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Novel Therapies to Manage OFF Episodes in Patients with Parkinson's Disease

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Dr. Hauser:
Hello and welcome to this webcast, entitled "Novel Therapies to Manage OFF Episodes in Patients with Parkinson's Disease." I'm Dr. Robert Hauser, Professor of Neurology and Director of the Parkinson's Disease and Movement Disorder Center at the University of South Florida. I'm joined today by my colleague, Dr. Stuart Isaacson. Stuart, please go ahead and introduce yourself.

Dr. Isaacson:
Hi, I'm Stuart Isaacson. I'm the Director of the Parkinson's Disease and Movement Disorders Center in Boca Raton, Florida.

Dr. Hauser:
Before we get started, I want to acknowledge Sunovion Pharmaceuticals and Kewal Kiran for providing independent educational grants to support this CME certified activity. Now let's take a look at our learning objectives for this webcast. Stuart, would you go ahead and review those, please?

Dr. Isaacson:
Sure. Well, upon the conclusion of this activity, hopefully participants should be able to evaluate the benefits and limitations of existing pharmacotherapies for reducing off episodes in patients with Parkinson's Disease. To identify patient scenarios where emerging pharmacotherapies may be beneficial in reducing off episodes in patients with Parkinson's Disease. And finally, to identify common adverse effects associated with emerging pharmacotherapies, as well as strategies for preventing or mitigating them.

Dr. Hauser:
Great, thank you. Well, we're gonna be concentrating on treatments for OFF episodes today. And to start at the basic level, it's very common for clinicians to use Carbidopa-Levodopa, 25/100, three times a day, early in Parkinson's Disease. And initially, this therapy will provide good benefit, that lasts from dose to dose. But over time, many patients find that the medication wears off, and so they have episodes through the day where Parkinson's symptoms re-emerge and they get symptoms such as slowness, stiffness, tremor, that come back, and these are known as OFF episodes. In addition, as time goes on, many patients develop a sensitivity to Levodopa, where they develop additional involuntary movements, often choreiform, twisting/turning movements called dyskinesias, which look like a sensitivity that develops over time. These motor fluctuations emerge in about 50% of Parkinson's Disease patients within five years, and 90% by 10 years, and again, we're gonna concentrate today on treatment of OFF. So, Stuart, can you tell us about motor fluctuations in Parkinson's Disease?

Dr. Isaacson:
Sure, but I think it's important to understand the words that we used. A patient is said to be "ON" when his Parkinson's medications are providing good benefit for his motor symptoms, and "OFF" when the PD medications are not providing good benefit. So an OFF episode is that time when the medicine effect begins to wear off and the benefit is lost until the next dose is taken and begins to work, and the patient is back ON. And if we add up all the OFF episodes throughout the day, we get a measure of OFF time throughout the day. And

these OFF episodes can occur on a temporal relationship to the dosing it could occur at the end of a dose, it can be a delayed onset of a dose, it can occur in relationship to a meal, and it can occur in relationship to a time of day, like a morning OFF or an overnight OFF, or a postprandial OFF. So I think thinking about these different scenarios of when OFF can occur can help us think about some of the novel treatments that are more recently available.

