Rajesh Pahwa: Hello, and welcome to Motor Fluctuations in Parkinson's Disease: Causes, Consequences, and New Choices for Management. This continuing medical education activity is provided by Vindico Medical Education. This activity is supported by an educational grant from Sunovion Pharmaceuticals. Hello, my name is Rajesh Pahwa, and I'm the Laverne & Joyce Rider Professor of Neurology and Chief, Parkinson's Disease and Movement Disorder Division, and the Director, Parkinson's Foundation Center of Excellence at the University of Kansas Medical Center in Kansas City, Kansas.

Today, I'm joined by Daniel Kremens, Associate Professor of Neurology and Co-Director of Comprehensive Parkinson's Disease and Movement Disorder Center at the Sidney Kimmel Medical College at Jefferson University in Philadelphia, Pennsylvania, and Stuart Isaacson, who's the Director of Parkinson's Disease and Movement Disorder Center of Boca Raton and an Associate Professor of Neurology at the FIU Herbert Wertheim College of Medicine in Boca Raton, Florida.

Today, I'm going to start off by talking about Off Symptoms of Parkinson's Disease – Causes and Consequences. So, what is off? Now, off in Parkinson's disease (PD) is when a patient has a change in clinical state, where the motor and/or non-motor symptoms may appear or worsen. This combination and severity of symptoms are unique for each patient and they improve with PD therapy. There are multiple different kind of off states. They may be end-of-dose wearing off. You could have a random on-off phenomenon. You can have early morning when the patient first wakes up and has an off episode. They can be delayed on—the patient takes a dose of medication and it doesn't work for them for a long period of time. The patient may have dose failures. They take a dose, and it may not work at all for them, even if they try to take an additional dose at that time.

The other thing that people may notice is what we call off dystonias, where they have a muscle spasm or dystonic movement when they are off. Although there are different names, depending upon when and how these symptoms occur, they are individually may be called an off episode or an off period. So these are what make up the off time that the patient may have during the day. Off episodes, or off time, is going to happen in the majority of patients over time. When a patient is newly diagnosed with Parkinson's Disease, and initiated on levodopa, they have a good period of time, which we often refer to as a honeymoon period.

So the patient takes their medication, they are on throughout the day, doesn't matter if they miss a dose, doesn't matter if they forget to take a dose. However, as the time progresses over months to years, the patient starts

noticing that maybe in the afternoon, that the symptoms come back or they get worse. Or the patient may notice when they first wake up in the morning they have off symptoms. So the patient begins to have early end-of-dose wearing off, early morning off, and, as the disease progresses, these off episodes may become more frequent, more random, and may be much more difficult to control.

It's not just related to how much the patient is taking and how often they're taking because the levodopa levels in the blood fluctuate, but there's a therapeutic window and, as the disease progresses, this window narrows. So the same amount of levodopa that the patient is still taking in early disease, where they may be having a good on without any side effects such as dyskinesias, as this window gets narrower, the patient may get to an on state and then end up having the dyskinesias. So the patient may be struggling between having an on, having an off, maybe having an on with dyskinesias, is what they end up being on a roller coaster that we call.

Does every patient develop these motor fluctuations? Well, the majority of the patients will develop it, but why do they develop these? Well, we believe there are two main mechanisms in play. One is what we call a *central mechanism* and one is what we call a *peripheral mechanism*. In the central mechanism, there is loss of dopaminergic neurons occurring in the brain. Parkinson's disease usually starts when you still have some degree of dopaminergic neurons still available in the brain. So what we believe happens is when a patient takes oral levodopa, it goes into those cells and is converted to dopamine, and it is still released as physiologically as possible. So initially, the patient may not notice these off periods are off episodes.

However, as the disease progresses, this buffering capacity is reduced. So what happens is, what they get from the periphery, they're using it at the post-synaptic receptors, and often the benefit of each dose may be as much as the half-life of levodopa. So later on in the disease course, the patient may be having only 1 to 2 hours of benefit with each dose rather than at the beginning of the disease where with 3 doses a day, they were on throughout the day.

The other thing we also believe is there is a peripheral mechanism that is at play. So what is that related to? First of all, the half-life of levodopa. The half-life of levodopa is about 90 minutes. So when you look at a drug which is only there for 90 minutes, if it was not for the buffering capacity in the brain, we would have to use this drug much more frequently. The other thing is, levodopa is mainly absorbed in the small intestine. In Parkinson's disease, there's often delayed gastric emptying. There's dysfunction of GI motility occurring.

So when a patient does take their levodopa, it stays in the stomach for an extended period of time and then goes into the small intestine. There, it

competes with neutral amino acids to get into the blood. Once it's in the blood, it has to compete and get into the brain through the blood-brain barrier. So this leads to some of the other issues related to the motor fluctuations because it's a long process going from the mouth to the gut and finally into the brain, which can also result in the motor fluctuations.

I mentioned a few different kinds of motor fluctuations earlier on. So one of them, which is the end-of-dose wearing off, which occurs at the end of the dose. We believe that might be related to the short half-life of levodopa and that's why the medicine does not last for 4 hours and is only lasting for 3 hours and then 2 hours. Then we talked about the delayed gastric emptying, where a patient may take a dose of levodopa and it may take a while for the dose to start working. That one we believe might be related more to the gastric emptying. So if the gastric emptying is slowed, it might take a while for the drug to actually get to the small intestine where it's absorption is also affected. If a patient has taken a heavy fatty meal or a heavy protein diet so that could also affect it, and we believe that might be playing a role in the delayed on.

Then you have the dose failure where a patient takes a dose and it doesn't work at all. And again, that we believe might be related to gastric emptying, maybe the pill stays in the stomach for too long a period of time, it can be related to the intestinal absorption, the competition with the neutral amino acids that's occurring, and then finally, the blood-brain barrier where also the neutral amino acids may be playing a role.

Finally, the complex on/off phenomena that occur. By these complex on/off phenomena, I mean that the patient may take a dose, they may kick on, and then randomly go off, and then again they may come back on even though they may have not taken a dose of levodopa. We believe these are more related to striatal pharmacodynamic changes that are occurring, rather than some of the peripheral mechanisms that we talked about, which may be playing a role in the development of these motor fluctuations.

