



Live Well Today Webinar Series:
OFF: What It Is and How to Manage It
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Davis Phinney Foundation

Lauren Costantini, PhD: (Member of the Davis Phinney Foundation Science Advisory Board):
Hi everyone and welcome to the Davis Phinney Foundation's Parkinson's OFF seminar: What is it and how to manage it. My name is Dr. Lauren Costantini and I'm a member of the Scientific Advisory Board at the Davis Phinney Foundation and I'm really looking forward to this conversation because we're going to talk about an issue that is relevant for nearly everyone living with Parkinson's and that's OFF times. So welcome Dr. Torres-Yaghi and thank you for agreeing to be our guest today.

Yasar Torres-Yaghi, MD (Movement Disorder Specialist and Assistant Professor, Georgetown University):
My pleasure thank you for having me.

Lauren Costantini:
Just to tell you all in the audience about Dr. Torres-Yaghi, he's a movement disorder specialist, an assistant professor in the department of neurology at Georgetown University and co-director of the Lewy body dementia clinic spearheading an initiative to care for a growing population of aging patients with neurodegenerative conditions. He has a broad background in clinical research with specific training and expertise in Lewy body dementia and atypical parkinsonism and has been an integral member of numerous clinical trials. So let's get to it. So first question, is what exactly is OFF and what are the different types of OFF?

Yasar Torres-Yaghi:
This is an amazing first question. So off is something that first of all you need to be on the same page with your patient about. I still remember 34 years including preschool is how long it takes to become a movement disorder specialist and I was in my 33rd year doing my first year of my fellowship which is, you become an MD, then you do your neurology residency, then you do a two-year fellowship if you want to do clinical research and in movement disorders. I still remember my first patient, what off meant to me was different than what my patient would off meant to my patient. Actually off to my patient meant that the Parkinson's was off. So my patient was explaining to me, he said, I'm off at these times of the day and I said well you know we have to fix that because he sounded happy he said I'm off all the time it's just amazing and I said okay well that's great and so I left the room and I said oh well you know my patient's doing you know very happy but but he's off all day and I so I came back in the room I said wait hold on a second so when you set off you mean Parkinson's off right for a movement disorder specialist

when we think off we think a return of Parkinson's symptoms right so that means that your medication has worn off or it hasn't really kicked in yet and people feel that their Parkinson's symptoms are back in action, their tremor, rigidity, stiffness, slowness and movement, is all present and that can come in all shapes and forms and they can enter our lives differently from moment to moment. It's not always the same, not all OFF episodes are equal and so you can have it in the morning.

For example, morning OFF means I wake up in the morning and it takes me a long time to get ready. What that means to me is that it's been many hours since your previous dose of carbidopa levodopa, right, so maybe you took your last dose at 8 pm and hopefully you wake up at 6 am or maybe even later, if you don't have a three-year-old like me and you wake up later and you say, you know I've taken my medicine and maybe it you know it takes a little bit of time before it kicks in. That's a morning OFF. Now wearing off just in general means you've taken your medicine it's kicked in, it's working, maybe it works for three four hours, maybe your next dose is due five or six hours after your previous dose was given and you have about a one or two hour period of time where you feel those symptoms re-emerge. That can happen just after your dose is given three to four hours for example. It can happen precipitated by actually eating. So if you eat a high protein meal like let's say at lunchtime, you're doing the right thing you're eating you know some some protein which is good for your body but it reduces the absorption and the effectiveness of the carbidopa levodopa, so that can happen.

The other piece here that's really important is understanding that OFF also includes the time it takes after you take your medicine. So that medicine kicks in, sometimes that can be on average sometimes 60 minutes. So people might say you know doctor I take my carbidopa levodopa and I feel worse for about an hour right after I take it and I say well I don't we have to investigate but it's possible that what you're experiencing is that time it takes before that carbidopa levodopa takes effect. That counts as OFF time. One more, because look you know 30, 40 years including preschool, we have to identify these OFFs because how you communicate with your team is very important. The healthcare team that takes care of you, let's not forget, nighttime. Let's not forget 2, 3, or 4 am in the morning. Our patients might wake up and feel restless, it might be hard to turn in bed, maybe their Parkinson's symptoms are bad, maybe their Parkinson's symptoms wake them up but then they have to urinate. That could be an OFF episode, right. So sleep fragmentation in the middle of the night is also something that we always need to screen for to make sure that we're not missing that aspect of OFF. That can happen at any moment throughout the day.

