Transcript

Welcome and Introductions

Rebecca Gilbert, MD, PhD

[Slide 1] Thank you, and welcome everyone. Thanks so much for joining us today. **[Slide 2]** My name is Rebecca Gilbert, and I'm APDA's Vice President and Chief Scientific Officer. I'm pleased to welcome you to this web/teleconference education program designed for people with Parkinson's disease, care partners, family members and healthcare providers. I'd like to thank Kyowa Kirin for funding this important program and acknowledge their appreciation for the critical need to provide educational programs like this one to people impacted by Parkinson's disease.

During this time of uncertainty, we know that you may still have concerns regarding your Parkinson's treatment and identifying ways to continue to live your best life with PD. American Parkinson Disease Association, or APDA for short, is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than one million people with Parkinson's disease fight this disease as best they can.

And now for our program. **[Slide 3]** We welcome our distinguished presenter today, Dr. Melita Petrossian, Director of the Pacific Movement Disorders Center, Neurology, at the Pacific Neuroscience Institute in Santa Monica, California. She is here to share the latest information on innovations in OFF therapy.

After the presentation, we'll open the program for questions from both our telephone and web participants. At any time during the program, you can submit your question using the Question & Answer tab in the lower left-hand window on your screen. We encourage everyone on the line to complete the evaluation after the program because your feedback is instrumental in helping us plan for future educational offerings, including teleconferences like this and other programs.

It is my pleasure to turn the presentation over to Dr. Petrossian.

Presentation

Melita Petrossian, MD

[Slide 4] Thank you so much for the warm introduction, Dr. Gilbert. Yes, I'm really excited to discuss this topic with the audience today. I think that it's really been amazing how much advances have been made recently. And it does get a little bit nitty gritty and into the weeds, so I hope that I can take you all on this journey with me together.

Starting off, I don't have any financial disclosures that are relevant to this talk.

[Slide 5] I'm going to start by discussing first what we're talking about when we refer to the use of the term OFF time by discussing what the motor manifestations are of Parkinson's disease. This may be familiar to most of you, but just as a review, when we talk about motor symptoms, we're referring to mainly slowness, stiffness, rest tremor and postural instability. Specifically, slowness is known medically as bradykinesia, and it is the most characteristic hallmark of Parkinson's disease and may manifest as slowness in activities of daily living, movement, a reaction time, impairment, or breakdown of fine motor movement, a soft, hoarse or monotonic voice, reduced facial expressivity, reduction of arm swing and reduced stride length. Handwriting may become small as well. Rigidity may be experienced by the patient as stiffness but is detected on exam as increased resistance throughout the range of movement and physicians may also use the term cogwheeling if there's tremor with the rigidity.

Rest tremor may begin in a finger or spread to the hand, may occur in the leg. Some patients may experience an internal tremor. Classically, we describe a rest tremor as that which is present when the limb is completely supported by gravity, although many patients with Parkinson's also have an action tremor or a postural tremor as well. Interestingly, about 30% of people with Parkinson's never manifest tremor so it's not a universal symptom.

And postural instability is a common motor symptom. Can cause falls and can result in a change in the gait mechanics such that patients are leaning forward trying to walk quickly to follow their center of gravity and thus develop further gait instability.

Freezing refers to a sudden transient inability to move and is most commonly experienced with freezing of gait where patients may use the term "stutter steps" because they feel that they just can't get their feet started to get going; but once they're going, they feel that they can move okay.

I wanted to also emphasize that motor symptoms of Parkinson's are separate from nonmotor symptoms of Parkinson's, which can include mood symptoms, cognitive complaints and difficulty with bladder control or constipation, among other symptoms. But for the purposes of this talk, we'll be mainly discussing motor manifestations.

[Slide 6] Motor manifestations occur mainly because of a loss of a neurotransmitter or brain chemical known as dopamine and, therefore, as we think about symptomatic treatment, meaning how we treat the symptoms of Parkinson's disease, our mainstay for a very long time has just been how do we boost the activity of dopamine or, put another way, how do we replete the activity of dopamine that's otherwise been reduced? And the oldest and sort of gold standard, most typical medication is levodopa, which is a precursor to dopamine, sometimes known as L-dopa, and it is typically given with a medication that enhances its ability to get into the brain called carbidopa. In other countries, it's other medications, but the main one in the United States is carbidopa given with the levodopa. The levodopa, however, is the most important aspect of the medication. It's the part that gets converted into dopamine in the brain.

Other brand names for carbidopa-levodopa include Sinemet®, and newer ones include Stalevo®, Rytary™ and now Inbrija®, which we'll talk about in more detail. Sometimes, if you hear me today use the term Sinemet, it's because that's got three syllables instead of eight, but the proper terminology should be carbidopa-levodopa.

Dopamine then within the brain acts on what are called dopamine receptors. And the analogy I like to give here is dopamine is like the key and dopamine receptors are like a lock, so dopamine agonists on the bottom right of the screen there are medications that are like a very similar key that works on the same lock as dopamine. They include pramipexole, ropinirole, rotigotine and apomorphine, and, again, we'll go into more detail about these medications. So, the way they work is a little bit different from natural dopamine or levodopa-derived dopamine, but we'll get into that as well.

