The unfortunate reality is that the vast majority, almost all Parkinson's patients, will eventually experience motor fluctuations. Their initial honeymoon response to levodopa, where their symptoms are rather covered, is not going to last forever. At some point in time, at some point in the duration of their disease, the effect of levodopa simply won't last long enough until the next dose.

And so the most common motor fluctuation is wearing off. Initially, they can be predictable, or they are predictable. And later on, they may not be predictable.

And then we have other labels or terms for motor fluctuation. Dose failure, for example, is a condition where they take their medication and they don't even feel it working at all. And a delayed on is another one, when they take their medication and it takes more than half an hour or 45 minutes for them to feel the on state or the medication working.

Unpredictable off is when the off state occurs at any time and not towards the end of the previous dose, and things like that. But the universal, the common currency, is that it's an off state. And there is a resurgence of their stiffness, slowness, their tremor, and sometimes there is the occurrence of non-motor symptoms such as slowed thinking, urinary hesitancy, panic attacks, anxiety, depression in these off state. Those are what we call non-motor off symptoms.

And when the medication works, they're no longer depressed, they're no longer anxious. They can pee again. They can think again. And certainly, they can move better.

So most FDA approved drugs in Parkinson's disease have been in the area of motor fluctuations and wearing off, and there's a big reason for this. The reason for this, the reasons are several fold. One, it is so prevalent, and therefore, there is an unmet need.

Two, most, almost all patients, are really bothered by wearing off. If you survey Parkinson's patients, what would be the most bothersome aspect of Parkinson's is, when you survey patients six years onwards in their disorder number one would be motor fluctuations. And then the third reason is because we're rather successful in trying to alleviate it, at least to some extent. And so there are many, many classes of drugs that can alleviate or try to alleviate motor fluctuations in patients on levodopa with Parkinson's disease.

Now, the other thing you'll notice is that there are lots of levodopa formulations, and there's a good reason for this as well. Because levodopa works, and it is the most effective. It is the simplest way and most rational way of addressing motor fluctuations.

So you have your standard levodopa, carbidopa /levodopa, regular or immediate release, and that's our best, our favorite drug. Most Parkinson's specialists, that's their favorite. That's my favorite. And the reason is because you give the medication and you can predict what it does. You know which drug or which dose to blame if it's not enough.

So let's say you have a patient, you give levodopa at 8:00. And the next dose is not until 12:00, but it doesn't last until 12:00. They start having wearing off symptoms at 11:00 AM. Therefore, you know it's the 8:00 dose that's the problem. So you may want to increase your 8:00 dose.

Now, when they take the 12:00 the next dose is not until 4:00, but that works. It connects, and therefore you know that the 12:00 dose is not a problem. And then they take their 4:00 PM dose, their next dose is not until 8:00 PM, and that falls short again. And so you know that the 4:00 PM is a problem.

So in this case, my strategy would be to increase the dose at the 8:00 AM and the 4:00 PM time slot, and keep the dose at the 12:00 noon, and the 8:00 PM dosing schedule. So that's one option. So there are many ways of addressing this through levodopa alone. You can stay with regular levodopa and increase or decrease the dosing as needed.

You can add a long acting or controlled release levodopa. The problem with that is that it may not be reliable in its jump start or kick in effect, but it may last longer. You have in generic form extended release levodopa, in brand name it's Rytary, which is a combination of short acting and long acting so you get the kick effect benefit of the short acting and the long term benefit of the extended release form of it. The conversion though of regular levodopa to that of Rytary or the extended release combination may be a little bit tricky, and so that's something you need to be familiar with before you start converting patients from the combo of levodopa to the combo of levodopa from regular levodopa.

Now, recently there is the fractionated and scored levodopa. What is this? This is the same regular levodopa dosing tablet that we love. This is our favorite, but it's scored three ways. And therefore, a patient can cut it conveniently in 25 milligram increments.

And so the patient can give himself or herself 25 milligrams, 50, 75, 100, or 125, 150, 175, 200, et cetera, et cetera. Whereas, a non-scored or fractionated levodopa, you have the benefits of the regular one, the predictability of it. But since it's not scored, the most practical way of fractionating it would just be in 50s, not in 25s and not in 75. So there is a limitation to that, which the fractionated levodopa tablet may alleviate.

At some point, a subset of Parkinson's patients will have either brittle motor fluctuations, where really half 50 milligram adjustments may not actually be enough and they require a little less than that. Because 50 milligram jumps may cause these abnormal involuntary movements called dyskinesias. Whereas, if you get rid of the 50, then they'll have wearing off. So what they need is actually something in the middle, which is 25. And so the fractionated levodopa dose may be a very practical solution for this because it uses the drug that you're very familiar with, but it customizes it for you and for your patient so that you give the exact dose that they need for that exact period of time in 25 milligram increments.