Lauren Costantini:

And it sounds like these different types of off can happen within one individual at any time, is that right?

Yasar Torres-Yaghi:

Very good question and I think it can happen differently it can be predictable or it can be unpredictable and then another feature can be tolerance right? They can be tolerable OFFs and sometimes intolerable OFFs and so that's a very very important question. Every time in the back of my mind when I was being trained to really analyze OFF as a as a movement disorder specialist with sub-specialized training thinking about the more modern advanced therapeutics we always need to figure out first of all, is this happening predictably? Can a patient tell me, you know it's really happening every three hours after taking my previous dose? That's a pattern, right? If there's a pattern that's helpful for us to know. Or like we said eating, if you eat and and you feel like you wear OFF of your medicines more easily that's also an important pattern and then that morning OFF that can be a pattern, right? And there's different ways to analyze how to treat those different OFFs.

Lauren Costantini:

Interesting. So what types of symptoms might a patient experience when they are OFF besides the ones that you had just described?

Yasar Torres-Yaghi:

You know that's a really good kind of neuroscientist question because you got it, the brain is complicated, as Dr. Costantini knows. The brain is not, it's not a straightforward organ. Unfortunately for all of us, right? You know, it's a very important organ but it controls a lot of aspects of our body, right? It controls our neurologic state right? Our neurologic state's very important, our brain capacity, our memory, our cognition, our alertness, right? It also controls our ability to move right? There are certain centers of the brain like our Parkinson's circuitry that can be affected, we might see tremors, rigidity, slowness of movement, gait impairment, falling, those are the motor symptoms that might happen. But also the brain can control our psychology, right, anxiety, depression, right? This is an organ that it can affect our behavior, our neurologic state, our movements, and so it's very different, it's unique in that in comparison to the other organs of the body. Also there's a nervous system throughout our body, right?

Our nervous system controls our other organs so it really is a multiple system type of condition especially OFF episodes because it's those non-motor symptoms, not the motor symptoms, those non-motor symptoms that also can be hard to detect and those are the things that we talk about, things that are very under detected based on research are things like pain, right? Pain can be a symptom of wearing OFF and that's something very very important to detect. Brain fog. Some patients might feel like I'm just cognitively slowing down, it's like my cognitive agility isn't at its full capacity. As a Parkinson's specialist that also handles cognitive patients with cognitive impairment, I see that a lot that I need to be able to distinguish between true cognitive impairment or a cognitive effect from a wearing OFF episode if it can happen episodically, panic, anxiety, depression, all of these things can be part of wearing OFF. Sweating can be part of wearing OFF. So all of these things we have to combine them together to understand hey is it just one a la carte thing that's happening? Some patients might experience just a little bit of anxiety. That could be a symptom of wearing OFF and sometimes those non-

motor symptoms do not necessarily happen in combination with the motor symptoms and sometimes they happen solely motor symptoms that occur and sometimes it's a combination. So this is a very intricate conversation, I'm so happy that we're having it.

Lauren Costantini:

It sounds more complex than we had originally thought. So you had mentioned earlier L-dopa, does this have to do, do OFF episodes have to do with the types of medication you take and your medication schedule or both? Obviously, a lot of patients are taking more than just one type of Parkinson's medication, does that play a role?

Yasar Torres-Yaghi:

Yes, and you got it, you're just nailing it with the questions, because it's carbidopa levodopa you know we think of carbidopa levodopa as our dopamine repletter right? When I teach, I'm an academic neurologist that's why I'm stuck in the river, the Potomac River here, with Georgetown behind me, but when we teach our medical students, residents, our fellows our goal really is to teach them about what it is that we're doing, our role as a physician is to identify a problem and think about the therapeutic solution to that problem. So wearing OFF occurs traditionally when we think about it in between our doses of carbidopa levodopa right? It can either happen like we said in the morning, in the evening, in between, due to diet, etc, and so when we think about it, it's traditionally thought of you know as a function of the medicine either not being absorbed as adequately as it could in patients maybe with constipation or because of diet or it's wearing off early, the effect as it's in your system wears off too early, but the way we practice as you mentioned is to combine therapies right so we think of carbidopa levodopa and we give that multiple times a day, but there's a lot of reasoning behind adjunctive and combination therapy.