Dopamine then gets metabolized and so that means it gets recycled, and the recycled elements – we call those metabolites – those then get recreated as dopamine. So, the process of metabolizing or breaking down dopamine are using enzymes known as MAO-B (monoamine oxidase B) and COMT (catechol-O-methyl transferase) which works on levodopa. And so, we can actually reduce the activity of these enzymes thereby reducing the breakdown or metabolism of dopamine or levodopa and boost the activity of dopamine. And the MAO-B inhibitors include rasagiline, selegiline and safinamide, and the COMT inhibitors include entacapone and opicapone. And the concept of sort of going through all these medications is just to give you a map of where everything is in the process, but we'll go into sort of the pros and cons and the nuances between these medication groups.

[Slide 7] So, typically, many patients, or I should say most patients with Parkinson's eventually get started on carbidopa-levodopa and many patients experience an early stage where the medication is working relatively well. They're taking it typically three times a day and with each dose, they find that their symptoms are well controlled. Again, the motor symptoms, meaning they feel like they're moving better, their tremor is reduced, they're walking a bit more easily, they're less stiff, less slow. And through the changes in the dosing levels, or that is to say the brain levels of dopamine with each dose, they still have enough what we call basal dopamine to help them feel well controlled during the day even if they're late for their medications, for example. Not that we recommend being late on medications, but it's very common in an earlier stage for patients to still feel fine even after six or seven hours after they've taken their medication.

As the disease progresses, with time, we see many, but not all, patients develop what we call motor complications. And this includes two really important and really, sometimes disabling elements, one of which is called OFF time. OFF refers to when the medication has worn off. Patients with motor OFF symptoms experience stiffness, slowness, recurrence of tremor, essentially a recurrence of the symptoms of Parkinson's they had before they started taking levodopa and this can result in difficulty with getting around, driving, walking, predicting when they can be where they need to be, etc. And in the same analogy of the three doses, a patient may experience a very short period of time in the what we call ON stage, which is when their symptoms are well controlled, and then they may have what is sort of simplistically thought of as an overshoot where they are ON, but they have what are called dyskinesias. Dyskinesias is Greek. Dys means abnormal, kinesia means movement, so dyskinesias refer to abnormal involuntary movements. And these can be very mild. Can manifest with just a mild head movement or lip or finger movement only with activation of other body parts. They can be minimally experienced by the patient but noticed by the family member. Or they can be bothersome, noticeable to the patient but only about 20% of people with dyskinesias are actually describing them as bothersome or disabling. So, dyskinesias are much more common than the subset where they're really bothersome to them.

So, it's relatively common in certain stages of Parkinson's to experience a day where they're swinging wildly between being OFF or dealing with dyskinesias and not enough time spent in the well-controlled period.

[Slide 8] And this can occur because either the medication has worn off too quickly, has not kicked in quickly enough or sometimes a dose just doesn't kick in at all, and we call that no ON. Some patients also experience nonmotor fluctuations where they experience with their OFF time, in addition to the motor or physical symptoms, they may feel anxious, fatigue, cognitively off or nauseous or experience sensory symptoms such as pain. And this is a more recent understanding of what we call OFF symptoms, so, this is something that can also be relevant.

[Slide 9] How do we evaluate for motor fluctuations? Well, what we often do clinically is we just ask the patient and/or the family member, "How is the medication doing? Is it lasting long enough? Does each dose last you to the next one?" In research settings, we will often use a formal Parkinson's disease motor diary, which might be a little bit hard to read here, but this is half of the diary. You can see that for each 30-minute block, the participant has to decide whether they were mostly ON, ON with troublesome dyskinesias, mostly OFF or mostly asleep. And, of course, it can be hard to do that, especially if they don't do it on an every 30-minute basis and they try to remember, you know, what was I feeling like an hour and a half ago? I don't know. So, there's obviously, some limitations with the use of this motor diary. But it breaks 24 hours down into 30-minute blocks, and the participant has to make one choice for each of those blocks. And then we sort of have a way of calculating OFF time and ON time.

More recently, there's been growth in the wearable sensor field, especially with Parkinson's disease. And there's one specific one I'll discuss. There are others, of course, but the one that I'm most familiar with is called the Parkinson Kinetograph, or PKG for short. And it has its benefit over the motor diary of not having to rely on the patient's recall of the event, but it is a little bit limited in being really just a wrist device and, therefore, doing a very good job of detecting tremor, slowness, meaning

bradykinesia or dyskinesias but mainly if it's relevant to that arm. So, for example, if somebody has dyskinesias in their lip or their head, it may not necessarily show up on their dyskinesia score.

What you see on the top picture there is an example of a person wearing the watch, or PKG I should say. It does have a watch element to it, and it will also remind the participant to take their medication. That gets programmed by the physicians ordering the PKG. So, then the patient, what she's doing in this picture, she's swiping across the screen to acknowledge that she took her medication. So, the report that the physician gets has these little red dots there that are the time that she acknowledged taking her medication. And then the green zones are where we want patients to be, where patients want to be I should say. So, the bradykinesia score we want it to be higher to represent better and smoother movements. So, you can see when she takes her medication, she gets better and then she wears off; she gets better and then she wears off. But also, when she takes her medications, she's getting some dyskinesias. Again, we want that to be in the green zone, meaning minimal dyskinesias. She's getting some peak dose dyskinesias.