Here I'm showing you an example of a patient who's going through Parkinson's disease symptoms throughout the day. This patient, as you see, has taken 5 doses of levodopa throughout the day. The blue coloring shows you that the patient's in off, and the green coloring is when the patient is in the on state. So if you look at it in the blue and the green, you see the patient has had about 4 episodes of off here. When the patient takes the dose at 7:00 AM, you see that there really is no rise in the levodopa plasma levels, the patient is basically staying off. So again, there could be multiple mechanisms why this patient is off.

When the patient takes a second dose, the patient does kick on, there's a good rise in the levodopa levels. Not only the patient goes into the on, which is the green zone, but also goes a little bit more dyskinetic. Then as the level comes

down, the patient gets off, takes another dose, and then kicks back on from the second dose. The third dose, as you see, it is taking a longer time to get back on so there's another problem that's occurring there. So this shows you an example of a dose failure occurring, a patient having a good on, a patient basically wearing off at the end of the dose, and the next dose not even kicking well on at that state.

Daniel Kremens: Raj, what I think that also shows is the challenges that patients face because here's an example of a patient who took their medicines regularly, the way we're telling them to, and yet you can see how disrupted this patient's day is with dose failures, wearing off, delayed ons. I think this is showing the challenges that off time in general and then off episodes presents the patients.

Rajesh Pahwa: Oh, definitely. It makes it a challenge because this is one day. The next day may be very different for this patient. So when a patient has off, what symptoms do they get? Well, they may have motor symptoms, they may have non-motor symptoms. The other thing is, these symptoms do progress as the disease progresses. So, earlier on in the disease course, the patient still has motor and non-motor symptoms, and as the disease keeps progressing, close to 90% of the patients may have off periods after 10 years of the disease course.

So when we talk about the motor and non-motor symptoms, as you see here, there are multiple symptoms you can have. A patient can have just slowness of movements, can have loss of dexterity, they could have weakness, they could have tremor. They could also have non-motor symptoms like anxiety, dullness as thinking, mood changes. They could have pain. They could have autonomic symptoms, such as abdominal discomfort, sweating. So as you can see, each patient can be unique in what set of symptoms that comes up with, whether it's motor, whether it's non-motor, and it does not necessarily mean that each of the off episodes they get, they will have similar symptoms from that kind.

Daniel Kremens: I think this is one of the real challenges for practitioners and patients to recognize off because if you're not asking these sorts of questions, the patient may not realize that that ache that they're feeling every time before the next dose of levodopa is actually a wearing off sign, or that sense of dread or anxiety, is a wearing off sign.

Stuart Isaacson: Yes, sometimes non-motor symptoms are more important that motor symptoms for some patients.

Rajesh Pahwa: Right, and then often they may have struggles trying to decide is this anxiety they're just having it, and they may not quite be able to make it out, "Well, I'm due for another dose. That's why I'm getting anxious from that part." So what is the number of patients who are gonna develop these motor complications? So it depends on what studies you look at. If you look at the retrospective studies,

50 to 60% of the patients will develop it over 5 to 6 years and most of us in conversation will talk to patients and say, well, 50% of people will develop motor fluctuations in 5 years.

If you look at community based studies, then you see that's about 30 to 40% after five years, which is still pretty close. The young onset is a big risk for the development of these motor fluctuations, and all 90% at 5 years could develop these motor fluctuations. If you look at more randomized studies, which have been done as part of clinical trials, you have seen 16% after 9 months, and greater than 30% after 2 years.

So often patients ask us, "When are we gonna develop these off times?" It can be very difficult to predict because there are a number of risk factors that may play a role in it. So why are these off periods very important? These are important because they can significantly impact the quality of life in our patients. So here you'll see examples of an end-of-dose fluctuation, nocturnal akinesia, early morning akinesia, unpredictable offs, and paradoxical fluctuations.

Paradoxical fluctuations after the patient takes a dose and may actually get worse before they get better. So if you look at it, not only is the overall mobility affected, the activities of daily living affected, the patient also have the stigma that they feel that's affecting them because they don't like when the off symptoms are affected, and also the communication skills that happen. So, it's really an important part that all these off periods, off episodes play a significant role as far as impacting the quality of life is concerned.

If you go back and look at who is gonna develop these earlier, like I mentioned earlier, younger onset of disease, younger the patient, sooner they will develop the fluctuation. We also know that severe disease state is gonna cause it earlier. So if you look at patients who don't start the drug for a long period of time, their disease has gotten worse, they're gonna much more likely to develop these motor fluctuations. If you start using very high doses of levodopa early in the disease course, that could be a risk factor, and the longer disease duration and the longer duration of levodopa therapy, also plays a part. Finally, female sex in another one that has been shown to be a risk factor for motor fluctuations.

The other challenge we often find in the clinic is these off periods are often under recognized. Now why is this the case? Well, first of all, you have patients who have never had an off period, or never had fluctuations, that you hear someone and they often come and say, "You know, I'm not having off periods. Why is that?" Well, unless a patient really goes through an off, and they have had the disease long enough, they have taken levodopa, they may not realize what off periods or off fluctuations are. When they start developing it maybe too mild for them to realize that it is a beginning of the off time they had.

The next thing is if a patient never has experienced an on, in other words, has been underdosed, never got a dose high enough to know what a good on is, they're never gonna realize that they are actually in the on state. Like I mentioned earlier, not all offs are the same. So some patient may feel anxiety, some patient may just feel they're having a little difficulty walking, some people may feel they're handwriting is getting worse. So, that also can make it difficult for the patient to recognize when they are off.

Like we talked about earlier, all patients may not appreciate the off symptoms. We talked about the long list of motor and non-motor symptoms and the patient may not appreciate that this is actually a part of the off symptoms that is happening. Even if patients recognize that they are having off, they may not understand the risk that affects it, that their quality of life may be getting affected, because they are so concerned that they don't want to increase their medication, that when they lead to undertreatment, they don't realize that they might be in off state throughout the day because they're not getting into the on state.

