When we look at the narrowing of the therapeutic window-- this is an important concept to understand-- we tend to think of it as the therapeutic window becomes narrower. But why does the window become narrower? Typically, the base tends to rise, and the time when we get a response from levodopa tends to shrink. We need to understand why. Over the course of time, there are probably two changes. And there are other changes that also affect the therapeutic window a little bit.

So one of the things that happens is the brain's ability to produce dopamine reduces because those dopamine neurons are degenerating. So the brain needs additional dopaminergic support. So somebody who started with maybe one tablet of carbidopa/levodopa 25-100-- that's typically the formulation I prefer to use-- may need a higher dosage of it, because they're now telling you that the dose is not working as well. What used to control the majority of their symptoms is not working as well. They need an additional dose.

They may also come back and tell you the dose is not lasting. Early on, individuals have fantastic buffering capacity. The very same neurons that are producing dopamine are also storing the levodopa. As those neurons are progressively degenerating, we have a need for more dopaminergic support, but we also need to give levodopa more frequently in order to have regular supply of it in the brain, because the brain's ability to store and buffer has reduced.

The buffering time is when there's a honeymoon period. You start individuals on levodopa three times a day. They might even miss the middle of the day dose and have no problem. They might feel the medications are working well. They take a dose on time. They may take it. They may say they experienced no gaps in their medications, and the medications work well.

Over the course of time, they may say the dose doesn't work as well. They may need more dosing. They may say if they come close to the dose, they tend to drop off. They have a wearing off at the end of the dose, and that end of dose off indicates that they need either more frequent dosing, or addition of adjunctive therapies on top to be able to buffer for that. So that's the concept of a therapeutic window narrowing.

But two other changes also occur in the brain with this. Well, two other changes occur in the body with this. One is the unpredictability of absorption of the medication. So medication may not necessarily absorb as consistently as we think we did. And years ago, we used to think the narrow therapeutic window was the entire story.

We know that now with taking medication more frequently, the irony is that your brain may need more frequent medications. They may need a higher dose of medication, but the gut absorption is not working. The gut is also impacted with Parkinson's, and we know that there's dysfunction and Lewy body pathology in the gut as well. And that slows down the gut, causing constipation, but also erratic absorption. And that can impact the availability of medication into the bloodstream, and therefore into the brain.

In addition to that, there are other neurotransmitter changes that also happen, not just the reduction in terms of dopamine availability, but dopamine drives a circuit in the basal ganglia that basically results in promoting movement and shutting down the systems that do not promote movement. Well, while we have the direct and indirect circuitry, with the decline of the direct circuitry, the indirect circuitry also becomes more recalcitrant, more rigid, more powerful, in that sense, if you want to think of it this way. So while the direct circuitry becomes less functional because of a decrease of dopamine, the dopamine is also supposed to shut down the indirect circuit. So while the direct circuit becomes less, the indirect circuit becomes more upregulated, more powerful.

So there are other neurotransmitters that also are working to reduce the movement. So there are probably three sets of changes, maybe four sets of changes. Just to recap, the first is, of course, needing more dopaminergic support. Two is needing it more frequently because of reduction of the brain's buffering capacity. Three is the gut's ability to absorb and regularly deliver medications becomes more erratic, irregular, and even unpredictable. And four, of course, other neurotransmitter changes occurring from a decrease in dopamine. So those four changes result in increasing offs for individuals.

A typical time period for when individuals will develop offs, typically, we say motor fluctuations start at three to five years. Now, I've seen individuals that have developed within six to eight months. And typically, they may either have an aggressive course of their Parkinson's, or on the other hand, we may simply not have a true picture of how long they've had Parkinson's for. They may have only noticed symptoms going back one year, but their symptoms really may have been ongoing for several years. Generally, we tend to see motor fluctuations come in earlier in the younger population of patients, because they may have a more severe progression of disease, and slower in individuals that are maybe a decade or so longer-- or a decade or so beyond the average typical age of Parkinson's that starts in the late 50's to mid 60's time period.

So three to five years is an average. I would tell you there are people that can have progression sooner. And there are some people that go out seven, eight years and have a much more gentler progression of this. And that's when we really need to become more creative about our medication regiment and parsing out how we add in or adjust levodopa, or even adjunct at that point.