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You have a patient who comes to you that has been initially started on immediate release carbidopa/levodopa or Sinemet, usually 25, 100, and 3 times per day, and then the patient develops wearing off. Well, classically, if a patient has mild wearing off between doses, you may add an extender such as entacapone or another COMT inhibitor, or an MAO-B inhibitor like selegiline or rasagiline. There's lots of different options for that patient.

But classically, what most clinicians do when you have a patient that's wearing off between doses initially, if it's an hour or so or 30 minutes or so, you may increase the dosing to four times per day of IR. So if they're taking it at 8, 12, and 4-- 8:00 AM, noon and 4:00 PM-- you may have them take it a little closer together, at three and a half hours or so, three hours. And then go to four times dosing, so maybe 8, 11 or 11:30, et cetera.

And that's typically the first step, because you're on the same medication, you're not having to add anything, and it's the most convenient for clinicians and patients. However, there are lots and lots of options for treating off in patients. I mentioned entacapone.

There's also a medication called tolcapone, which requires liver enzyme monitoring. There's a medication called opicapone which is relatively new, which can reduce wearing off as once daily, as well. So that's the COMT inhibitors that inhibit catechol-O-methyltransferase enzyme and keep more levodopa going to the brain.

MAO-B inhibitors like selegiline and rasagiline and are also out there, and they can reduce off time between doses. And then you have different formulations of carbidopa/levodopa, which include the extended release formulation that's in a capsule form, called Rytary.

And it has three different forms of levodopa-- one that releases immediately, one that releases a little while later, and one that's even later than that, along with some tartaric acid in the capsule, and that may help absorption. But that has a lot smoother profile of release in the blood, and maintains levels that are therapeutic for four or five hours, compared to the two hours up and down that occurs with immediate release carbidopa/levodopa.

There's also fractionated levodopa, scored levodopa called Dhivy that can be tweaked for a patient that needs very frequent, close dosing at smaller than one pill intervals. And those folks usually may be very brittle when they have significant off time, or they're on with dyskinesias. And getting them to the sweet spot of levodopa therapy may be achieved best, in some patients, by using Dhivy.

So rescue medications can be very useful for patients with Parkinson's disease. And those are for folks who have a wearing off before their next dose. So Kynmobi, or sublingual apomorphine, can help turn folks on in about 15, 20 minutes or so, and they can do real well before their next dose of levodopa kicks in.

There's also injectable apomorphine called Apokyn, which can be very helpful for wearing off in patients and is a rescue medication. And then there's an inhaled levodopa formulation called Inbrija, which can help rescue folks when they're having an off, and then keep them on or get them back to on relatively quickly.

Also if folks have significant wearing off and dyskinesias, we're pushing folks a little more toward DBS-- Deep Brain Stimulation surgery-- earlier than we used to. It used to be 10 to 12 years. Now it's probably 8 to 10 years as the average time frame for DBS, or even earlier in some patients who may have levodopa-resistant tremor or other features. But DBS is an option in patients with significant wearing off that are down the road in their Parkinson's disease.