We call that rational polypharmacy. Not irrational polypharmacy, that's not what we want right? We don't want our patients on a million medicines you know although that sometimes happens, we have our patients on so many meds but the idea is, how is it that we really kind of combine and create a cocktail approach? We use adjunctive medications, and those families of medicines can be monoamine oxidase inhibitors, dopamine agonists, and there's different medications within each category. You can think about other formulations of carbidopa levodopa, extended-release formulations, to help potentially extend the duration. You can think about COMT inhibitors, which are medications that might prolong the duration of effect of carbidopa levodopa, and now we have multiple other avenues right? We think about the medications that are derivatives of amantadine, which can help with wearing OFF and dyskinesias and then we have other medications like A2A receptor antagonist, those are adenosine 2A receptors antagonist, that's another family of medication, those are the medicines that we combine together. And now we have as needed therapies right? We have medicines that can be given as needed for patients that need an on-demand or an as needed way of rescuing them from an OFF, to get them from an OFF state to an ON state so that they feel better.

Lauren Costantini:

Excellent, fantastic. So I'm a big fan of nutrition and hoping to change the body through what we eat. As you know, things that we put in our mouth every day play a role in our physiology as well as our disease state, so are there any nutritional choices, like hydration that can play a role in OFF times and improve or even cause a problem and increase OFF?

Yasar Torres-Yaghi:

Great. Yeah you know I think it's a very important topic, you know, thinking about the condition that we all deal with in our world, our dopamine deficiency condition, thinking about it holistically and not just you know, I'm talking a lot from an MD allopathic lens talking about modern therapies, therapeutics, but there's so much more to life than medication right? Sometimes it doesn't feel like it because we have all these you know wonderful medications at our disposal, but it has a lot to do with lifestyle and diet and exercise and so these non-pharmacologic measures can make a difference in our life. Exercise is important, diet is important, sleeping is important, hydration is important, you know especially in patients with Parkinson's disease we might actually feel low blood pressure.

So low blood pressure actually can be part of Parkinson's not necessarily part of OFF, but you can see blood pressure changes, this volatility of blood pressure, especially with OFF episodes we might actually see sometimes the blood pressure come up and so it's important to manage all aspects of our body. Hydrating is important in terms of recommendations we try our best to adequately hydrate. We usually say it's kind of that old adage, you know, eight ounces of, eight glasses that are eight ounces of water in a day right that's 64 ounces, a little bit more than half a gallon. And then our patients say but wait but then I have to urinate a lot and I say I know, that's the drawback, right?

We do unfortunately have pluses and minuses to everything. The other thing we say is that diet is very important, you know diet actually can dictate how we sleep, the better we sleep the more deeply we sleep, the better our days are going to be, but we usually say for a good brain healthy diet we consider the Mediterranean diet right, so the Mediterranean diet is something that is usually high in vegetables, it's a very colorful plate right, maybe half of your plate has color, might be fruits, vegetables, whole grains. You actually have a lower carbohydrate amount as part of that diet, and you do in fact have things like fats and and protein as part of that diet but then that leads us to the second part of Dr. Costantini's question is are there any drawbacks? And I mentioned that we alluded to it earlier but protein can unfortunately reduce the absorption of carbidopa levodopa and I don't want to overdo it because I don't want people, because what ends up happening is, when you're on a medicine multiple times a day like a carbidopa levodopa pill or in any formulation oftentimes we're on it multiple times a day and patients might say but when do I eat? You know how am I supposed to eat when I'm eating, and I'm supposed to space my medicine away from food, so that's a very individual conversation and so it's important to know but I don't want it to alter our way of thinking.

And then one last point on diet. Constipation is one of the non-motor symptoms of Parkinson's disease and so imagine, we have our upper GI tract and our lower GI tract. Constipation is something that we suffer from but also esophageal dysmotility, sometimes it's hard to bring food down, our stomach does not always empty into the small intestine and so that kind of dysregulation makes it even harder for us sometimes to rely on the pills that we take orally, so that they take us into an ON state from an OFF state and that's part of the problem of wearing OFF and so that's one of my first questions, whenever a patient calls us and says you know it feels like my my carbidopa levodopa isn't working as well as it used to or our medications to help us with movements, they're not working as well as they used to, the past three days has been really rough.

You know the first question I'll ask, the first question I'll ask is, are you constipated? And patients will say, wait hold on a second, and they'll think, and some will say no and I'll say wait, what do you mean you're not constipated? They'll say well I had a bowel movement today and then I go even deeper I say wait, is it a, was it a full, did you fully evacuate? If you didn't fully evacuate, if you're straining, if it's hard to go and you're noticing even if you're going that still is sub optimal bowel movements, so our goal really is, it's a multimodal approach. If we can have you eating properly, hydrating properly, that's where hydration is a major piece right? If you're hydrated, your colon is going to move that stool down. Hydration is important for bowel movements, exercise is important for bowel movements, so all of these things come together.

