



Parkinson's
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Motor Fluctuations in Parkinson's

What are motor fluctuations?

Motor fluctuations are associated with long-term use of levodopa (trade names Sinemet or Madopar, Co-careldopa or Co-beneldopa), and usually occur in people who have had Parkinson's disease for some time. The term 'motor fluctuations' means that after a number of years of levodopa treatment, people may find that the smooth and even control of symptoms that their drugs once gave them is no longer dependable.

When motor fluctuations occur, people initially find that the effects of their regular dose do not seem to last until the next dose is due (this is known as 'end-of-dose deterioration' or, more simply, 'early wearing-off').

As Parkinson's progresses, people may find that their symptoms can reappear quickly and unexpectedly, a sensation that some have described as being like a light switch being turned on and off (this is known as the 'on/off' syndrome). Some people find that they start to develop involuntary fidgety movements, which occur initially when the level of levodopa in the bloodstream is at its peak, but may appear at any time later on (these are known as 'dyskinesias').

Why do they occur?

'On/off' swings are likely to be caused by an interaction between the Parkinson's itself and the drug treatment. They cannot be simply attributed to the levodopa alone, since fluctuations and involuntary movements rarely occur in people who are not taking levodopa and are not experienced by people taking levodopa who do not have Parkinson's.

The best explanation for these complications is that as dopamine-producing cells in the brain are gradually lost in Parkinson's, the remaining cells must work overtime to compensate for the dopamine loss. As Parkinson's progresses, and more cells are lost, their capacity to produce dopamine, even with the help of levodopa, is exhausted more quickly (this would explain 'early wearing-off'). The brain attempts to compensate for the shortage of dopamine by becoming more sensitive to smaller dopamine levels. When levels of dopamine are increased temporarily by taking levodopa, this has the effect of overstimulating the part of the brain concerned with motor control, and involuntary movement results (this would explain dyskinesias).

The explanation of 'on/off' swings is more complicated. In the early stages of Parkinson's, 'off' periods appear to be related to 'early wearing-off', as they occur before the next dose of levodopa is due. However, as Parkinson's progresses, 'on/off' fluctuations become less closely related to the timing of the levodopa dose, and more unpredictable. It is thought that these fluctuations are related to other processes in the brain, and are sensitive to other factors as well as to medication. This second type of 'on/off' fluctuation is more difficult to manage.

Because they are related to levodopa treatment, motor fluctuations can be difficult to treat – reducing the dose of levodopa might mean less fluctuation, but it can also mean the return of other symptoms, such as tremor, rigidity or slowness of movement. The remainder of this information sheet describes



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the three most common motor fluctuations – early ‘wearing-off’, the ‘on/off’ phenomenon, and dyskinesias – and methods that can be used to treat these fluctuations while maintaining good control over symptoms.

What is early ‘wearing-off’?

After some years of treatment, people with Parkinson's can often begin to feel the effect of each dose of levodopa – they can tell when it begins to work, and when the effect on their symptoms begins to diminish or ‘wear off’.

This effect starts gradually, and may begin with someone experiencing some return of their Parkinson's symptoms in the morning, before their first dose of the day. Later on, they may begin to feel this effect during the course of their daily drug regimen.

How is early ‘wearing-off’ treated?

Because early ‘wearing-off’ is related to drug treatment, the most effective ways of dealing with its effects are also drug related. As this might mean a change or addition to your drug regimen, it should be discussed with your GP or Parkinson's specialist.

- Keep the total daily levodopa dose at the same level, but take smaller doses more frequently.
- It may be useful to change to one of the controlled-release forms of levodopa (trade names Sinemet CR or Madopar CR). These can help to keep the drug levels in the bloodstream constant, and can prolong the time needed between doses by 30 to 50%.
- Your doctor may suggest adding a dopamine agonist drug to your regime (for example bromocriptine, lisuride, pergolide, ropinirole, cabergoline or pramipexole). These drugs work

by ‘tricking’ the brain into thinking it is receiving dopamine, rather than requiring the brain cells to work overtime to produce extra dopamine from levodopa. They may help to smooth out some of the fluctuations.

- Your doctor may suggest adding a drug called entacapone (Comtess) to your regime. Entacapone slows the breakdown of levodopa by the body, prolonging its duration of action. Recently, a stronger and more effective alternative to entacapone, tolcapone (Tasmar), has been re-introduced in the UK. This drug is potentially dangerous for some people, and those who use it require regular blood tests to ensure they do not develop liver damage. Your Parkinson's specialist will be able to advise you about this.
- Another drug called selegiline (Eldepryl) may be suggested by your doctor. Selegiline slows the breakdown of dopamine in the brain, and can be used to prolong the effectiveness of the levodopa dose.

For more information on any of these drugs, see the booklet *the Drug Treatment of Parkinson's disease*.