The other thing is, when we talk about off and on, we are talking about off time, like I said, and then you have off periods and off episodes, and often when you start talking about the treatment, it's gonna be slightly different when we talk about these treatment options that are there. So, to summarize my section, off symptoms develop due to both peripheral and central mechanisms. Off symptoms can include both motor and non-motor symptoms. Off symptoms impacts quality of life and can impact mobility, emotional well-being, social stigma, and bodily pain.

Younger age, longer disease duration, high levodopa dose age are the main risk factors for the development of motor fluctuations. Off is often underrecognized and appreciated.

So this was kind of giving you an overview of what off is, what off symptoms are, and what the mechanisms are behind this. How do you look in the clinic, see a patient, and talk to them if they are having an off symptom or an off episode?

Stuart Isaacson: I think patients have to understand that when they have these motor and non-motor symptoms that reemerge during the day, it's not just their Parkinson's disease. This is a factor of medication that's stopped working. If we can get that medicine working longer, or working quicker, again, these off periods can be shortened and the off time throughout the day will be a few hours.

Rajesh Pahwa: Do you feel that we, as physicians, don't spend enough time with the patients, talking to them about the off symptoms and the off episodes that we are under appreciating from our standpoint because all of us in the clinic are busy trying to finish our patients?

Daniel Kremens: Yeah, I think one of the big problems is for many people, there's such a focus on the motor symptoms, right? It's pretty obvious if a patient's tremor's returning, or if they're becoming markedly bradykinetic, and the patients can appreciate that pretty easily. I think the bigger challenge is trying to recognize non-motor offs, right? So, is the patient having the sense of dread that they can't figure out why that's happening during the day and seems to be some sort of pattern.

So, one thing I like to do is spend some time discussing, really trying to figure out, when are you taking your medicines? Are you taking them consistently? Then trying to see, is there a pattern to their off symptoms emerging. Sometimes, for some patients, keeping a little bit of a diary for a week or two and then going over that with them to see if there's any pattern that emerges can be helpful.

Stuart Isaacson: Sometimes we're using technology, these wearables, that can help us decipher when medicines are working and when they're not working. This may be an emerging way of identifying it better. Also, trying to understand which doses take too long to work, which doses don't work well enough or don't work at all, and which ones do work well, and maybe focusing on trying to fine-tune the schedule to get more consistent ons.

Rajesh Pahwa: Do you try to differentiate in your patient whether they're having an off episode, or do you just look at it off and let's just read the off or look at specifically at an episode that they're having that maybe focus to us treating them?

Daniel Kremens: I think that's a great question and sort of leads into some of the stuff I'm gonna be discussing in my section, but honestly, I think you have to look at both because you can absolutely optimize a patient's medications to reduce their overall off time, and, as I'll show you, even in that setting, they will still have off episodes. So you really have to address both. It's not an either or or.

Stuart Isaacson: Unfortunately, for so many decades, we haven't had therapies that were easy to use, and really try to address off episodes so we focused our energies on off time, and medications that can reduce throughout the day, all the off time. But now that we're having the emergence of new therapies that can really kickstart it and turn someone back on, it's a new era, I think.

Rajesh Pahwa: So, with the treatments you're gonna discuss with off episodes, maybe we need to focus more on the off episodes because a patient may forget to take a dose and have an off episode. They may not take anything all night because often a patient goes 10, 12 hours without taking medicine. They wake up early in the morning and they are off, and necessarily adding a medicine may not help with that early off, for example.

Same thing with dose failures. Some of these treatments we have had does not help and whether looking at other forms of therapy might be a better answer on treating them.

We talked about some of the risk factors of off, for example, young age, high levodopa dose. Do you do anything in your clinic? Do your patients say, "I don't want to start any medicine because I'm afraid I'll have off?" How do you talk to them about that?

Daniel Kremens: Well, I think everybody has patients that are fearful of levodopa, so we have a long discussion around some of the myths surrounding levodopa, and I think that's one of the big challenges. I think for some patients, the notion that they need more medicine, to them, reminds them that their disease is progressing. What I try and focus on with patients is improving quality of life, really, and allowing them to function the best that they can. Now, we actually do have options to treat these off episodes that are so disabling.

Stuart Isaacson: I think clinicians, and patients, family, and caregivers have to understand that when symptoms emerge, that respond to dopamine, when they come back, it's not a good enough medicine problem. We need to give medicines at the right dose as consistently as possible to really change the focus from reducing off time to maintaining good on time throughout the day.

Rajesh Pahwa: Because ideally, we should have patient in on throughout the day without any off even that if it means we are using a little extra dose here.

Stuart Isaacson: We know patients who have lots of off time and lots of off episodes, and we put them on infusional therapies, experimentally perhaps. That off time really goes away. This is really a problem with delivering dopamine and dopamine therapies to the brain consistently and getting an even response, not interrupted by off episodes.

Daniel Kremens: So with that, that leaves my portion of this discussion, which is Current Approaches to Off. Carbidopa levodopa remains 50 years after its introduction, the gold standard for the treatment of the motor symptoms of Parkinson's disease. The introduction of levodopa caused a dramatic improvement in the motor symptoms of Parkinson's patients. Then, later, we saw the results of from the L-dopa study, which again demonstrated that levodopa in a dose-dependent fashion, improved the motor symptoms of Parkinson's disease.

The problem is as we heard in Dr. Pahwa's portion of the talk that with time, there are both central and peripheral mechanisms that are going to interfere with this honeymoon period that we see early on with levodopa. That leads to the motor fluctuations. So, what are some approaches to managing motor fluctuations? Well, as you just heard us discuss, I think assessing the experience

of off time and off episodes in patients with Parkinson's disease is critical. That means taking some time in the clinic to try and figure out the patient's experience.