Dr. Hauser:
Yeah, I agree these days a lot of medications are approved for treatment of OFF, and yet in clinical trials, we are often evaluating reduction in OFF time, so we may talk about that as we talk about these individual medications. Well, let me hit on what's happening as time goes on in Parkinson's Disease so people can understand why OFF episodes or OFF time develops in Parkinson's Disease. You know, I think the two basic fundamental issues – one is that Levodopa itself has a short half-life. Levodopa alone has a half-life of about 60 minutes, and here in the U.S. we give it together with Carbidopa, and Levodopa when given with Carbidopa still has a very short half-life of 90 minutes. But despite this, as I mentioned earlier, we give Carbidopa-Levodopa immediate release, three times a day, typically in early disease, something like 7 AM, noon, 5 PM, and early on, patients typically get good benefit for slowing small movement and stiffness, and it lasts those five-hour intervals. So patients say, "Oh, I'm doing well. The medication is lasting from dose to dose." And we think the reason is because Levodopa travels up to the brain, is taken up by remaining dopamine neurons, and is converted to dopamine, and most importantly, stored and slowly released over time, to provide that benefit lasting from dose to dose. But as time goes on, and patients lose more and more dopamine neurons, and that storage and release capacity is diminished, and that's when patients begin to notice, "Hey, my medication is only lasting four and a half hours, and four hours, and three and a half hours." And ultimately they find that their clinical benefit begins to mirror the pharmacokinetics of Levodopa, and ultimately it only lasts about two and a half hours or so. The other thing that happens is that relates to Levodopa being absorbed not in the stomach, but in the small bowel, so when they take oral Carbidopa-Levodopa immediate release, the pills need to go down the esophagus, get past the stomach, and get down into the proximal small bowel where it gets absorbed. And Parkinson's Disease not only affects the brain, it also affects nerves to the GI tract, so many patients with Parkinson's Disease have GI dysmotility, or they have gastroparesis, so it may take longer for these pills to get through the stomach and it also becomes more variable, and so this leads to so-called delayed ON over time, and this also contributes to OFF time or OFF episodes. One other thing that I'll mention is that over time, patients experienced upregulation of adenosine A2A receptors, and also an increase in NMDA glutamate activity, and these two mechanisms worsen PD symptoms and increase OFF time in Parkinson's Disease. Those are all these mechanisms going on in Parkinson's Disease that we clinicians need to have tools to fight, to treat for our patients. Stuart, you wanna talk about the novel PD medications that we have now?

Dr. Isaacson:
Yeah, so based on these mechanisms of how we think about OFF nowadays, we have new medications to try to address some of these mechanisms. For instance, we have new Levodopa formulations and enzymatic inhibitors that may extend the clinical benefit of a dose. We have non-dopaminergic medications for example, that can antagonize adenosine receptors. And we have non-oral medications that can address, perhaps, the GI dysmotility and the delayed gastric emptying of oral medications, and give patients an on-demand, or as needed way of taking medications. So let's go through some of these. Bob, you wanna start with some of these newer Levodopa formulations?

Dr. Hauser:
Yeah, so, let me start with Carbidopa and Levodopa extended release capsules. These capsules contain beads that provide both immediate and extended release pharmacokinetic properties, and following administration, there's an initial peak in plasma Levodopa concentration at about one hour, similar to immediate release Carbidopa-Levodopa. And then the Levodopa concentration is maintained for about 4-5 hours before declining. The manufacturer of Carbidopa and Levodopa extended release capsules did a pivotal trial comparing extended release to immediate release, and what was seen was that Carbidopa and Levodopa extended release reduced OFF time by 1.17 hours compared to immediate release, even as patients dosed with extended release took it 3.6 times a day, compared to 5 times a day for immediate release. In addition, during dose conversion from IR to ER, 5% of patients withdrew, due to adverse events, and 3% withdrew due to lack of efficacy. In the maintenance period on extended release, the most common adverse events were insomnia, nausea and falls, and it is important for clinicians to understand that dosing conversion from IR to ER is not 1:1, so clinicians have to have a dosing conversion strategy when they make this change, and they have to get early feedback to do adjustments. The other newer Levodopa formulation is Carbidopa-Levodopa enteral suspension. This is a suspension of Levodopa that can be infused via pump device. It can be infused up to 16 hours a day, via a portable pump that's connected to a tube, that goes through the abdominal wall into the stomach, and has the tip positioned in the small bowel. This is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's Disease, and provides sort of a continuous delivery of Levodopa to the small bowel, where Levodopa is absorbed. In a pivotal trial, Carbidopa-Levodopa enteral infusion reduced OFF time by about 1.9 hours compared to adjustment of oral Carbidopa-Levodopa immediate release. Overall, approximately 89% of patients did experience device complications in this 12-week study, and these included things like tube dislocations, tube occlusions and pump failures, so clinicians

need to be prepared to handle these kinds of things. Often, GI doctors need to be involved in taking care of these. Additional adverse events included nausea and incision site erythema.