Lauren Costantini:

Excellent, perfect. That was another question is what about OFF episodes and exercise? Sounds like that just exercising is going to help some of these other problems like constipation but could they have a direct effect with OFF episodes, exercise in general?

Yasar Torres-Yaghi:

Wonderful, wonderful question because it's a, that is a tough one you're right, you know making that connection is a tough one and it's a very higher-level question because you got it, so exercise is very important, and we kind of talked about the reasons why exercise is important for your GI system. Exercise is also important to help increase endorphins. Endorphins are good for your muscles, good for your brain, it's good for your alertness, it's also, when you exercise based on animal models and based on what we know, if you see and if you study the chemicals that are elevated there's something called a neuronal growth factor that is increased with exercise. That's very very important for your overall functional state and it might be really good that neuronal growth factor might be very good at maintaining the health of your nerves and your brain. And then the third part about exercise that's important is that there's a concept called neuroplasticity, kind of retraining the circuitry of your brain, right? We have different circuits that lead to movement. In Parkinson's disease we have our basal ganglia circuitry that might be affected but there's different circuits that help us move and so you can kind of strengthen the other circuits and the circuits that are affected in Parkinson's disease so

that we can walk and move and be more functional and in a more smooth fashion. So the more we exercise, the better we're going to feel and that may have a positive effect on the amount of OFF time that we have.

One last point on that is it's not uncommon for patients of ours to do what they're supposed to do, they're all they're trying their hardest, they're trying to feel better, they're trying to exercise, they're trying to go to their physical therapy, we know how important physical therapy is, and an OFF episode stops them from being able to do that. So it goes both ways. We need to tackle OFF in order to exercise and we need to exercise in order to kind of beat OFF and so both of those things are very important that that piece of if OFF impairs our ability to exercise or OFF impairs our ability to go for our physical therapy session, that's an important point and we have to be able to have maybe an on-demand strategy in case that were to happen in an unpredictable fashion because I don't want my patient to miss their physical therapy appointment. I want them to be able to feel better if they if they're in an OFF state maybe we can get them back in and ON state so they can exercise.

Lauren Costantini:

Yep, mind body connection, it's important. So one question here from a patient is are there safe ways to extend the life of your carbidopa levodopa so you have less OFF time? Sounds like the goldmine question there.

Yasar Torres-Yaghi:

Yeah, you know and that is a debated question. Yeah, it's a gold mine question so you know it's a tough question because there's different ways of looking at this because it's a very much, it's very much an individual conversation and it's a personal one in many ways to everybody, but the way I kind of describe it is we want people to feel as functional as possible. And so as we mentioned, we don't want our patients not to be able to move, not to be able to walk, we want them to be at their optimal capacity, so that they can exercise, so that they can walk, so that they do maintain functionality over time and how we do that is to try and maintain what we call dopaminergic tone. We want that tone to be as steady as possible given our oral medications so that our patients can feel that stability and so it's very much I believe, it's very much dependent on each person, but we don't want also, we don't want to overdo our dopaminergic tone, right? There is a therapeutic window that, our goal is to stay within that therapeutic window so we don't supersede that threshold into dyskinesia and then so that we don't undershoot so our patients are experiencing multiple hours of OFF time in a day and that's where that multimodal approach to therapy comes in. There are ways to extend our ON time you know with therapies, exercise, lifestyle modifications, that can, all of those things can help kind of extend that duration of effect throughout the day, but the overall longevity of that effectiveness from our medication is very much dictated by the way the condition progresses.

So if the condition progresses, that's the true function you know when you think about the the function of of the cause I think the idea that medication may not last in terms of longevity, in

terms of effectiveness, over many many years is very much based on how the condition itself is progressing.

Lauren Costantini:

That is the, you led me right into our next question on the list here. Do OFF times increase when Parkinson's progresses, is this a function of the progression of the disease? Or because the medications are no longer treating symptoms as effectively?

