

So let's take somebody who is currently on levodopa who gets titrated onto fractionable levodopa, and then we'll talk about a patient that was de Novo started on levodopa after they couldn't tolerate the previous immediate release formulation. We'll talk about both cases slightly differently, because they both have similar needs that can be resolved and managed with fractionable levodopa.

The first is an individual that's on 1 and 1/2 tablets of levodopa that tells you there are times in the day where the dose is not as powerful. It's not that it doesn't take effect, but it's not as powerful. The first dose isn't robust enough to give them a full on. They have to wait for the first dose, and then maybe the second dose to feel a full on, but at the end of the day, they feel that they're getting more dyskinesias at the end of the day if they stay on a consistent dose.

And so this one size fits all approach does not work for this patient. It may work for some. It may not work for others. And especially because we may not have the same need for the amount of dopamine throughout the day. When individuals are dependent on medication to produce dopamine, their ability to modulate that dopamine numbers are not as easy. You may need to fine-tune what we give them based on their activity, based on the food they intake or other factors.

So in that individual, starting at 1.5 all four doses may not be the right approach. They may need a little bit higher dosage in the morning, say 1 and 3/4, which can be reliably achieved. The 3/4 can be achieved with a fractionable levodopa. Middle of the day, they might be at 1 and 1/2, or maybe at a 1 and 1/4 based on their needs. And towards the end of the day, keeping at 1 and 1/2 might be too much.

Maybe keeping them on 1 and 1/4, or even down to maybe even 3/4 so they're not having so much dyskinesia in the evening time, or as many vivid dreams as they go to sleep, which can really disrupt an individual's functioning for the next day because they haven't gotten an adequate amount of rest and sleep. And their motor functions can be worsened by not having regular, consistent sleep.

So there's an individual where the dosing is different throughout the day recognizing that they need different dosing and being able to achieve that with the smallest increment dosage up or smallest incremental dosage down, which is 25 milligrams of levodopa, and get it reliably so they can get the consistency of the same dose and maybe not have jagged pills throughout the day, or powderized portions that they're taking unreliably throughout the day.

Now let's switch gears and talk about a de Novo patient. Let's say an individual comes to your office. They've been started on 25/100 previously. They did not have a good experience with it. They had a significant amount of nausea. They had a significant amount of orthostasis. And they even tried taking half a tablet of levodopa, and just were very sensitive to it, to the nausea or the lightheadedness of it.

They're not able to tell you if they've benefited from it. You and your examination find that they do indeed have Parkinson's, and should respond to levodopa dosing, but getting them to that dose is a challenge. They're simply just not able to stay on that dosage or build up to a higher dosage.

Well, one approach to that is to start with the fraction of levodopa and tell them to take a quarter of that tablet at every dose, starting with three times a day and then building that up and letting themselves titrate slowly. And I'm a fan of self-titration to an extent. Maybe not every neurologist is, but I am within a small amount of range.

And as long as we don't go too crazy in one direction, and we're not making wild changes up and down, I'm OK with taking maybe a half a tablet of levodopa up or down, or a quarter to two quarters of the fractionable levodopa up or down to be able to fine-tune their dosing so patients can determine how their motor symptoms are best controlled.

With that said, you might realize that starting with a quarter tablet of fractionable levodopa, carbidopa-levodopa, and building it in for the first week, then over the time, building it to two quarters or half of that, letting the person settle in on that, then going up to $\frac{3}{4}$, and building them up slowly so they adjust to the medication without being miserable with the side effects or without wanting to turn and discontinue the medications because they find the side effects to be too much of a bother, so they just don't want to even try getting on the medication to receive benefit from it.