[Slide 10] So, that's sort of what is OFF time and how we measure it or how we monitor for it.

Now I'm going to move on to what can we do? So, the oldest way to manage OFF time was just take your medications more frequently. You were taking your medications three times a day, now take them four times a day. So, four times would become five times, five times would become six times and it gets a little bit cumbersome to the patient to take a medication every two hours. And also, again, as I mentioned, sometimes the medication may just not kick in at all, which can be very frustrating to the patient because sometimes they don't have a clear reason as to why it's not working or it's not lasting as long. So, they've developed longer acting levodopa. The oldest one of this is controlled-release carbidopa-levodopa, which comes as the 25/100 and 50/200 doses, but there's actually been some doubt raised as to whether controlled-release carbidopa-levodopa can, in fact, reduce OFF time because there is some variability in the absorption of the CR forms.

Therefore, a more recent development is the extended-release form of Rytary, which has different dosing than the traditional immediate-release carbidopa-levodopa. They come as 95s, 145s, 195s and 245s, and those dose numbers refer to the amount of levodopa. What's interesting is that it includes microbeads of both an immediate- and an extended-release component and, therefore, combining them together you get a reasonably quick onset and a longer-lasting effect compared to immediate release alone. And because they're microbeads, if the capsules are too large for the patient to swallow, they can be opened and sprinkled onto applesauce.

It's very important to know that these numbers, the 95, etc., are not dose equivalent with immediate-release carbidopa-levodopa and, therefore, most people require a conversion typically around 2:1, sometimes 1:5, 1, meaning that if somebody is taking 100 milligrams like carbidopa-levodopa 25/100 and then they take the 95, they would probably experience less effectivity. They would probably feel like it was only half of their dose. And typically, we would probably convert them to a 195 for each dose. But that can differ for the patient, so that takes a little bit of changing dosing at the beginning to verify what dose the patient actually needs.

[Slide 11] Then there's even longer-acting levodopa, which is available as Duopa™, which is a levodopa intestinal gel infusion. This is actually more popular in Europe than has been used in the

United States but has been available in the United States for several years now and has been shown to clearly reduce OFF time by about two hours more than placebo does. And the way it works is there is a tube that does require placement into the intestine, but it's not a traditional feeding tube in the sense that it's not being used for tube feeds. It doesn't require any change in the diet per se, it's just being used as a portal to get medication directly into the small intestine where it's absorbed rather than having to go through the oral, then the esophagus and stomach, etc. And because it's a continuous infusion during the day, it does result in a smoother concentration over the course of the day. It is the same carbidopa-levodopa as immediate release. It's just that it's lasting longer.

Complications can include, of course, tube malfunction. The tube could get pulled out. Patients may develop a vitamin deficiency, neuropathy so, therefore, physicians and patients need to know to monitor for this and adjust accordingly. And it can sometimes result in stomach or gut dysfunction, but this usually is occurring in the first two weeks and many patients are able to tolerate it afterwards.

It is FDA approved for a 16-hour administration, but it has also been studied for 24-hour infusions as well. And it does require the patient to carry around a pump, which the pictures on the bottom right show, one person is wearing it in a fanny pack, another person is wearing it in a vest. But it does require a couple of buttons to be pressed and the tube to get flushed on an every morning basis.

[Slide 12] Moving on to inhalable levodopa. So, because we know that many patients with Parkinson's have difficulty with a slowed gut or difficulty with absorption through the gut, the thought was why not see how the lungs can take levodopa. Now this is levodopa alone. This does not have any carbidopa with it. And inhalable levodopa or Inbrija, which is the brand name, is not a daily substitute for the oral carbidopa-levodopa. It's what we call a rescue treatment, or I like to call it a bridge. Let's say the dose has worn off too quickly and they're not due for their oral medication for another hour or so but they are out and about, and they need to be ON so that they can drive home or what have you. The patient can use the inhaled levodopa and have a faster time of onset typically around 15 to sometimes 30 minutes of onset, and it can last about an hour or sometimes longer. It has been FDA approved for use for up to five times per day, but in the clinical trial and in my clinical experience, most patients are using it less frequently than that. Sometimes they only use it once or twice a week when they need it for their unpredictable or sporadic OFF periods. But there are some who use it every morning or every day.

There, of course, can be cough associated with it or an upper respiratory infection, as well as a change in the sputum color. But by taking a slower breath, drinking water before and after, the cough can be mitigated, and it just takes a little bit of trial of the patient to work through how to use the inhaler. The inhaler comes with capsules and each particular dose is two capsules one after the other. And there's a nice big sign on that that says, "Do not swallow capsules."

The kind of con of using a rescue drug is this isn't a preventative. This isn't something that's going to, in the long run, prevent people from having OFF time in their regimen. It's, really for dealing with OFF time when it occurs.

[Slide 13] Future options for levodopa delivery include other nonoral formulations, such as subcutaneous levodopa. There are two medications that are in phase III trials now. One of them is made by Neuroderm and the other one is made by AbbVie, and these are patch/pump forms of carbidopa-levodopa. The way they work is going to be similar to an insulin pump where the insulin gets delivered into the subcutaneous tissue and, therefore, won't require the tubing that the Duopa does but just a smaller tube into the skin and then a pump that is programmed on a daily basis. So, this is looking promising but, of course, not yet available, and still just in phase 3 trials.