Yasar Torres-Yaghi:

Yeah, great and I, you know, there's a lot of ways of looking at this and there's data out there you know about the utility of using dopamine sparing medications versus just using dopamine or levodopa, dopamine sparing strategies. Now more recently there's been a lot of scientific and clinical discussion about kind of this continuous dopamine type of therapeutic strategy, kind of keeping everything as continuous as possible and so there's different ways of thinking about it, but what we do know is that over time as the condition progresses, we know that the overall amount of medication that is needed can increase in order to provide benefit and we're seeing more and more OFF time as the condition progresses and so anywhere between five to 13 years after either disease onset or the time that we start our medications right there's different start points that have been studied, but ever since because when we think about the progression of the condition, because it is a progressive disorder, we have to think about the more and more need to address OFF as the disease progresses over years usually 5 to 13 years after, we might see more and more OFF time start to develop and another way of kind of categorizing OFF time is actually talking about it just as return of symptoms right, peeling off that extra layer, just saying return of symptoms in between doses does tend to progress become more pronounced and the duration of those time periods does tend to get worse.

Lauren Costantini:

Yeah, so what are the most effective ways to treat OFF currently? Pharmacological, you mentioned a couple I think people want to hear a little more specifically about some of those on demand, and are there any non-pharmacological or even surgical ways to treat OFF?

Yasar Torres-Yaghi:

Yeah, you got it. So this is the joke is the 34 years including preschool, this is why you know neurology has become so sub-specialized right? Clinical neurology has become so sub-specialized that a movement disorder specialist can be very helpful in analyzing these sorts of scenarios, similarly an MS specialist for multiple sclerosis would be much better suited to be able to handle a 2021 case of multiple sclerosis because of the advancements in therapeutics both in movement disorders and multiple sclerosis and so this advancement in therapeutics has kind of paved the way for the need for more sub specialization within neurology. So the positive about all of this is that, hey, look at all these medicines that I mentioned right? Dr. Costantini was like wait I just asked one quick question and you're talking too much with all these things, but you got it there's so many families of medications and now there's different categories right

you said we want to hear more about those on-demand therapies, hey, look, just since 2017 you know there's been this development of on-demand therapeutics.

So let's start there, right, so on-demand therapeutics so traditionally what we may have done back in the 1970s and 1980s is, hey, take an extra dose of carbidopa levodopa. Hey that's a way of thinking about treating an OFF episode, right? In between your doses if you're having an OFF episode maybe you can take an extra dose, right? Here or there and that's again very individual so it has to be planned by your healthcare team and each individual person. That's one way of thinking. Now, but that still doesn't bypass the problems that we that we run into with the gut dysfunction, right? And so you might be doing the right thing by taking your medicines orally but what are the medication options that are on-demand therapies that, as needed therapies that might help us bypass that GI tract. We have injectable apomorphine right? Apokyn. We have an inhaled option with Inbrija or Inbrija, right? I've been told Inbrija because it's supposed to bridge you to your next dose, depends if you're what coast you're on but I guess I say Inbrija but it really kind of has this idea of bridging you till your next dose because you're using an inhaled option in an on-demand way for OFF.

And we have a sublingual apomorphine that's helpful, it goes under the tongue, and it can get you from an OFF to an ON in a more reliable way than using those oral therapies um that we that we traditionally used to use. I'll stop there and and clarify any answers Dr. Costantini has.

Lauren Costantini:

Are there any non-pharmacologic or even surgical approaches for OFF? Specifically? I don't think in my knowledge that there is but...

Yasar Torres-Yaghi:

Yeah, so well you can think about them as maintenance therapies right, so surgically yes, those surgical treat, we call them surgical treatment modalities, right, you got it so that's exactly kind of where we there's a now a a continuum right? So we think about the condition as a continuum. If we are experiencing motor fluctuations or wearing OFF and and we're at a stage where we need to consider surgical treatment modalities there is a medication infusion port that actually gives carbidopa levodopa intestinal gel on a reliable and consistent basis through a medication infusion port directly to the small intestine where the carbidopa levodopa gets more effectively absorbed and that's pumped it's a pump basically that infuses medication on an hourly rate and that allows us to fine-tune you know the amount that we're actually giving by 0.1 ml increments, which equates to two milligram increments. Imagine being able to titrate, go up and down, by two milligrams per hour. That's an infusion port. What we have also at our disposal are three kinds of deep brain stimulators, right, so there are the different kinds of deep brain stimulators that we can place, and you put them in different parts of the brain depending on what sort of condition we're dealing with. There are three main targets, there's more, but

three main targets that we think about when treating tremor and Parkinson's disease for deep brain stimulation.

Lauren Costantini:

Excellent. Okay well we're about halfway through our timing and we want to now switch over to questions from the attendees so Leigh is typing them out for me here we've got five questions so far, so I encourage all of you listening to start typing in your questions in the chat, so first question from our attendee is what is your experience with the Neupro patch and does it help with wearing OFF?

