

So for initial therapy in Parkinson's disease, it depends on the patient very much what you start. Some patients require levodopa when they walk in the door because they're down the road and have significant symptoms of slowness, and tremor, resting tremor, and rigidity. And levodopa has been the gold standard of therapy for Parkinson's disease for 40, 50 years now.

And the problem with levodopa is that it has a very short half life. It's about 90 minutes or so in the body, and developing therapies that are more continuous has been a goal over many years to try to treat patients with Parkinson's. There's been-- excuse me. There's been periods of treatment of Parkinson's disease where levodopa fell out of favor as initial therapy and dopamine agonists were used for a long time, but I think the pendulum has swung back towards levodopa as initial therapy for most patients.

The carbidopa-levodopa that we have today is the same formulation that's been around since the 1970s, the early 1970s, but we've improved it in some forms with fractionated levodopa. And we have also a delayed release or extended release levodopa preparation as well, which is in capsule formulation.

So an early Parkinson's patient will come in and start typically on carbidopa-levodopa 25-100 TID classically for treating their Parkinson's symptoms, their motor symptoms. And initially, they have what's called a honeymoon phase. The honeymoon phase is where you experience nice response and smooth benefits throughout the entire day despite taking it just three times per day. Usually before breakfast, lunch, and dinner.

Patients with Parkinson's tend to live in the honeymoon phase for months to a couple of years or three years, depending on the patient, and then they begin to have wearing off classically as the first symptom of motor fluctuation. That's where their medicine doesn't last quite as long between doses and they wear off with tremor slowness and rigidity returning before their next dose is do.

Wearing off can happen relatively quickly, in less than a year. And a study that was done published in *The New England Journal of medicine*. There was folks who actually had 16% chance of wearing off by less than a year, and by five years, half of patients have wearing off by 10 years, 90% of patients have wearing off with their immediate release levodopa.

So that's a problem that we're trying to address and get better at delivering levodopa in a more smooth fashion. Extended release carbidopa-levodopa has been helpful in that realm. It's in capsule formulation and it gradually releases different concentrations of levodopa over time where the peak dose lasts out to four or five hours and is smoother for patients. So that's been very good.