[Slide 14] Also thought to be promising is an accordion pill technology, which the folded shape of the accordion is thought to help make the medication last longer in the GI (gastrointestinal) tract. However, a recent phase III trial did not meet the primary endpoint of improving OFF time though a secondary analysis found higher doses were more effective and, therefore, a new phase III trial is being planned for this technology.

[Slide 15] Moving away from just levodopa alone, we're now going to talk about what is often given with levodopa as an adjunct. Again, going back to that image that I showed earlier of how to reduce metabolism, COMT inhibitors reduce the breakdown of levodopa and, therefore, they only work when given with levodopa. They don't do anything on their own.

One of the older ones, a more traditional, is known as entacapone, also known as Comtan®. When given as a combination of carbidopa-levodopa and entacapone, it's known as Stalevo®, and it's 200 milligrams per dose given with each dose. And the newer formulation is opicapone, also known as Ongentys®, which has the benefit of only needing to be a once-a-day dosing, again, with those daily multiple doses of carbidopa-levodopa. So, it can improve ON time by about two hours. And, in fact, Ongentys in some studies was shown to be even more effective than entacapone, the older drug in the class, and has been shown to reduce early morning OFF time. However, these two medications can exacerbate dyskinesias and other levodopa side effects, such as low blood pressure, hallucinations, and impulse control disorder. They can cause somnolence and constipation. Entacapone but not opicapone can cause a discoloration of the urine, which isn't really a major issue but just patients need to be aware of it, so they're not alarmed when that happens. And then cost can be an issue, of course, as with any of these new medications. I should say cost is an issue with Rytary in some cases as well.

[Slide 16] MAO-B inhibitors some of the medications in this class are older, some are newer. Selegiline is an older one and then came rasagiline and then now most recently safinamide was developed. These reduce the metabolism or breakdown of the brain's natural dopamine as well as dopamine that's derived from levodopa. And they can also reduce OFF time by one and a half to two hours. These tend to be milder medications, not so many side effects per se, but they can interact with medications including antidepressants, over-the-counter medications, and supplements, so that needs to be cautioned for. MAO-B inhibitors can cause nausea, lightheadedness, insomnia, anxiety and dyskinesias as well.

[Slide 17] Moving on to dopamine agonists, as I said earlier, these act on the same receptors as natural dopamine. Pramipexol, ropinirole are often used separate from or prior to the use of levodopa, but the Neupro® patch, which is rotigotine, has been shown to reduce OFF time by about two and a

half hours. On its own it's less effective than levodopa, but as an adjust, it can improve OFF time. Some patients can experience somnolence, leg swelling and hallucinations as well as impulse control disorders, such as compulsive overeating, gambling, spending and sexual behaviors. In addition, with the patch form, there are, of course, skin side effects that can occur and there are potential withdrawal syndromes if someone stops taking the medication. We'll discuss apomorphine in the next slide.

[Slide 18] Apomorphine has nothing to do with morphine. The terminology is just sort of a similar word, but there's no relation to opiates at all. So, apomorphine is one of the most potent dopamine agonists. It works very well. However, it is not really stable as an oral medication and, therefore, has been developed as an older medication called Apokyn®, which was a subcutaneous injection of apomorphine. Sort of the original rescue medication for OFF time from several, many years ago I should say. And so, this is the same medication, the apomorphine, as was available in the Apokyn injection but now it's available as a sublingual film, meaning it goes under the tongue. And what that refers to in terms of a film is that you don't swallow it. You don't want it to go down into the GI tract. You want it to dissolve with the saliva to be absorbed through the blood vessels underneath the tongue.

So, this works really well, again, for OFF time which is unpredictable or sporadic. Kicks in within 30 minutes. Lasts an hour or two. Again, just as with the Apokyn before it and the Inbrija, the inhaled levodopa, as we discussed, these are not substitutes for the oral carbidopa-levodopa regimen. These are adjuncts to them for managing or bridging or rescuing from OFF time.

Kynmobi™, the sublingual apomorphine can cause nausea, so patients need to premedicate with antinausea medications three days prior to starting. It can cause oral swelling and redness because of if it's irritating the sublingual film, as well as other dopamine agonist symptoms such as lightheadedness, somnolence, and OFF time. And, again, as with other rescue meds, this isn't a preventative for OFF time, this is just a management or a rescue.

[Slide 19] Moving on away from dopamine for a moment, we'll talk about adenosine A2A antagonists, namely istradefylline known as Nourianz®. Some of you may know this as, oh, the medication that came from Japan. Yes, it was approved in Japan prior to coming to the United States. And what's interesting here is that, and this is a little bit of a speculation, I should say, in terms of mechanism of action, but the way I like to explain it is that in our motor circuitry we have a stop and a go. And the go pathway, let's just sort of, just for the sake of simplicity, say that the majority of what gets you going is your dopamine. So, that's what's called direct pathway; it promotes movement. So, if we don't have enough dopamine, we don't have enough go.