Then, we look at the traditional therapeutic approaches that focus on off time now. So, the first thing that we generally will do with the patient on oral levodopa is try and modify their oral levodopa dosing. That typically includes things such as increasing the dose or trying to give it more frequently. So, if a person says, "Well, my medicines are wearing off. I'm taking 3 times a day and now my medicines are wearing off about half an hour or so before my next dose," we'll have him go from 3 to 4 times a day, which is a very common strategy.

You heard Dr. Pahwa discuss the concern about amino acids in the diet so often having the patient taking their medication either half an hour or so before a meal, or an hour or so before they eat can avoid problems with malabsorption secondary to protein. Then we can also try to modify the levodopa formulation, and this involves using...we don't do this so much anymore but in the past we would try and make liquid forms of levodopa by dissolving the levodopa sometimes in a carbonated beverage and having the patient drink it. Or there were oral dispersible levodopa formulations, and this generally showed some inconsistent results. Dr. Isaacson is gonna tell us later about some more novel formulations of levodopa that may help with some of these problems with off periods.

Another thing that we can do is we can use adjunctive therapies to help enhance the action of levodopa. This include things such as MAO-B inhibitors, or COMT inhibitors, or dopamine agonist drugs. These things may alleviate the severity of off periods but not always reliably so these will reduce your off time but you still have off periods. In addition to our longer-acting dopamine agonist including transdermal preparation or once-daily preparations, again this can improve motor symptoms but sometimes using these products patients won't get to a full on. Again, they will not break an off period once it begins. Then there are surgical options such as deep brain stimulation or as Dr. Isaacson will tell you about, a carbidopa levodopa intestinal gel.

So, let's review some of these medications that we can use to treat off. A COMT called entacapone is one, and what this does is it prevents the degradation of levodopa to 3-O-methyldopa peripherally. By doing this, this may extend levodopa dose effect by approximately 60 minutes in most studies. One of the larger studies looking at this was the LARGO study, which was actually a study that was looking at patients comparing rasagiline with entacapone and placebo. This was a European study. So, entacapone was used as an active competitor. What they saw in that study was both rasagiline at the 1 mg dose and

entacapone at 200 mg reduce the mean daily off time by approximately 1 hour versus 0.4 hours by placebo.

Rajesh Pahwa: One hour time is a pretty good in the clinical trials when we talk about time.

Daniel Kremens: Yeah, I think what you're gonna see is basically in just about every trial that's been done for adjunctive therapy you get roughly one to one-and-a-half hours of decreased off time over the course of the day. Then there are the MAO-B inhibitors and this include drugs such as rasagiline, selegiline, and a newer drug called safinamide. There were a number of studies that supported this, again for off time. The PRESTO study was a large study looking at rasagiline versus placebo as adjunctive therapy and again, got about 1 hour of less off time.

Selegiline has been looked at number of times. It's an older drug. Dr. Lou and colleagues in 2007 presented an open-label like extension study of selegiline, where, again, they reduced off time by about 1 and a half hours versus placebo. Then Shapiro in 2017 recently presented data on safinamide, which is a newer MAO-B inhibitor that was used in Europe, and then recently came to the United States, and, again, they got about 1.42 hours more on time without troublesome dyskinesia compared to the placebo group.

Then we also have the dopamine agonist drugs, and these include drugs such as ropinirole, pramipexole, and rotigotine. I'm going to focus a little bit of data right now on rotigotine, which is a transdermal delivery system of a non-ergoline D3 and D2 as well as D1 dopamine agonist. This was the preferred study. It was done in 2007. It was a large study looking at 351 patients with Parkinson's disease who are experiencing motor fluctuations. These patients were titrated up to both an 8-mg patch to 12-mg patch or placebo. Ultimately, in the United States we did not get a 12-mg patch. The 8-mg patch is the highest one that was approved. Again, off time was reduced by close to 2 hours in that particular study.

What differentiates ropinirole from the other dopamine agonists, aside from the fact that it's a patch, is that it's the only dopamine agonist that has some data that may improve off time upon awakening. All of these approaches help to reduce total off time, but they don't alleviate the off periods once they occur. Right now, we need to have therapies. I'm going to focus on one, and then Dr. Isaacson is going to tell us about some emerging therapies that focus on treating off periods.

Rajesh Pahwa: Dan, before you go into that, you talked about the MAO-Bs, the CMTs and the dopamine agonist. But you could have a patient who could be taking levodopa plus the CMT plus an MAO-B, plus dopamine agonist if they need it.

Daniel Kremens: Sure. In all those studies, all those studies were adjunctive therapy. So, in each of those studies, patients were optimized on their medication, and despite optimization, they were still experiencing off time.

Stuart Isaacson: Usually the off time in these studies at baseline. despite adjunctive medications was 5 to 6 hours throughout the waking day. When you reduce that by an hour and half or so, you're still left with about 4 hours of off time, despite adding another adjunctive medicine, really highlighting the need for therapies that are on demand to treat these off episodes.

Daniel Kremens: Yeah, it's clearly one of the most pressing and unmet needs in Parkinson's disease. Why are we having these issues? Why can't I just take another levodopa? Why won't that solve it? Why are they still having these 4 hours of off time? Part of the reason is because of this GI problem that Dr. Pahwa described. GI symptoms such gastroparesis are very common in Parkinson's disease. There's also an issue potentially with small intestinal bacterial overgrowth. This is highly prevalent in Parkinson's disease and maybe due to impaired GI motility.

As I mentioned previously, dietary proteins impair levodopa response. You get this competitive inhibition for levodopa absorption, which perhaps suggesting meals may help for some people. Therefore, non-oral strategies are needed to treat off episodes. As you can see in this slide, you see an hour and a half after the patient has taken their levodopa, the pill is sitting there in the stomach, undigested. This is an example of probably a dose failure. After an hour and a half I don't think we can even call it delayed on at that point. Taking another oral pill is not going to solve this problem. We need non-oral therapies to help address this.

Stuart Isaacson: There have been lots of studies that really show this idea. If you take your next levodopa sooner or half of a levodopa, trying to turn back on, it may be stuck with dysmotile esophagus. It may be stuck in the stomach with delayed gastric emptying. It may get into the intestine and not be absorbed due to presence of protein or a bacteria as you point out. The oral road is just not a very efficient way of replenishing the precursor for an essential neurotransmitter.

