fluctuations might be avoided or at least delayed if the brain receives more continuous dopamine stimulation from early on in the disease, rather than the pulsating stimulation provided by levodopa pills. So far, this remains a hypothesis, rather than a confirmed fact. Further research is continuing to answer this important question.

## Resources

APDA provides information, education, and support to those impacted by Parkinson's disease and funds scientific research into the causes, prevention, and treatments. We provide a nationwide network of programs, activities, and events to facilitate a better quality of life for the Parkinson's community. Through our website, **www.apdaparkinson.org**, you can find the full range of resources we offer, as well as links to other important sources of information and support.

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