So, what we've been doing for these last several slides is talk about how do we give you more dopamine to get you more go. But more recently people have sort of turned away from dopamine and looked at well what about the indirect pathway which inhibits movement? That is the stop pathway. So, we found that the adenosine A2A receptors are very prevalent in the indirect pathway. So, if we can blunt or reduce the impact of adenosine A2A, we can stop the stop if you will; or we can lift the stop sign. So rather than just giving you more go, we can stop the stop, meaning that you would be go, go, go.

So, again, an antagonist is a terminology referring to a chemical that works against a particular receptor, in this case adenosine A2A. So, istradefylline can reduce OFF time, 1.2 hours compared to placebo. That's not total; that's compared to placebo, with just once-a-day dosing.

In my anecdotal experience, I found that some percentage of our patients responded really, really well to this medication, others not so much. But those who respond well sometimes develop dyskinesias or hallucinations which might be mitigated by reducing the levodopa dose; but this is completely not in the label. This is just with my personal experience and my kind of conceptualization of that sort of balancing between stop and go. And therefore, I think this is a medication that we're hopefully going to see more use of in the future. However again, as with many of our new medications, insurance coverage can sometimes be an issue.

[Slide 20] So, we've talked about how do we manage OFF time and, unfortunately, with all of our newer medications for OFF time that we have, we haven't really made as much progress, I think, in managing dyskinesias. The traditional way of managing dyskinesias is reducing the levodopa dose and/or frequency, but of course that often results in more OFF time. And so, when patients are stuck between a rock and a hard place, between OFF time and dyskinesias, we'll often add in amantadine, which is an NMDA (N-methyl-D-aspartate) receptor antagonist. It works differently. It might sort of potentiate dopamine if you will, but it also has other affects as well. So, it can improve the efficacy of levodopa but can reduce dyskinesias.

The problem is that some patients can't tolerate amantadine, and they can have insomnia, hallucinations, or edema. And the two new medications that got approved earlier in this past few years are both long-acting forms of amantadine, namely Gocovri® and Osmolex®. Gocovri also has the added benefit of a more recent FDA (Food and Drug Administration) labeling showing that it can, indeed, improve OFF time and, again, with improvement of dyskinesias and certainly without adding or exacerbating dyskinesias.

So, for those who can tolerate amantadine, these two newer medications are promising to them. But obviously, we'd like to see more options for our patients. So, there are some clinical trials being done to try to identify newer agents to try to improve dyskinesias, and often patients with dyskinesias can turn to advanced treatment options such as deep brain stimulation, which is, of course, also being used to treat patients with OFF time as well.

[Slide 21] I do want to take a few moments to talk about, we've talked about like these really fancy, expensive, brand new medications which are, of course, very promising, and very important. But sometimes it's the simple solution that's important. So, sometimes when patient comes to see me and says, "I'm having OFF time," and then I review with them, "Well, are you taking your medications on an empty stomach? Are you taking it consistently? Are you exercising, etc.?" sometimes it's the simple things, and it's not the complex issues that we need to discuss.

So, it's really important for people to take medications on an empty stomach and to take them at consistent times every day. But it's not easy to do that, so here I'm quoting my nurse practitioner who likes to say it's simple but not easy because we're humans. We're not robots. So, we have to use what we can to help remember to take our medications on time. Medication sets, which are filled once a week, can be helpful to verify whether the medication has or hasn't been taken. They can be taken

out. The day can be taken out of the week so that you can take it with you, and I always recommend to my patients, "Make sure you take your levodopa with you. Wherever you're going, even if you're just going to the market, take your medications with you because you don't know."

I have so many patients that came to see me, "Oh, I didn't bring my medication with me." So, I use it as an opportunity for learning. Some patients will use their smartphone or medication watches or smartwatches to remind them, which can be really helpful. But neither of these will necessarily verify that the medication has been taken, and often the patient will silence the alert without taking the medication.

For patients who are having a great deal of difficulty or when a family member or caregiver has to be certain that the patient's taking their medications, there are these devices that will dispense the medication. And then if the medication isn't pulled out of the dispenser, the family member gets a text message or an alert saying that such and such medication hasn't been taken.

And again, why is it important to take medications on time? For those who don't yet have OFF time, there is some reason to believe that taking meds on time, even in early stages of Parkinson's, may help reduce the risk of subsequently developing dyskinesias and reduce the risk of ON/OFF fluctuations, although that's a little bit less clear.

[Slide 22] And again, as I said before, when people are like, "Well, I don't know why it's not lasting as long," I'm like, "Well, are you exercising? How are you sleeping? Let's talk about constipation. Let's talk about your water intake, your stress levels, etc." And when I say stress, I don't like to have people think of oh well, I'm stressed therefore my Parkinson's isn't going to be as well-managed. I want people to think about what techniques, what tools do they have to manage their stress. So, it's not about, what's happening around them. It's also about how are they managing those issues and, therefore, thinking about mindful awareness, mindset, etc. Sometimes people need counseling, etc.

[Slide 23] So, I do want to spend just a little bit of time on the gut/brain connection and, again, apologies for getting a little bit into the weeds here. But what's really, really fascinating is in the past few years, we've discovered something sort of, I would say brand new compared to when I was in training and in med school, which is that gut bacteria themselves can actually inhibit the action of levodopa. So sometimes when patients are like, "I'm doing everything. I'm exercising. I'm taking my meds on time on an empty stomach; why is it not kicking in or why does it not last as long this day compared to the other day?" I wonder about whether their gut bacteria levels are playing a role. And so, this is still again an area of research in terms of how does that translate to action. But what's interesting is that what can happen is that the enzymes of gut bacteria can themselves inhibit levodopa action.