Daniel Kremens: Yeah, and then you have a situation where it turns out so they take the extra dose and it turns out it's a delayed on. Now they're very dyskinetic because now they have too much levodopa in the system. It really is a challenge. One potential solution to this is apomorphine subcutaneous injection. Apomorphine is a highly effective dopamine agonist that selectively acts at dopamine D1 and D2 receptors. This drug has been around for a very, very long time, but it was first looked at in Parkinson's in the 1980s where Stibe and colleagues demonstrated that apomorphine had an equivalent anti-Parkinsonian effect to levodopa for helping them manage off periods in patients with Parkinson's

disease. That ultimately led to it being licensed for the treatment of Parkinson's disease in the United Kingdom in the 1990s.

Ultimately, it was approved in the United States in 2004 as a subcutaneous intermittent injection to be used as adjunctive therapy to oral Parkinson's disease medications in patients who are experiencing off episodes. This was a result of a seminal trial that was done by Rich Dewey and colleagues. What they did in this study is they took patients and they were initially admitted to the hospital. There they were randomized to different subcutaneous apomorphine doses, ranging from 2 to 10 mg or placebo.

Following the hospitalization, they were then followed for a month where the patient was allowed to use the medication up to 5 times a day to see when they were having off episodes, how they responded. What we saw in this study was during the inpatient phase, Unified Parkinson's Disease Rating Scale motor scores were reduced by 23.9 points in the apomorphine patients versus 0.1 point in the patients taking placebo, demonstrating that strong levodopa-like effect that you can get with subcutaneous apomorphine.

In addition, when they went to the outpatient phase, when they were allowed to use the apomorphine subcutaneous injection as they liked over the course of the day, 95% of off episodes that the patient experienced were reversed during that time period with apomorphine when it was used as needed. I think one of the other real challenges of off, as Dr. Pahwa, mentioned are these morning offs. These are very, very common in Parkinson's disease. There was a study that was done in Europe called the EUROPAR Study that was looking at the prevalence of morning off, and particularly the non-motor symptoms in morning off.

What they saw there was that patients experiences really throughout the course of their disease, even mild disease where we don't necessarily think very much about morning off, 44% of the patients were experiencing morning off in the EUROPAR study. It's thought that this is a result of–the patient takes their levodopa in the morning. They have this delayed on that prolongs their morning akinesia. Dose failures are not uncommon. Despite all the adjunctive dopamine agonist and monoamine oxidase inhibitors that these patients were taking, they still were experiencing off. As EUROPAR demonstrated, it negatively affected their quality of life.

This led to a study that my colleague, Dr. Isaacson, actually did called the AM-IMPAKT Study. This was an open-label study to assess the effects of apomorphine injection on timed on in patients with Parkinson's disease who are experiencing morning akinesia. You can see in this slide the number of adjunctive medications that the patients were taking. They were taking dopamine agonist, MAO-B inhibitors, COMT inhibitors, amantadine. The key to

this is, despite that optimized medication regimen, patients were still experiencing morning akinesia.

What they did in this study is they had patients complete a 7-day levodopa baseline period when they were recording their timed on following each of their morning doses of levodopa. It was self-recorded in 5-minute blocks. This was followed by a 7-day treatment period, which, instead of taking their morning levodopa, the patient took apomorphine. That was injected each morning and then the time on was similarly recorded in 5-minute intervals.

What they found in the study was this…Patients during their levodopa baseline period were experiencing a timed on of roughly about 61 minutes, and when they switch to their apomorphine treatment period, their timed on decreased to about 24 minutes. Similarly, during their levodopa baseline period, about 40% of the patients were experiencing dose failures, but when they switched to apomorphine subcutaneous injection, 7% of the patients were experiencing dose failures. You can see this had a real impact on the morning off that these patients were experiencing.

Rajesh Pahwa: You brought up a very interesting point. A couple of things is, one, are patients often like to keep dosing themselves 4 times a day, 5 times a day? In my experience usually if we go over 4, 5 times a day, the patient's compliance decreases. Patients have more difficulty trying to remember it. They're more already have interaction with the food. Do you find that in your practice, too?

Daniel Kremens: There's no doubt. I think once you get above a certain number of doses during the day you're going to have compliance issues. The other thing that I started to worry about, particularly in some of the younger patients because I might be seeing somebody who has a dopamine dysregulation syndrome, which I want to be careful about as well because they say they're off, but when you examine them, they don't appear off and they're very dyskinetic. That's something I'm careful about too in those patients.

Stuart Isaacson: I think the other thing that hinders compliance is if you're taking a medication, you don't really know if it's going to work quickly or take a while or take longer, this day or that day, or if it's going to work well, or not so well, or not at all, and having dose failure. Sometimes, you may not be so eager to take that next pill because you don't know if it's really gonna make those symptoms go away. You may begin to feel that these symptoms are part of your Parkinson's and are just something you have to put up with.

Rajesh Pahwa: The other thing I see in these patients that are referred to me who are having these off episodes. They're often undertreated. Whether it's the patient or physician, either having a set idea that a patient can't take more than X milligrams of levodopa or the patient might, oh, if I take more levodopa, I'm

gonna have the dyskinesias. But the fact of the thing is, if we don't give our patients enough, they will have off. But if we do give them enough, yes, there is a risk of dyskinesias, but it doesn't mean they are going to have it. It really comes down to is, are we undertreating our patients.

Daniel Kremens: Look, I think certainly they're particularly outside of the movement disorder specialist. I think there remains a lot of fear about levodopa and so patients probably are being undertreated. I think important thing to point out is, these studies that I showed you were conducted largely of movement disorder centers with patients who are optimized. Even when optimized, adjunctive therapy with their levodopa, patients were still suffering increased off time and off episodes. Even with optimization with current management strategies, patients are experiencing this, which is why we need therapies.