Yasar Torres-Yaghi:

Yeah, so, great question. So Neupro is a dopamine agonist right so it's a patch it's transdermal, we call it transdermal, through the skin, and what makes it unique in comparison to the other dopamine agonist is that it is a patch but also that it's an extended release formulation right? So we think more extended release, right, we think about more extended-release carbidopa levodopa. We like to use perhaps depending on each case but extended-release formulation of dopamine agonists but the Neupro patch is a helpful tool to help kind of think about you know creating some sort of stabilization of benefit so it could, yes, dopamine agonists like Neupro could be helpful in extended-release form to help reduce wearing OFF, that's the short answer. There are risks and benefits to each drug class right and so we think about dopamine agonists as their own drug class different than the other drug classes but really what dopamine agonists are and so we can conceptually think about them as a pharmacologist right if we put on our pharmacology hat what they are are molecules that they're like dopamine imposters. They sit on dopamine receptors you know these are receptors by the way or like little cups and then the molecules sit on those receptors on the neurons and act like dopamine would act they they are not dopamine. Levodopa actually enters the neuron and converts into dopamine. Dopamine agonist might be used adjunctively or as monotherapy on their own without any other medications to provide benefit and reduce symptoms.

Lauren Costantini:

Excellent, great. Another question from one of our webinar attendees is does strenuous exercise quote on quote burn through the carbidopa levodopa quicker which invokes OFF quicker? Can you actually burn through that and cause the medication to be metabolized quicker if you're intensely exercising?

Yasar Torres-Yaghi:

Well I can tell you in my clinical experience I hear that from patients, that on days where they are expending more energy, right they might actually note that they're wearing OFF potentially more. It's almost like, yeah, I have not uncommonly heard this from patients and that's kind of more clinical experience kind of what I've heard from just having we have 12,000 patients in our clinical practice, very big Parkinson's center, we're very busy we have a high volume and you got it. I've heard that and it's not uncommon for me to hear that now it's possible that

maybe when we're trying to exert ourselves we're noticing that maybe we're wearing OFF rather than if we were just sitting there not really exerting ourself, maybe we wouldn't necessarily feel that wearing OFF effect as strongly or it's possible you're right with expenditure of energy you know your metabolism you're using your cells are using the energy that you have and our medications help us but it's possible that we are kind of somehow in certain cases kind of exhausting some of those energy that some of that energy capacity that we have.

Lauren Costantini:

Excellent, good. This is not in the clinical journals but you're hearing it first here folks from clinical experience. So, next question is when OFF time occurs late in the afternoon would adding a late afternoon dose of levodopa be as effective as switching to an extended-release dopamine?

Yasar Torres-Yaghi:

So yeah, so there are different ways of evaluating OFF time right and if we're seeing that throughout the day we have a predictable experience, where we are wearing OFF of our medicine or we're feeling like a certain time of day we can predictably say, hey, I know I know I'm wearing OFF, right, this is it, I found it, this is the time, it's not unpredictable, it may or may not be intolerable right? Those are the two factors that kind of when we have those two questions in the back of our mind about how we, when we add therapies. You know it's not uncommon for us to do two things at once right, it's a dynamic condition and sometimes we need a dynamic strategy. So we are thinking about now that we have all these categories, definitely, hey, how do we improve our OFF time, improve our ON time, reduce our OFF time. Extended-release formulations of of carbidopa levodopa for example right those are those are ways that we can help prolong duration from our previous dose. Data has shown that uh the more extended-release formulations of carbidopa levodopa like if you think about Rytary, it actually can show based on clinical data extended duration after each dose in comparison to the immediate release carbidopa levodopa if dosed right and done properly. Now what about patients that we have that in the back of our mind where we're thinking about extended release formulations of carbidopa levodopa, maybe we've added an an adjunctive to reduce OFF time right? These ON extenders or ON augmenters, the different families that we mention but we're also maybe thinking in the back of our mind well let's have an action plan similar to what an asthmatic might have right? You have, or a diabetic person might experience right? How do we combat these sugar fluctuations that despite being on multiple formulations of medicine that might tackle diabetes, we still might need an as needed plan to kind of modify that sugar level, same goes for asthma, we might have our patients on three or four different doses or different medications for maintaining or preventing asthma crises but if you have an asthma crisis there's an action plan there to help reduce the symptoms.