This is a review here, this slide, where the gray line is the blood-brain barrier; and levodopa has to cross from the gut into the brain in order to be active, in order to have its positive effects of reduced tremor, slowness, and stiffness. However, when it gets broken down by an enzyme called DOPA decarboxylase in the periphery and it gets converted into dopamine- I shouldn't say broken down. I should say when it gets converted into dopamine in the periphery, before it makes it into the brain, that can cause nausea and light-headedness.

So, when they discovered this, they added an inhibitor of DOPA (dihydroxyphenylalanine) decarboxylase, in our case carbidopa; and in fact, fun fact of history, that's where they came up with the term Sinemet, because it was sort of a play on the Latin sine, meaning without and emet for emesis meaning nausea. So before when it was just levodopa being administered orally, people were developing a lot of nausea and vomiting. And when they added carbidopa to get it into the brain, there was much less nausea and vomiting and therefore sine-emet, Sinemet.

[Slide 24] So, then we have these other enzymes such as the PLP (pyridoxal-5′-phosphate)-dependent decarboxylase that carbidopa has no effect on. And therefore, if the levodopa, because of these bacterial enzymes, is being converted into dopamine outside the gut, it means that the effective level in the brain is going to be lower; and the patient may experience OFF time.

[Slide 25] So, it has to do with specific bacteria, some that have been identified are *Enterococcus faecalis* and *Eggerthella lenta* as well as specific enzymes from those specific enzymes, specifically tyrosine decarboxylase. And even there's been identification of specific genes from those bacteria that code for these specific enzymes. So, this is really promising in terms of moving forward, in terms of how do we identify either the bacteria, the enzyme, or even the genes to then understand whether somebody's having difficulty with their levodopa metabolism.

[Slide 26] What's also interesting is that as the years go by, as well as with prolonged use of levodopa, there's an association with more of these quote/unquote "bad bacteria," the *tdc* (tryptophan decarboxylase) gene-carrying bacteria. And so, then if they're having ultra-levels of gut dopamine, there's a theory that that's associated with impaired gut motility, small intestinal bacterial overgrowth, worsening of motor fluctuations, higher doses, and then presumptively that might be associated with then having more abnormal bacteria or the sort of bad bacteria resulting in a vicious cycle.

So, what's interesting is that this may result in us eventually identifying biomarkers for proper levodopa dosing as well as potentially use of probiotics or prebiotics to shift the gut bacterial profile to reduce bacteria that contain these enzymes. However, I would caution because as of right now, we don't have specific probiotics that have been shown to help for properly balancing the gut microbiome in people with Parkinson's. And in fact, some probiotics may contain those quote/unquote "bad bacteria" or those *tdc* gene-carrying bacteria.

[Slide 27] And so, really this was a fascinating research development in terms of understanding that bacterial decarboxylase is not being inhibited by carbidopa, but there has been an amino acid that has been identified that could do this. Now this was in mice, so this may be a potential treatment in the future.

[Slide 28] And so, what does this mean for Parkinson's patients? So as gut symptoms continue to progress, the gut can slow down, impacting the onset of action of levodopa. Again, as I said before, levodopa should be taken on an empty stomach; and constipation should be treated aggressively. So, that's sort of where we're at now, but I think in the future we'll see kind of more interesting manipulation of the gut microbiome to manage these issues.

[Slide 29] And finally, again, I just wanted to leave with that sense of optimism that I have, which is that in the last seven years, there have been nine new medications FDA approved for management of motor symptoms. In chronological order, you can see them on the list here: Rytary, Duopa, Xadago® (safinamide), Gocovri, Osmolex, Inbrija, Nourianz, Kynmobi, and Ongentys (opicapone). And I think that more are coming our way, and it's just really, really gratifying to be able to see people improve their quality of life with these medications.

And I would ask APDA to help us physicians advocate for our patients by trying to see if we can get the insurance companies and Medicare to actually pay for more of these medications because it's somewhat frustrating to have these wonderful tools in our toolbox that can be difficult for accessibility due to cost. But I think again it's important for the participants in today's webinar to know about these options and to advocate for themselves and/or their family members and discuss with their physicians, neurologists, movement disorder specialists, etc. Are these medications potentially an option for themselves or their loved ones? And to just know that we have a lot more tools in our toolbox; and of course, we didn't really get into deep brain stimulation surgery, but we have more tools in that toolbox as well. So, there's a lot of real excitement and real reason for gratitude and optimism in the management of Parkinson's, especially in the management of OFF time.

And that's it from me, and I'll hand it back over to Dr. Gilbert. Thank you so much.

Question & Answer

Rebecca Gilbert, MD, PhD

Thank you so much, Dr. Petrossian. That was excellent, extremely detailed, and very informative.

[Slide 30] It is now time for our Question & Answer session.

I think we're going to get started because we have so many questions and not a lot of time. So, Dr. Petrossian, I'm going to select some of the really good ones here, although all the questions are really good actually.