Stuart Isaacson: I think it's the theme that you'll see in this next section about new therapy so we're trying to get patients to stay on longer, to keep them on, and when they turn off to get back on quicker, and more reliably. This is really the focus, and moving it away from dyskinesia and off time as focuses. We're really trying to keep people on a consistent on.

Let's turn now to some new options that have become available recently and are under study to find better treatments for people who have Parkinson's off time and off episodes, both experiencing motor and non-motor symptoms.

You've heard already about this idea that wearing off is only part of the story of off time. The turning back on, the late onset is the other part. I mean you put the delayed onset and the wearing off together, you get to full off episodes. There was study not too long ago that was published by Merims. They really identified that the delayed onset of medicine, waiting for the next dose to work, was about double the time that patients experienced compared to the time of wearing off.

It really has led to a focus of not only trying to keep people on more consistently but also trying to get them to be in control and having on-demand therapy. We've had loads of medicines over decades in trying to replenish dopaminergic tone in the striatum, and you've heard about MAO-B inhibitors and COMT inhibitors and dopamine agonists, and we have longer acting levodopa formulations and infusional therapies, and even some therapies that have recently been approved for non-motor symptoms in Parkinson's.

This is a study that looks at an old medicine, amantadine, in a new formulation. It's really time to give a high bedtime dose that rises throughout sleep and is there in the morning and throughout the day to try to reduce dyskinesia. This study met its primary endpoints in reducing dyskinesia and also met its

secondary endpoints of improving off time. Probably to a glutamatergic mechanism, this drug is able to both reduce dyskinesia and improve off time.

When we look at the overall improvement in patients, it really focused on taking patients good on time—on time without troubles and dyskinesia—and took patients from roughly about half the day where they spend good on. After the use of this medication at the end of 12 weeks, patients had about three-quarters of their waking day where they had good on. The other quarter being made up of troublesome dyskinesia or off time.

Other attempts of trying to keep patients in the on state have led to new formulations of levodopa or new ways of delivering levodopa. Recently, we had approval of an extended-release carbidopa/levodopa called the IPX066. We also had approval recently of an intestinal gel formation that's delivered by a pump, bypassing the paretic stomach directly into the intestine of levodopa. Most recently, we had the approval of an orally inhaled levodopa formulation that can be used on-demand. I will review these 3 different novel formulations of levodopa.

In clinical trials right now, in phase 3, there are number of exciting new molecules being looked at. For instance, there is an accordion pill, an extended-release levodopa/carbidopa formulation that's gastroretentive and gradually opens over hours, releasing layers of levodopa that can then exit the stomach and be absorbed in the intestine. There is a new extended-release carbidopa/levodopa called IPX203 that may provide levodopa levels in the plasma for up to 8 or maybe even longer hours.

There are 2 novel subcutaneous pumps that can deliver subcutaneous levodopa delivery, NDO612 and ABBV-951. Both these formulations are in phase 3 and hopefully can provide 16- to 24-hour delivery of subcutaneous levodopa that can then enter the plasma and the brain. Looking at the extended-release carbidopa/levodopa and IPX066, we can see that this contains multiple small little beads that have different weights and stickiness and dissolve at different pHs and time, to come together these 3 different beads and give an extended plasma pharmacokinetics of about 5 hours in many Parkinson's patients. Many patients can use this novel formulation of carbidopa/levodopa to improve their on time and reduce their off time when compared to immediate-release carbidopa/levodopa alone.

Another big focus is trying to develop and identify non-oral therapies due to the problems delivering levodopa through the gastric paretic system and delivering it into the intestine, where its absorption can be impeded by protein or bacteria perhaps. Subcutaneous delivery of apomorphine through injection or through subcutaneous pump has been available in Europe and Australia and is under phase 3 trials in the United States, and these 2 levodopa subcutaneous delivery

pumps that are under phase 3 trials in the states are all exciting avenues of trying to keep patients on more consistently. You've already heard about the transdermal delivery of the dopamine agonist rotigotine and of the delivery of selegiline by dissolving in the mouth, the so-called Zydis Selegiline preparation.

Let's turn now though to some other novel ways of delivering levodopa through the jejunum directly and to orally inhaled powder, and a new formulation as well of apomorphine that can be delivered sublingually and absorbed through the mucosa. Levodopa/carbidopa intestinal gel had been available for decades in Europe and was approved in the United States in 2015. This provides a gel formulation of levodopa that is delivered through a peg tube into the stomach with a J-tube extension, delivering gel levodopa directly into the small intestine, where it can be absorbed by the neutral transporter.

Doing this bypasses the difficulty in getting levodopa out of the stomach and into the transporter region of the intestine. By delivering levodopa in this fashion, starting it in the morning upon awakening and continuing throughout the waking day and stopping it before bedtime, patients are able to maintain a very, very stable plasma pharmacokinetic delivery of levodopa. This translates to a reduction in off time throughout the waking day.

Recently, we had the approval of an orally inhaled levodopa power, CVT-301. Now this is FDA-approved. Patients are able to have a self-administered delivery system where they can inhale levodopa when they're in the off state and turn back on without having to wait for their next oral dose to be swallowed and get out of the stomach and be absorbed. The delivery of orally inhaled levodopa may be a major advance for patients to take control of their off symptoms and turn back on more regularlyl without having to resort to an injection.

Rajesh Pahwa: The patient in this one has to put the capsules into that inhaler and then one capsule at a time, and then inhale it?

Stuart Isaacson: Right.

Rajesh Pahwa: It doesn't come like a metered inhaler or something?

Stuart Isaacson: No. This is a type of delivery system that involves what's been called the Arcus technology, where levodopa molecules opened up and can be breathed in with minimal inspiratory effort through a little whirler. They put a little capsule in, they close it, and they breathe it in, and they do it again to get the full dose. Some dexterity maybe required that patients may be able to do when they're off or may not and need help.

Daniel Kremens: Although in the studies, over 99% of the patients were able to do this when they were in their off state and use the breath-actuated inhaler, so I don't know that

that's...we'll have to see once this becomes available in practice. Certainly, there weren't signals in this study that this was something that a patient couldn't do in their off state.