In some people, protein in the diet can interfere with the absorption of levodopa into the bloodstream. It may be useful to try a protein redistribution diet, where most of the daily protein intake is restricted to the evening hours. This can help the levodopa treatment to be more effective in the daytime, when you are likely to need it more. However, as protein is essential for a healthy diet, you should not reduce the amount of protein you consume. The effect of such dietary manipulation is usually small, and you should discuss protein redistribution with a state registered dietician or with your GP or Parkinson's specialist before you try it.



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For more information, see the booklet *Parkinson's and Diet*.

What is the 'on/off' syndrome?

The 'on/off' syndrome can best be described as an unpredictable shift from relative wellness to move – going off, although off to on can occur just as suddenly. The speed of this shift can be so dramatic that some people have likened this effect to a light switch being turned on and off, and others use the term 'yo-yoing' to describe it.

'On/off' fluctuations are different from the phenomenon known as 'freezing', which can also affect people who have had Parkinson's for some time. 'Freezing' is the word used to describe the experience of stopping suddenly while walking, or when beginning to initiate walking, and being unable to move forward again for several seconds or minutes. People feel as though their feet are 'frozen' or stuck to the ground, but that the top half of their body still wants to move on. While freezing episodes tend to last only a few seconds, 'on/off' fluctuations can continue for minutes, or even hours. It is also thought that different processes of the brain are involved for each phenomenon. For more information, see the information sheet *Freezing in Parkinson's*.

'On/off' effects do not just affect a person's mobility, however. They are often accompanied by changes in other symptoms, such as an increase in anxiety, visual disturbances, sweating or, sometimes, pain in the limbs. Some people can find 'on/off' fluctuations very distressing, especially as they can happen suddenly and unexpectedly. Other people are able to judge in advance when an episode is likely to occur.

How is the 'on/off' syndrome treated?

Many of the strategies that can be used to treat 'wearing-off' effects can also be tried when someone is experiencing 'on/off' fluctuations, such as increasing the frequency of dosage, changing to a controlled-release preparation of levodopa, or adding other drugs such as a dopamine agonist, entacapone (Comtess), or selegiline (Eldepryl). Effective treatment of the 'on/off' syndrome can sometimes be difficult. Some other treatments can help:

- It can sometimes help to take an extra dose of levodopa treatment, although this can often be ineffective and should be discussed with a medical professional. If it doesn't work, a dispersible preparation of levodopa, which is absorbed more quickly than standard levodopa tablets, may be more effective, producing a more rapid surge in the blood level of levodopa than a controlled-release preparation.
- Alternatively, some people have found benefit from the drug apomorphine (APO-go), which is a dopamine agonist given by injection under the skin. This drug does not always help, but it is sometimes tried with people who have frequent 'off' periods of half an hour or more and who have not improved after adjustments to their ordinary medication. The main advantage of apomorphine is that it can act as a 'rescue treatment' when tablets or capsules fail to take effect. For people who are assessed as suitable, it will work within 5 to 15 minutes much more quickly than tablets or capsules. The effect of each injection is short, usually about 45 minutes, but may tide someone over until they come 'on' again. Because of this predictable response, it can sometimes help people with Parkinson's who are in employment



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to go on working for longer than would otherwise be possible. For more information, see the information sheet *Apomorphine*.

What are dyskinesias?

Dyskinesia is a medical term for movements, other than tremor, that are not intended or willed by the person concerned. These involuntary fidgety movements can include twitches, jerks, twisting or writhing movements, or simple restlessness. The exact cause of dyskinesias is unknown, but they seem to be connected to the excessive dopaminergic stimulation brought about by levodopa treatment. Like early 'wearing-off' and the 'on/off' syndrome, it is assumed that they are the result of a combination of levodopa treatment and the progression of Parkinson's.

It has been suggested that dyskinesias may be the result of the brain's attempts to compensate for the loss of dopamine in Parkinson's. One way that the brain might do this is to increase the sensitivity of its brain cells to dopamine, so that a smaller amount can bring about the same response. The brain cells that respond to dopamine may then become supersensitive. Alternatively, it may be that over time, other cells that do not normally respond to levodopa begin to convert it to dopamine, but may release it at the wrong time, or to the wrong parts of the body.

Dyskinesias can appear in different forms, and their frequency and timing can differ from person to person. Some people can have dyskinesias for most of the day, but for others they may only appear after taking a tablet, or just before the next is due. Also, some people may barely notice their dyskinesias, while for others they may be a source of great concern. Often,

involuntary movements can be more upsetting to an observer than to the person actually experiencing them.

What kinds of dyskinesia are there?

Dyskinesias can affect various parts of the body, but often involve the limbs and trunk. They can take the form of rapid, dance-like movements known as 'chorea' or 'choreiform' movements. Some people have said that chorea is almost the opposite of their Parkinson's symptoms, since instead of rigid muscles and slowness of movement, the person will have loose and floppy muscles, and too much movement.