Lauren Costantini:

Great analogy, yeah, now we can start using an asthma protocol for maintenance versus as needed that's excellent. Looks like we're going back on our next question to diet, you struck a

chord with the protein and says how much time should you avoid protein before and after eating to allow maximum absorption of the levodopa.

Yasar Torres-Yaghi:

Yeah, so yeah, it's a good question.

Lauren Costantini:

Sounds personal.

Yasar Torres-Yaghi:

Yeah so, it's a good question and it's about so what we tend to say and patients that might be experiencing that is protein if taken within half an hour to an hour of taking your carbidopa levodopa may actually reduce the benefit from those doses and so we tend to say, try and space your carbidopa levodopa half an hour to an hour away from eating a protein-packed meal. What I tell patients though is if you're hungry and you gotta eat you eat right and maybe think about that knowing that it's protein mainly try and find out you know what are those kind of, those meals that may not have a lot of protein so that you can maybe eat something, but it may not affect your absorption or benefit from carbidopa levodopa.

Lauren Costantini:

Yeah, have a big salad with lots of vegetables and a little bit less protein.

Yasar Torres-Yaghi:

Yeah, that's a good thought.

Lauren Costantini:

Next question is about sun downing, so my father is having some evening symptoms that we thought were an extreme OFF period, but an experienced in-home caregiver is suggesting maybe a sun downing effect, can you speak to the difference between OFF symptoms and sun downing?

Yasar Torres-Yaghi:

Yeah great, and they could be the same. You know, it's possible just as, it's a multi-layered process right and that's why it's possible that in the evening hours you know we might be seeing an increase of neurobehavioral changes right. So it is important to distinguish sundowning from an OFF episode and it's possible that there's a cycle there right? You know maybe anxiety and panic is setting in because of a wearing OFF episode and that can kind of then trigger some neurobehavioral changes that seem like confusion or brain fog. Those things can be, sometimes they're non-specific, so they could be wearing OFF, but sundowning is an important an important topic to discuss because cognitive change is also part of our condition in certain cases, and so it's important always to evaluate your patient's cognitive state, their abilities, their cognitive abilities, their neurocognitive kind of level. If there's cognitive

impairment or if there's dementia, we may be more prone to sun downing or confusion in the evening hours and it's important to know that because if we have cognitive impairment detected on either an MMSE or a Montreal Cognitive Assessment those are ways that we can determine our patient's cognitive status.

Let's not forget psychosis, right? When we think about psychosis that is part, can be part of our condition and can be made worse or caused by our medications and so understanding the cognitive overall, all those components is very much a part of understanding our movement disorder. You need to know about your cognition in order to help your movements and vice versa.

Lauren Costantini:

Yep, sounds like a balancing act. You had talked about this a little earlier how much wearing OFF should you tolerate before increasing your carbidopa levodopa? Do you worry about obviously dyskinesias caused by the higher levels, how do you strike that balance or is it a very personal thing?

Yasar Torres-Yaghi:

Yeah, you're right, and that's where it is personal and it's individual for each person but there's different strategies. You know you you might be able to think about a strategy to help reduce dyskinesias and improve OFF right? So there are medications that we might think about for that, there's FDA indicated medications that are FDA indicated for both right. So a medication like an amantadine derivative might be thought of during that time. So but but there's different ways of thinking. You can even sometimes lowering the dose of levodopa and making it more frequent thinking about extended release formulations, adding on extenders, those adjunctive medications that we've talked about can be helpful, but sometimes then we push ourselves into that threshold of more dyskinesias and that's where, whenever we're having a tough time with our combination therapies or just our therapies in general, finding our way to thread that needle into a narrow therapeutic window, where small changes make big impacts, that's a very important conversation to have and understand because that's exactly when we start having that conversation about surgical treatment modalities right? So it doesn't mean we're not going to still think about optimizing our oral medications, but we might really start thinking and having that conversation about, hey, you know these are the options for surgical treatment modalities. Which ones make more sense you know given the individual?

Lauren Costantini:

Yep, personalized approach. So what meds may be coming down the pike that can help with OFF? Anything in development that you've been hearing? Your clinical trials or in your network?