Here's the first question that I think many people are probably wondering about. Why do OFF times vary so much from day-to-day? Talk to us a little bit about it in terms of the bacterial component of the gut. But what are the factors that go into this? Why a variation that some people experience?

Melita Petrossian, MD

Yes, fantastic question; and sometimes it's really maddening to the patients because sometimes there are things we can point to. For example, they didn't sleep well the night before or they're just more stressed out that day or they've not been exercising as consistently.

But often patients are telling us that they're doing everything the same. They're keeping their regimen the same. They're taking their meds on time, and they're still having unpredictable OFF time. And the thought is that it has to do with the basal level of dopamine as that shifts. The other changes that occur in the brain with the progression of Parkinson's is that the receptors become a little bit more awry in terms of how many receptors are available to pick up the dopamine. And the enzyme within the brain that converts from levodopa into dopamine can be impacted as well.

And in fact, there is some research happening into gene therapy to just increase the gene for the enzyme that converts levodopa to dopamine within the brain. That's an experimental treatment where the gene is being injected directly into the brain with a neurosurgical procedure.

So, the biochemical answer is, somewhat complex; but I think the three things in the brain, meaning the changes in motor circuitry, the basal dopamine levels, and the enzyme action, and then combine that with the gut microbiome, I think those are the things that I think of. But from a practical perspective, I ask my patients about have you been taking your meds on time? And often that's where we have to start. And what's your exercise regimen? How are you sleeping? What's your constipation like? Are we drinking enough water, etc.?

And again, I don't think I clarified it well enough. I'm just going to say it one more time. A lot of my patients misunderstand some of the development of symptoms of Parkinson's as OFF time. So sometimes there are symptoms that are developing either as a nonmotor or even sometimes just not particularly levodopa symptoms. For example, some people with freezing, their freezing happens whether they're ON or OFF, meaning whether their medications are working, or they've skipped a dose or what have you. And so, we don't call that OFF time.

Similarly, a lot of people, cognition isn't particularly related to their levodopa dosing, although again in a subset it is. So, therefore, if the cognition is shifting and they're having more difficulties with their Parkinson's in general as the disease is progressing, we wouldn't necessarily call that OFF time. So just wanted to make sure I clarified that.

Rebecca Gilbert, MD, PhD

Okay, fantastic. Yes, that's a great framework to go to your neurologist with, so thank you very much for that.

We have a question here which I think may be relevant to many people. Somebody wants to know what is the maximum dose that you can take of Sinemet per dose and the most frequent interval between doses as a strategy to work on OFF time? What would you say to that?

Melita Petrossian, MD

That's a really good question. Again, as a clarification, everybody should just be discussing this individually with their neurologist. But what I would say in general to my patients is our ceiling of levodopa dosing is dependent on what the patient's experience is with it. So, what can they tolerate?

But from a practical perspective, per dose, I don't tend to push my patients very much past 300 milligrams of levodopa in the immediate-release formulation. And I don't, again, I try to, once I have somebody on four times a day, if they're still having OFF time, I'm already looking at what should I be adding in here. Should it be adding in a COMT inhibitor or an MAO-B inhibitor or a dopamine agonist? Should we be talking about Rytary, a longer acting form?

But in a pure sense of if I didn't have any of those tools, if I kind of transport myself back in time before these things were developed, the most frequent, and again still even despite these options, sometimes I see people taking their medications as frequently as every two hours.

I worry when people are taking them more frequently than that because the doses can sort of buildup upon themselves and really exacerbate the risk of dyskinesias and hallucinations and other side effects of levodopa. So, I find that it's just not a road I want to take my patients down if we're starting off. So that's why I start to discuss all of these newer options when we're already at that four times a day, meaning every 3-1/2 to 4 hours mark. That's when I start to talk about it.

Rebecca Gilbert, MD, PhD

Fantastic. Thank you so much for that. We have a great question here about using a combination of immediate release and extended-release carbidopa-levodopa potentially to achieve the same effect as Rytary or maybe use Rytary in combination with immediate release. Do you ever do those kind of combinations?

Melita Petrossian, MD

That's a fantastic question. It certainly has been done a lot before the development of Rytary. I find Rytary just a bit smoother and easier to utilize than that combination, but for people who, for whatever reason or cost reason, I've certainly seen people use that combination.

Again, the question about the controlled release, the older controlled release, not Rytary formulation, is whether it's consistently absorbed. And I think probably as with Rytary that we have to do a dose conversion. We probably have to do a dose conversion of the controlled-release carbidopa as well.

As I showed in that one slide, the Rytary has three sort of components to it. It may mean that it works just a little bit differently in terms of how quickly it kicks in and lasts. But I think if some of my patients, if they've gone that route and they've found something that works for them, then it's a good thing to continue. Certainly, this doesn't necessitate a switch if it's working for them.

Rebecca Gilbert, MD, PhD

Okay, wonderful. We have a question here about leg cramps. Can leg cramping or foot cramping be a sign of OFF time?

Melita Petrossian, MD

Great question. Again, important to discuss the specifics with a neurologist who's examined you. But the short answer is yes it can be. Sometimes that is a representation of dyskinesia which we call dystonia. Cramps are a very kind of broad term, so it's important to try to understand with each individual patient what they're referring to. But yes, sometimes patients can have not just ON time dyskinesias but also OFF time dyskinesias which often manifest as dystonia. And again, that's another Greek word, dys meaning abnormal, tone meaning the muscle tone or posture.