Dr. Isaacson:
Other ways to try to extend the ON time is – and reduce OFF episodes – is to use an enzymatic inhibitor of breaking down dopamine. Essentially, we have selective MAO-B inhibitors that we have used over time, and a novel molecule called safinamide was recently approved, and this is a very high selectivity for MAO-B over MAO-A, and thus doesn't require any dietary modifications. Um, it's thought to increase dopamine levels at the synaptic level perhaps by blocking breakdown of dopamine after it's released at the synapse, and safinamide may also have activity at the glutamatergic system with hope that may have some clinical benefit, although it's unclear how much of a benefit that would be. In the pivotal trials, what we looked at specifically was a reduction in OFF time, and found that safinamide reduced OFF time by approximately one hour over placebo in two pivotal trials – one demonstrating a 1.03 hour reduction, the second pivotal trial about 0.6 hour reduction. Another enzymatic inhibitor is a COMT inhibitor. Bob, a new one has recently been approved.

Dr. Hauser:
That's right. This is opicapone. This is a once-daily COMT inhibitor, and it's approved as an adjunct to Carbidopa-Levodopa in PD patients experiencing OFF episodes. And basically, you can think of this medication as sending more Levodopa up to the brain, over a longer time. The recommended dosage is 50 mg at bedtime, and it should be taken away from food. In a pivotal trial, opicapone 50 mg reduced OFF time by about an hour versus placebo, and 8% of opicapone-treated patients and 6% of placebo-treated patients discontinued due to adverse events.

Dr. Isaacson:
So, those are two enzymatic inhibitors that can extend the On time for a dose of medication for people with Parkinson's Disease. Other mechanisms have been explored as well, including non-dopaminergic medicines. Bob, recently a non-dopaminergic medication that addresses antagonism of the adenosine-A2a receptor was approved.

Dr. Hauser:
Yeah, that's right. This is istradefylline, and as you mentioned, it's a non-dopamine medication. It's an antagonist of the adenosine-A2a receptor. It's approved as an adjunct to Carbidopa-Levodopa in PD patients experiencing OFF episodes. So, in Parkinson's Disease, adenosine acts as a brake on the dopamine system, and adding istradefylline is like helping to release that brake. The recommended dosage is 20 mg orally once daily, and this can be increased to a maximum of 40 mg daily. So, in the label for istradefylline, the FDA reviewed four pivotal trials, and istradefylline reduced OFF time compared to placebo by 0.67 to 1.16 hours. The incidence of patients discontinuing for any reason related to adverse reaction was 5-6% for istradefylline and 5% for placebo. The most common adverse event was dyskinesia, which occurred in 15-17% of patients for instradefylline versus 8% for placebo.

Dr. Isaacson:
Another non-dopaminergic medication recently approved was one that addressed an overactivity of the glutamatergic system an antagonist of the NMDA glutamate receptors that are also overactive in Parkinson's Disease. Using an older medicine, amantadine, in a new, high bedtime extended-release formulation, was studied to see if it could reduce Levodopa-induced dyskinesia, and it met its primary endpoint. What was interesting is it also met a secondary endpoint, which was an improvement in OFF time. And it – what we found overall in the trial is that in patients at baseline, who spent roughly about half of their waking day – approximately eight of their 16 hours awake – in a good ON state, without troublesome dyskinesia or without OFF time. After taking this high bedtime dose of extended-release amantadine 12 weeks later they spent about three-quarters of their day in a good or functional ON time, and only a quarter of the day was made up of troublesome dyskinesia or OFF time. Of course side effects have to be considered when using this type of medication. We've known about side effects from amantadine – hallucinations can occur this is probably the most common side effect that can occur, as well as pedal edema, libido reticularis, as well as anti-colonergic side effects that we've been aware of. But, but these are two non-dopaminergic medications that can be thought of as an adjunct to Levodopa – any formulation of Levodopa – to try to address non-dopaminergic mechanisms of OFF.

Dr. Hauser:
That's great. So, we've covered some new Levodopa formulations, and we covered adjuncts, and now we come to a different kind of category, so-called "on demand" therapies. Can you tell us about those?

