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.

- **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 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.

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.

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- **Additional medications.** Drugs that delay the breakdown of dopamine can help reduce wearing off. These include catechol-O-methyl transferase (COMT) inhibitors (entacapone, tolcapone) and monoamine oxidase B (MAO-B) inhibitors (selegiline, rasagiline, safinamide). Dopamine agonists (pramipexole, ropinirole) mimic the effect of dopamine, providing symptomatic benefit directly.

- **Apomorphine rescue.** Apomorphine is a very fast-acting dopamine agonist that is injected subcutaneously. It is used as a "rescue" medication when a person with PD experiences an unexpected off episode.
- **Levodopa gel delivered to the small intestine.** 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, reducing off time.
- **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.
- **Experimental treatments under development.** A form of apomorphine is being developed that is delivered under the tongue on a dissolvable film, avoiding the need for injection. An inhaled form of levodopa is being developed, which delivers the drug quickly to the bloodstream, avoiding the problems of absorption through the stomach. Focused ultrasound treatment is being tested in PD. It is a non-invasive way to inactivate a small amount of brain tissue to rebalance the activity of movement control circuits in the brain that are affected in PD. Focused ultrasound has been approved for treatment in a condition called essential tremor.

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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