So sometimes the toes are curling down, or the foot is moving in, and it's a manifestation of dystonia, although I've certainly seen people develop dystonia from Parkinson's before they even get started on any levodopa. So, it’s not necessarily levodopa-induced, but it can be a manifestation of OFF time.

Sometimes people are getting cramping as a symptom of Parkinson's because they are, just for whatever reason or they need to drink more water, or we might try magnesium or what have you. And sometimes people use the term "cramping" when it's really more like a restless leg type symptom, and sometimes that is experienced when people are often, sometimes restless legs can be a symptom of Parkinson's that has nothing to do with their levodopa responsiveness. Therefore, it's not considered an OFF symptom.

So, it really depends on the patient and the description. But as I mentioned briefly, some people with nonmotor symptoms of OFF time, nonmotor fluctuations as we call them, sometimes those are sensory, pain-related symptoms; and, therefore, yes. If I can try to pin the patient down on when the cramping is occurring and if it makes sense with what time their medications are, then I would try to treat it with how I treat OFF time in general and see if that makes an improvement.

Rebecca Gilbert, MD, PhD

Okay, great. Thank you so much for that. We have a couple questions about your statement about needing to take your medications on an empty stomach. Do you have to take medications on an empty stomach? What happens if you take it with food? Can you address that a little bit more?

Melita Petrossian, MD

Absolutely. The short answer is, again, just go with what your physician recommends and what's working for you. But in general, when people take levodopa with food, it's not absorbed as consistently. And it was originally thought that it was the protein in the gut that most interfered with the absorption of levodopa, although I've seen research suggesting that it can be any food. So really the most efficacious for somebody who's experiencing OFF time will be to take it on an empty stomach.

I have a small minority of patients who have nausea, and they literally cannot tolerate taking it on an empty stomach. They have to take it with some food. And as long as it's working for them, that's fine. Some of my patients I will recommend, "Well, take it with a nonprotein food like a cracker or bread or a banana or something like that," and that can reduce the nausea while still not having that protein element of it. But it really depends on the patient and what they're noticing they can tolerate.

I also will make a note that for many of my patients, it becomes very challenging to figure out the logistics, especially if they're taking their medications five or six times a day. On a three-times-a-day dose, it's reasonable for me to ask my patient to take the medication, wait at least half an hour, and then have their breakfast. And the same with lunch and dinner, for example.

But for somebody who's taking their medications every three hours, by the time they're done eating, they might be due for a dose again; and therefore, it can be quite maddening to the patient. So, my general recommendation, and again this is something that varies quite a bit physician to physician, so please discuss this further with your physician.

But my suggestion is take your meds on time. Let's say it's a three-times-a-day dose, I'll say seven, noon, and five. And then I would say try your best to have your meals such that there's a half-an-hour gap. But because let's say 7:30, 12:30, and 5:30, what have you, at least I should say, at least a half-an-hour gap. But because people's mealtimes vary very commonly in life and because food is important, not just for sustenance but also social engagements and family gatherings, and enjoyment, I hate the idea of somebody sitting there and staring at an empty plate while everybody else is eating around them just because they're waiting for their medication to kick in.

So, I say try your best with the meals, but at least take your meds on time so that you don't drive yourself crazy because I've seen people who've then said, "Well I ate at such and such time, so I'm going to push my medication back," and then I think it just gets very messy, very difficult to create that regimen of every single day, same time of day kind of military precision. And so, I ask people to try to take their meds on time every day, and then try your best to have your meals at the appropriate spacing but not to drive themselves too crazy.

Rebecca Gilbert, MD, PhD

Fantastic. What an incredible amount of information, and we have reached the end of our hour, and we have to stop our Question & Answer session, even though I know there's so much more that people have been asking.

But I want to thank you so much, Dr. Petrossian, **[Slide 31]** for joining us today for all the information you provided, all the answers to the questions, and my many thanks to everyone for participating in today's telephone and Web education program.

I really do apologize we couldn't get to all of our wonderful questions. If you have a question and would like to speak with someone from our Scientific & Medical Affairs Department, I encourage you to visit our website at apdaparkinson.org or call 1-800-223-2732.

Closing Remarks

Rebecca Gilbert, MD, PhD

[Slide 32] If you enjoyed today's webinar, we hope you'll consider supporting APDA with a donation. With your help, APDA can deliver more programs and services like this one which are needed more than ever during these challenging times.

[Slide 33] I also wanted you to remember to check out the APDA Symptom Tracker, which is an app that helps you or your loved one track their PD symptoms. The symptom tracker is available in English and Spanish and can be downloaded from the App Store or Google Play.

[Slide 34] I also want to emphasize to everyone on the phone and the Web that we do appreciate your feedback and comments and want to make sure that you complete the program evaluation form. To join us in this fight against Parkinson's and to learn more about the support APDA provides across the country through our network of chapters and Information & Referral Centers, as well as our National Research Grant Program and Centers for Advanced Research, please visit us at apdaparkinson.org.

We all agree that being informed about your disease and treatment options is the best way to empower yourself and take control of your care. Have a wonderful day.