Dr. Isaacson:
Well, sure, I think one of the problems we're focused on for a very long time in thinking about treating OFF in Parkinson's Disease is the end-of-dose wearing off, and trying to make a dose last longer. But of course, ON doesn't return until the next dose is taken and begins to work. And there can be a delay in this onset of action, caused by esophageal dysmotility, delayed gastric emptying of medication,

and as Bob, I indicated earlier, Levodopa is absorbed only in the small intestine. It has to exit the stomach in order to be absorbed, and this type of delay can not only be prolonged but can be very variable. And, studies have demonstrated large variability, not only between patients, but on individual patients – at different doses and different days. One dose may work quickly, another dose may be delayed by 20, 40, 60 or more minutes, and once it begins to work, it may work optimally or sub-optimally. And a lot of this problem has to do with delivery to the intestine, and also by problems with absorption in the intestine, caused by protein and – and perhaps bacteria. Another formulation of Levodopa is an orally inhaled Levodopa, and this way of delivering Levodopa bypasses the delayed gastric emptying that can occur due to gastroparesis, and can deliver Levodopa directly through the alveoli into the plasma, giving a very rapid onset. And in studies that were done to evaluate orally-inhaled Levodopa, we found that onset of action within 10 minutes with a primary endpoint significantly different than placebo at 30 minutes, and patients remaining ON 60 minutes after inhaling Levodopa. This inhaled Levodopa has to be taken when patients begin to note the recurrence of symptoms of OFF, so that they can then take this in and come back onto ON, bridging the gap between an ON episode until the next dose can be taken and begin to work as well. Subcutaneously delivered apomorphine, a dopamine agonist that has a robust Levodopa-like response, has been used as an injection for patients who are in an OFF state, and want to rapidly and reliably return to an ON state. Injecting subcutaneous apomorphine works very rapidly and, in pivotal trials, demonstrated a 20-minute, so significant difference from placebo. This type of medication though, can lead, perhaps due to its rapid increase, to adverse effects that often dopaminergic and sometimes dose-limiting, including sleepiness nausea low blood pressure or dyskinesia. Nonetheless, this has been a half-helpful adjunct, to really focus attention that patients who are in an OFF episode can return to an ON, bypassing orally swallowed Levodopa. And together with orally inhaled Levodopa are two options that can be used by patients on demand, as needed, when they're entering or in an OFF episode to return to ON. More recently, a new formulation of apomorphine, that's delivered sublingually into the mucosa beneath the tongue, was approved by the FDA. This apomorphine sublingual strip contains apomorphine in a buffered formulation in a strip that goes beneath the tongue when patients are in an OFF episode, and gets absorbed through the mucosa there, entering rapidly the plasma circulation into the brain to return a patient to an ON state. In the pivotal trials that were identified that apomorphine sublingual has an onset that can be demonstrated within 15 minutes in many patients with an – full on occurring within 30 minutes, and persisting for the 60 minutes. Adverse reactions that are seen were typical of what's known for dopaminergic medications, including apomorphine, and included most commonly nausea as well as reactions that can occur in the oral or pharyngeal mucosa – redness or swelling or ulcerations, and patients should be evaluated for this. Sleepiness and dizziness can occur but weren't as common as we might have expected from this rapid onset medication. So I think that all these new novel medications that have different, non-oral deliveries, have non-dopaminergic mechanisms, really expand our armamentarium in addressing OFF episodes in our patients, as they progress over the years and decades of Parkinson's Disease. And it might be helpful to think about some of the scenarios, where we might consider and contrast some of these medications that are newly available.

Dr. Hauser:
Yeah, that's great. So let's take a look at some scenarios. The first scenario here is patient is on Carbidopa-Levodopa 25/100 QID. Of course, this is the immediate release. He is wearing off a half an hour before each dose and the next dose takes about half an hour to kick in. What do you think about here?