Stuart Isaacson: Patients now have a choice between using an injection pen to get subcutaneous apomorphine to turn back on or to orally inhale levodopa to turn back on—two ways of turning back on and taking control of the symptoms. When they inhale this levodopa, it's absorbed directly through the lungs into the circulation. There is no gastric-induced delay in getting levodopa into the plasma, so patients can get plasma levels very, very rapidly within minutes and, with the dose that's been studied and approved, get to a level where they begin to feel their motor or non-motor symptoms emerge. They can take the inhaled levodopa to sort of bridge that gap and stay back on.

Rajesh Pahwa: It's important to point out, this is just levodopa without carbidopa.

Stuart Isaacson: Right, so patients have to be taking carbidopa/levodopa in order to use this product because you need carbidopa in the system.

Daniel Kremens: Yeah, it's not a substitute for the oral pill.

Stuart Isaacson: Right. When patients use this in the...as they enter an off state, we saw motor score improvement within 30 minutes that was significant. Sooner, that did not reach significant values but some patients had improvement within 10 minutes or 20 minutes as well. Looking at the use of this in a pilot study looking at its safety and for early morning off, we're also able to identify patients who took the orally inhaled levodopa with their first morning dose of oral levodopa, turned on quicker, and about half to two-thirds of patients had an onset within 30 minutes and some within 15 minutes.

Daniel Kremens: Potentially a strategy for patients experiencing morning akinesia?

Stuart Isaacson: It may well be. It has not been studied to look at its efficacy specifically, but at least now we know that it's safe to try it. We're anticipating a new formulation of apomorphine as well that has completed phase 3 trials. This sublingual formulation of apomorphine is present in a strip, a strip that can be placed beneath the tongue when patients enter an off state, and then the mouth is closed, and this strip dissolves, allowing apomorphine to be absorbed to the mucosa in the oral cavity and directly into the plasma.

In doing so, patients will have a third option on-demand to turn back on. This type of sublingual apomorphine strip was designed to have a buffer because apomorphine is acidic. Now, instead of only being able to inject it subcutaneously, patients now will have an option sublingually to have this absorbed. Apomorphine does not have any bioavailability orally so you can't

swallow apomorphine been a big impediment, and while we look for alternate routes of delivering for this medication.

Apormophine is the only medication that we're aware of, as you've heard from Dr. Kremens, that has the robust efficacy of levodopa, and it's the only medicine that's been demonstrated in trials to have the same UPDRS motor score improvement as levodopa. We saw in the phase 3 program that at 30 minutes post-dose of the apomorphine sublingual strip that patients had a significant improvement in part three motor scores. This was maintained out at the 12-week prespecified primary endpoint.

When we look at patients who use this sublingual strip as a secondary endpoint in the phase 3 program, the time to onset of the on period reemerging after the patient took this in the off state, occurred in some patients within about 10 to 15 minutes and in many patients by 30 minutes. This is really a new medication that we await its approval, hopefully in the short time, so we'll be able to have a third option for our patients to turn back on.

I think when we think about all the root causes and consequences that occur from the emergence of off time, and we begin to look at off time as being due to different types of offs episodes and dose wearing off, morning off, delayed on, dose failures and they all add up to in many patients 4 to 6 hours of off time a day, we have to begin to think about what treatment strategies are best for which of our patients and really individualize therapy, and use I think shared clinical decision-making in cooperating what we know about the medications, how our patients view them and want to do and perhaps including their family and caregivers, their age, their comorbid medical conditions, and really thinking about the efficacy, tolerability, and safety of each of these medications that we have on the horizon to find the best strategy for each patient.

Rajesh Pahwa: Because the bottom line is each patient is different, and like I mentioned earlier, the off symptoms are different, but how they may respond to these on-demand therapies would also be different from that part. One thing we are talking a little bit about early morning akinesia, and the question some people may have is how long is long, because no one has ever said, "This is long."

In my practice, I usually ask a patient—after you take your morning dose, how long does it take to work? You have people all the way from 15 minutes to 2 hours. I'm okay with a patient taking it and getting on within 15 to 30 minutes. To me, anything over that is really too long a time, and that is early-morning akinesia. You did a study in early-morning akinesia…did you come up with the time where you would say a time, or this much would be early morning akinesia?

Stuart Isaacson: Well, we like to think about a delayed on is when a dose of levodopa first thing in the morning or a meal time or some other time takes longer than usual to work for that patient. That would be my definition, but we have to come out with the number for the trial and we chose 45 minutes. But it was interesting. I had a patient who came in, and I asked him about the morning akinesia and he said, "Well, I think it works in like half an hour." I said, "Take this home. We had made up a turning on questionnaire, and we had a 5-minute diary patients could take their levodopa and circle every five minutes when it began to work."

He came back after that week of doing this in the study, he said, "Doc, I had no idea how long it took. I took my medicine. I'd go into the bathroom and shower and dress and shave. I didn't know it took an hour for this to work until I sat down and really measured it." I think patients may not really recognize that it takes a long time and then may be a consequence to doing all these morning activities before your medicine begins to work, you could lose your balance and fall. You could slip in the bathroom or the shower. You can be in the kitchen making breakfast and turn or a freezing of the feet and then fall over. So, I think it's important to try to have these tools to identify how long it takes.

Rajesh Pahwa: Just like when we look at clinical trials, how much is the off time during the day, we ask for 2 to 3 hours, and they have 6 hours. Same thing when we're talking about early-morning akinesia, a patient may be thinking 20 minutes, but it maybe an hour.

Stuart Isaacson: Sometimes they turn on, but it's a suboptimal one with the first dose because enough doesn't get in. We were really surprised in the morning akinesia trial. We found out that about 40% of patients had a dose failure of 1 of those 7 days. I think those failures are probably underrepresented and recognized as well.

Rajesh Pahwa: The other thing comes down to the food. Is some of these other routes, whether it's inhalation or buckle, is another option to consider when we are looking at people in home, food interferes with their levodopa kicking on.