Other people may experience what is known as 'dystonia', a sustained involuntary contraction of the muscles, causing the affected part of the body to go into a spasm. Dystonia can also occur as a separate condition in itself, but it can often be associated with a number of other conditions, including Parkinson's. In such cases, it is often referred to as 'secondary' or 'symptomatic' dystonia, and is often, but not always, related to the timing of the anti-Parkinson's medication. For more information on dystonia, see the information sheet *Muscle Cramps and Dystonias*.

The timing of dyskinesias can also vary greatly between individuals. The most common form can be found when the dose of levodopa is reaching the peak of its effectiveness, and brain dopamine levels are at their highest; this is known as 'peak-dose dyskinesia'. Much less commonly, dyskinesia can occur both when the dose of medication is beginning to take effect, and when the effects begin to 'wear-off'. This is known as 'diphasic' or the dyskinesia-improvement-dyskinesia pattern. This can appear as a combination of chorea and



dystonia, and can be more difficult to treat than peak-dose dyskinesia.

How can dyskinesia be treated?

Dyskinesia can be difficult to treat. Because it appears as a result of the build-up of an increased sensitivity to dopamine levels in the brain, the first option would be to reduce the amount of levodopa treatment. However, as this approach could lead to the return of Parkinson's symptoms such as tremor, rigidity or slowness of movement, and could also mean more early 'wearing-off' or 'on/off' effects, this is not always possible.

Usually, if people are having trouble with dyskinesias, they will seek to find a balance between better mobility and involuntary movements.

Other approaches may be useful. As always, these should be discussed with your doctor or Parkinson's specialist:

- It may help the person to switch to a controlled-release preparation of levodopa, as these produce lower peak concentrations of brain dopamine. This might help to smooth out the response to the treatment, resulting in less dyskinesia.
- It is often helpful to maximise the dose of dopamine agonist drug a person is taking, and reduce the levodopa to the minimum they can tolerate. Some people may benefit from switching from one dopamine agonist drug to another.
- The drug amantadine (Symmetrel) can sometimes help dyskinesias. Amantadine promotes the release of dopamine in the brain, and allows it to stay longer at its site

of action. Unfortunately, it only works for a minority of people, its effectiveness is generally mild and may be short lived.

Can surgery help with fluctuations and dyskinesias?

Surgery is not suitable for everyone, but it is generally used to treat people who have had Parkinson's for some time and who are finding that their symptoms are no longer controlled effectively by medication and/or they are experiencing very troublesome dyskinesias. In particular, lesioning techniques (e.g. pallidotomy, thalamotomy) and deep brain stimulation have been used with some success in controlling motor fluctuations. Each form of surgery for Parkinson's carries risks, however, and should be discussed with your Parkinson's specialist. For more information on surgical techniques, see the publication *Surgery and Parkinson's disease*.

What can I do myself?

There is some evidence that the chances of developing these complications of Parkinson's are reduced by taking dopamine agonists at reasonable doses from early on in treatment.

When people begin to experience 'wearing-off' and 'on/off' fluctuations, it is important that their regime be managed to maximise 'on' time. This becomes much more complicated if a person also begins to experience dyskinesias, as they then have to decide on a compromise between more 'on' time with dyskinesias, or more 'off' time with other Parkinson's symptoms. Many people tend to prefer more 'on' time, even with the dyskinesias, but this will vary between individuals and you should discuss this issue with your GP or Parkinson's specialist.



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To maximise 'on' time with the least possible dyskinesia, it can be helpful for the person with Parkinson's or their carer to complete a 24-hour diary, where they can indicate the times and frequency of their symptoms and fluctuations, along with the times and frequency of their dosage. This can help both you and your Parkinson's specialist to understand your response to medication, and the proportion of the day that you are experiencing difficulties. It can also provide a better idea of the most useful strategies to try and smooth out the fluctuations. A sample diary, and suggestions on how to use it, are included in the information sheet *Keeping a Diary: For People with Parkinson's*. There is also a separate sheet *Keeping a Diary: For Carers*.

Using the record of your fluctuations can help you work with your doctor to get the best effects from your medication. Fluctuations can be difficult to treat, and people can differ over how they want them managed. It is important to get the right balance for you, to ensure that you have the best quality of life possible.

Further information

More information on the drugs mentioned in this information sheet is available in the booklet *Drug Treatment of Parkinson's disease*.

Information and advice are also available from the PDS Helpline, which you can call on 0808 800 0303 Text Relay: 18001 0808 800 0303 (for textphone users only), Monday to Friday, 9am to 8pm (except bank holidays), Saturdays, 10am to 2 pm, or email: enquiries@parkinsons.org.uk

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215 Vauxhall Bridge Road, London SW1V 1EJ, UK

Tel: 020 7931 8080 **Fax:** 020 7233 9908

Helpline: 0808 800 0303 **Text Relay:** 18001 0808 800 0303 (for textphone users only)

(The Helpline is a confidential service. Calls are free from UK landlines and some mobile networks)

Email: enquiries@parkinsons.org.uk **Website:** www.parkinsons.org.uk

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