

Motor Fluctuations and Parkinson's "Off" Times



Many people with Parkinson's disease (PD) experience motor fluctuations as part of their disease progression. Motor fluctuations are changes in the ability to move and are also referred to as "on-off" times. When Parkinson's medications (levodopa and dopamine agonists) begin to take effect, you experience periods of good symptom control, called "on" time, when you can move and function well. As levodopa begins to lose its effect, known as "wearing off," you may have periods where symptoms are suddenly much more noticeable and movement becomes more difficult, known as "off" time. Sometimes, people experience involuntary movements (dyskinesias) when medication levels are at their highest point. These variations throughout the day are known as motor fluctuations.

Why Do Motor Fluctuations Happen?

As Parkinson's disease progresses, it is common for more dopamine-producing brain cells to die, causing the benefits from Parkinson's medications to not last as long as they did before. The brain eventually reaches a point where it stops producing dopamine in large amounts and therefore must rely on medicine to replace dopamine. Researchers think this happens for two reasons:

- As Parkinson's progresses, cells become less able to store dopamine. When this occurs, the cells are unable to release dopamine without medications, such as levodopa. When the dose fades, 60-90 minutes after taking it, there is no more levodopa for the cells to use, resulting in lower dopamine levels and a worsening of symptoms ("off" times).
- The cells in your brain become more sensitive to both higher and lower concentrations of levodopa. There is a higher likelihood of experiencing "off" times when levodopa levels are too low and a higher likelihood of experiencing dyskinesia (involuntary movements) when levodopa levels are too high.

As a result, your doctor may advise you increase your medication doses to achieve optimal control of motor symptoms, such as tremor, slowness and rigidity. The goal is to maximize symptom control without increasing side effects.

Non-motor fluctuations

Many non-motor symptoms can also be affected by "off" time. Non-motor symptoms are Parkinson's symptoms that are not related to movement, such as mood, cognition or fatigue. Mood fluctuations are particularly common and are often experienced as a general state of dissatisfaction with life, irritability, depression, or anxiety. If you notice a relationship between mood changes and the timing of your PD medication, tell your neurologist. He or she might be able to adjust your dopamine replacement medications or dose to reduce "off" time, which may help your mood. Many people experience anxiety as their anti-Parkinson's medications wear off, near the end of the dosing cycle. If you or someone close to you notices a pattern of anxiety associated with "on-off" fluctuations, talk to your neurologist about adjusting your medications. Psychotherapy can also be helpful in this situation.

If there is a pattern of "off"-state anxiety, a therapist can help you learn to anticipate the anxiety and cope with it through relaxation techniques and other cognitive behavioral strategies.

Treating "On-off" fluctuations

The goal of managing motor fluctuations and dyskinesias is to help you remain as active and independent as possible. Depending on your current medications, there are several approaches your doctor can take to help smoothen your response to medications to minimize or avoid fluctuations. Your doctor may:

- Adjust the dose of levodopa, either by increasing the dose or adjusting the frequency
- Add different medications to your current regimen to help keep levels of dopamine more consistent to avoid "off" time. Examples are COMT inhibitors, dopamine agonists, or MAO-B inhibitors.
- Try a controlled-release or extended-release formulation of carbidopa-levodopa, designed to extend the benefits from the same dose of carbidopa-levodopa and possibly decrease the number of pills needed per day.
- Bring up surgical options, like deep brain stimulation or Duopa therapy. Read our book, *Surgical Options*, for more information on various surgical techniques used to treat PD at Parkinson.org/Library.

Other Common Issues

In addition to a return of PD symptoms and onset of dyskinesia, some people experience dystonia and/or freezing with motor fluctuations.

Dystonia is when muscles continuously contract, causing parts of the body to twist or curl. Dystonia may occur at peak dose, when the medication is working at its best. More commonly, dystonia occurs when dopamine levels are the lowest ("off" periods) or when medications are just starting to kick in.

"Freezing" is the temporary and involuntary inability to move. If freezing happens when the next dose of medication is due, it is called "off" freezing.

Medications Management of Motor Fluctuations

Usually, freezing episodes decrease after taking medication. Different medications are available to treat "off" episodes, including:

Levodopa: Changing how you take Levodopa can impact off episodes.

Dopamine Agonists: Stimulating the parts of the brain that are influenced by dopamine, the brain is tricked into thinking it is receiving the dopamine it needs.

- Apomorphine Hydrochloride Injection (APOKYN®)

Amantadine: Used in early and advanced PD to help tremor. It can also be useful in reducing dyskinesias that occur with dopamine medication.

- Amantadine ER capsules (Gocovri)
- Amantadine ER tablets (Osmolex ER)

Adenosine A2a antagonists: Can reduce "off" time by 30-60 minutes per day without worsening dyskinesia. However, dyskinesia can still be a side effect.

- Istradefylline (NOURIANZ™)

COMT Inhibitors: This class of PD medications has no direct effect on PD symptoms, but prolongs the effect of levodopa by blocking its metabolism.

- Entacapone (Comtan®)
- Tolcapone (Tasmar®)
- Opicapone (Ongentys®)
- Carbidopa/levodopa/entacapone tablets (Stalevo)

MAO-B Inhibitors: By blocking the MAO-B enzyme, which breaks down dopamine, this makes more dopamine available to the brain.

- Selegiline (l-deprenyl, Eldepryl), (Zelapar)
- Rasagiline (Azilect®), Safinamide (Xadago)
- Safinamide (Xadago)

For more information on Parkinson's medications, read our book *Medications* or our fact sheets, "Medications for Motor Symptoms" and "Medications for Non-Motor Symptoms".

Call our Helpline at 1-800-4PD-INFO (473-4636) for more information.