Daniel Kremens: Yeah, or certainly subcutaneous as well, which is currently available. It's really great for patients that these options are emerging, right? Because we have subcutaneous apomorphine available now. For many patients, they're averse to needles so it's a real challenge. I have patients who I think would benefit but are not interested. The fact that we now have inhaled therapy that's available and hopefully sometime in the new future we'll have a sublingual therapy that's available, we can help our patients who are already optimized. Give them another pill, it doesn't work. We've tried that strategy. Hopefully, now we're going to have these other strategies going forward.

Stuart Isaacson: Yeah, we'll have these ways of trying to think about it. If someone can take an oral pill, a half a pill, and turn back on, great. But if it takes too long to work, or

it's too unreliable, or you just don't know if it's going to be now or later and they want more reliability, they can have injection with 95% reliability, they can inhale levodopa, where they don't have to inject themselves. They could put a sublingual strip in where they're able to get apomorphine that protein won't impede, like it could levodopa. We'll have lots of different options to really fine-tune and individualize for our patients.

Rajesh Pahwa: The other thing is when we talk about medications to reduce off time, those are being down in studies where patients have kept a diary and actually looked at reducing off time. With these medications for off episodes or off periods, whatever we call it, we are hoping that when they have an off episode they take it and they turn back on or turn back on faster from that part.

Stuart Isaacson: And keep them on until the next dose.

Rajesh Pahwa: And keep them on for the next dose. It's a different concept that we are talking about than treating off time here.

Stuart Isaacson: Yeah.

Daniel Kremens: Exactly.

Stuart Isaacson: I think it really returns control over the disease or at least off of these motor and non-motor off symptoms back to the patient. They don't have to wonder what's it going to be every time they turn off ,when and if and how will they turn back on. They'll have that control right there in their pocket to be able to use an injection pen, use a sublingual strip, or use an inhaled levodopa to turn back on.

Rajesh Pahwa: They could be on a inhaled levodopa and an apomorphine, whether it's an injection or buckle, correct?

Stuart Isaacson: I think we're going to find there'd be different roles for these medications and patients will identify which is best at which time for what type of off.

Rajesh Pahwa: The other thing we didn't talk about is on and off is not a switch. One is not on and one is off. It's a thing that goes slowly from, or could go faster, from an on state to an off state or an off state to an on state. Some of these on-demand therapies could be at a suboptimal on or a slight off, where you could take it and come back on. If you look at some of the studies, it may not fully reflect that it reduced the off time but it is the off is not as bad or the on is fully optimal.

Daniel Kremens: Right, and ideally a patient would use these therapies as they're starting to turn off so they don't go into that full off state. That would be the hope. This is really going to be the notion to have on demand therapies for patients and

Parkinson's disease. It's really a paradigm shift in the way we treat because we haven't talked about that until now, with the exception of subcutaneous apomorphine, which a fair number patients are just reluctant to use because of the needle, and we kept on talking about, well we're going to do this to try and reduce your off time.

Despite that, patients still had off episodes. I think it's important to point out, even with something like a carbidopa/levodopa intestinal gel pump, people still have off episodes. The fact that it bypasses the gastrointestinal tract doesn't solve the problem entirely. There's protein effect. There's still the blood-brain barrier. So, even with continuous therapies, people still experience off.

Rajesh Pahwa: One other thing we should touch on is that all these therapies are dopaminergic. We have non-dopaminergic medications that are under study that look at adenosine receptors, look at glutamate receptors, and this is an exciting field. All these dopaminergic therapies that we've spoken about, the levodopas and apomorphines and dopamine agonist, all have dopaminergic side effects. Sometimes we have to choose therapies based on tolerability and safety, and trying to avoid things like nausea or an orthostatic hypertension, hallucinations, and compulsive behaviors because sometimes the medications of one class might be better tolerated by an individual patient than another.

Rajesh Pahwa: Sure. The other thing we didn't discuss much was nocturnal akinesia—that because we think patients are going to sleep at night, they're going to be in bed when they wake up in the morning that they have some sleep benefit. I personally have found pretty good luck using levodopa infusion therapy 24 hours, and people using that and trigeminal levodopa suspension and feeling that they are doing much better because their nighttime akinesia is gone. They are sleeping better.

Stuart Isaacson: This is really the new era, talking about different types of off. It's not just the antidotes wearing off anymore. It's not only adding delayed on and dose failures. We can talk about nocturnal akinesia. We can talk about postprandial akinesia, right? Because postprandial akinesia you'd want to use a non-levodopa formulation to avoid any effect in protein. This may be a place where the strip of apomorphine might be useful.

Rajesh Pahwa: We've got to start talking about some optimal ons, nocturnal, trying to actually differentiate these different off episodes and trying to see is one more optimal than the other. When we talk about on-demand we have, like you said, in some people, an oral tablet of carbidopa/levodopa will be good enough. Some people they may need levodopa infusion, some people may, I'm sorry, inhalation, some people may need subcutaneous apomorphine. It is going to come down to as what works the best for an individual patient rather than having a set thing that is going to work. It gives our patient more choices.

Stuart Isaacson: And they should takes these choices. For too long, for a variety of reasons, whether patients are fearful or don't want to try something new or their clinicians don't want to try something new or are afraid of side effects or unaware of the efficacy, they need to try these new things because there's so many options out there now for patients to do better than they're doing now. It would be a shame not to try the new options.

Rajesh Pahwa: Some of these medications for off episodes, someone doesn't even have to take it every day. It may be that they may take it once a day, once a week.

Stuart Isaacson: It's really an on-demand therapy.

Rajesh Pahwa: It's on-demand, and that on-demand doesn't have to be X number of times a day. It can be whatever the frequency could be. That also would make it less likely that they may have side effects because they're not taking the same amount every day. Again, when we are talking about a disease, which is different every day for different patients, that really would make it a little bit more easier for them.

I would like to thank the faculty for participating in a great discussion. Thank you for watching the CME Activity titled Motor Fluctuations in Parkinson Disease: Causes, Consequences, and New Choices for Management. Please take a moment to complete the posttest and evaluation to receive the CME credit. Thank you.