Dr. Isaacson:
Well, here we have sort of a mixed bag as well, of patients. They're not quite making it to the next dose, and that dose takes a bit of time. Perhaps we could use an on-demand therapy when patients enter OFF here, and then they could sort of bridge that gap until the next dose works. We could switch to an extended-release and keep it at QID, and then that was probably help a lot of problems, and often we'll think about doing both, giving a longer acting formulation or giving the same dose of Carbidopa-Levodopa with an enzymatic inhibitor, or a non-dopaminergic medication, and also giving an on-demand medication so when patients still have an OFF episode, they can have that ability to have a, be empowered to turn back ON.

Dr. Hauser:
Yeah, I agree. I think this was sort of the classic fluctuator. We have a lot of options here.

Dr. Isaacson:
Sure is.

Dr. Hauser:
Open to us. So let's move on. Carbidopa-Levodopa immediate release, 25/100, one and a half QID, plus a bedtime dose. This person notes slight dyskinesia at times during the day, and he is a little different now. He reports one or two OFF periods most days, but not always at the same time of day, so it's kind of a little unpredictable for this patient. What d'ya say here?

Dr. Isaacson:
So this is a common patient as well, and I think one of the things I think about is either we have to go down a road where we're gonna

add something, increase perhaps dyskinesia, then have to lower Levodopa. Then have this multi-step process, and we can do that with an enzymatic inhibitor, a non-dopaminergic medication added on. This might be a good patient to think about an extended release formulation of Levodopa that we can more finely titrate, and try to have the right conversion, and then find the right adjustment throughout the day. It also might be a patient tends to unpredictable or unexpected OFF, so they're not the same time every day to keep what we're doing if the dyskinesias are slight. We could always add a medication to lower dyskinesia and help OFF, like the bedtime extended release version of amantadine. Or use an on-demand therapy here, and have a patient carry around a strip or inhaler or injection pen, and be able to, when they go into an OFF episode, have the ability to turn back ON.

Dr. Hauser:
Yeah, that's what I think. I think most adjuncts, if you add on, you might increase dyskinesia. This was sort of the perfect scenario for an on-demand therapy, that you're just treating that period when they go into an OFF state. So I would definitely think about an on-demand therapy there. OK, our last scenario - Carbidopa-Levodopa immediate release, one and a half tablets QID plus a bedtime dose. This person says it – reports that it often takes an hour or more for his first Levodopa dose of the day to kick in, so he is really complaining of morning OFF. What d'ya think here?

Dr. Isaacson:
Well, so many patients do okay throughout the day. He's tolerating the Carbidopa-Levodopa. We know that once you exceed 600-800 mg a day, at least in several of the clinical trials there tends to be perhaps more dyskinesia, especially if they have pre-existing dyskinesia. So if, I think, we can find a temporal pattern that is mainly first thing in the morning, until that first dose begins to work, we can think about delayed gastric emptying of the first dose. This is a great place to think about a medication that can take someone from an OFF to an ON – an apomorphine can give a robust Levodopa ON and it can do that without having GI dysmotility impede the onset of Levodopa. And this is where the apomorphine injection or the new formulation of the sublingual apomorphine strip would be useful to try to help patients turn ON, and then the oral medicine might be able to keep them ON. Of course, if they had another OFF episode throughout the day, on certain days, they could always use the sublingual apomorphine strip or the injection again.

Dr. Hauser:
Yeah, I completely agree. So, our time is up here. Let me just review some summaries and key takeaways. We mentioned that there are a number of new medications available now to treat OFF episodes. Selecting the right strategy or medication requires considerations of how the treatment matches the clinical problem. Add-on therapies generally reduce OFF time by about an hour per day and are relatively easy to use. On-demand therapies are particularly useful for unexpected OFFs, delayed ONs, OFFs associated with meals, and morning OFFs. Amantadine extended release may be useful in patients who also have dyskinesia. Carbidopa-Levodopa extended release reduces OFF time and allows less frequent dosing, but knowledge of conversion and adjustment by the clinician is required. Carbidopa-Levodopa enteral suspension is reserved for patients who cannot be adequately controlled on less invasive regimens. So, thank you for your time and attention, and thank you Dr. Isaacson for all of your experience and wise comments.

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