Yasar Torres-Yaghi:

So there's plenty of so this is one of my favorite things is to talk about the momentum in clinical research, right? So as an academic neurologist we have one foot in clinical research at all times

and and we have to think about this as an ever-changing field, as a dynamic field, and as a field that has all this research momentum behind it and we've talked about everything that we can prescribe in clinic, but you got it, there are there's so much going on. We have clinical research, multiple sites throughout the country looking at an extended-release formulation already of an extended-release formulation of carbidopa levodopa. We have so maybe a medication that might be in the future taken less frequently but maybe you know successfully of course we still don't know, but maybe we'll take it less frequently and and get similar benefits to a more immediate release alternative that's given more frequently. We have different types of devices right we have a dopamine agonist subcutaneous pump that is being studied in the United States and we also even have a subcutaneous carbidopa levodopa device, that's subcutaneous meaning in the skin, that might be able to deliver a continuous infusion of carbidopa levodopa. That's not to mention all the other clinical trials looking at how to target the proteins within the brain that are causing the problem and all the other clinical trials that have to do with devices, that implantable devices, and where to target in the brain, so there's a lot here in movement disorders and in neurodegenerative diseases that's being studied.

Lauren Costantini:

So exciting, love it. A couple more personal questions... I have OFF times when I don't move much for a long time like when I'm watching a movie is this common?

Yasar Torres-Yaghi:

Well you know what happens sometimes also in my clinical experience that I hear⁸ from patients is that you know when we have long periods where we're not moving, sometimes, we can kind of feel rigidity and stiffness set in and so it can feel a little bit like you know to get moving again you kind of have to, to feel fluid again and less stiff and rigid you kind of have to walk and stretch out those muscles and you're right so you can you can combat that with exercise, stretching, core exercises, things like tai chi, things that are gonna be good for your core. Stationary biking is something that's both safe and effective but yes it also could be a wearing OFF episode, right? So stiffness and rigidity can be a sole symptom of wearing OFF and that's where a strategy of kind of writing down when you take your medicine throughout your day and how you feel on an hourly basis can be very very effective, that's a nice effective communication tool to be able to kind of hand your health care team a picture of what of what you might be experiencing.

Lauren Costantini:

Ah interesting, excellent. My husband has fatigue when he is OFF what can he do?

Yasar Torres-Yaghi:

Yeah, fatigue is a symptom that may have many causes. So when we think about it, we really have to kind of put it all together and try our best to determine that if fatigue is part of OFF then we can target OFF and maybe fatigue improves. It's also possible that fatigue may actually be a symptom of low blood pressure, right, so low blood pressure can happen in Parkinson's,

might cause fatigue. Fatigue can also be caused potentially by, if you eat a, it can happen to anybody. If you have a big pasta meal at lunch time carbohydrates can make it so that all the blood from your body goes to your brain to absorb all that food and carbohydrates are usually harder to absorb and that can lead to fatigue too, so it could be induced by food. Another type of fatigue can be caused by just overall tiredness right, low energy, that can be part of Parkinson's disease, kind of hard to pinpoint, or we really really need to think about remember I said let's not forget sleep, we think a lot about our day time but what about our night time, remember Parkinson's patients might have sleep apnea and that might make them feel fatigued or insomnia during the day they might experience REM behavioral sleep disorder they might act out their dreams making them sleep less soundly. And then that sleep fragmentation right if you're waking up several times at night because maybe your dopamine levels are low right because that's what happened overnight or you need to go to the bathroom a lot urinate that's going to contribute to daytime fatigue and so you got it, it's so many factors and that's why you kind of have to think about everything as a whole and get to the bottom of each one

Lauren Costantini:

Right and that actually leads to the next question if insomnia is an OFF problem how is that treated? Yeah, so you got it, and so insomnia can be an OFF problem. Restless leg you know can be something that we feel it's kind of like a sensory issue that can happen um where we feel like like it's hard to control our leg or feel a discomfort that could be a wearing OFF episode. So wearing OFF prior to bedtime sometimes can contribute to sleep onset insomnia right and we have to distinguish between sleep onset insomnia and then maintenance insomnia, in the middle of the night, sometimes our patients can fall asleep easily but then they wake up predictably at the same time every night or maybe there is a pattern there. Maybe their last dose of carbidopa levodopa was at 6 pm but they're going to sleep at midnight right and that's been a long time potentially and if you're uncomfortable you're not going to sleep you're not going to be able to fall asleep easily and then a third point is depression and anxiety can very much affect our ability to fall asleep and stay asleep and so if we're not screening for depression and anxiety then we might be in trouble because you kind of have to in order to regulate your circadian rhythm you have to tackle anxiety and depression too.

Lauren Costantini:

Absolutely. Next question is does chewing medication help decrease wearing OFF, do you have any suggestions as to what to take levodopa with to enhance efficacy prevent or help with OFF episodes and this person has said I've tried vitamin c, orange juice as well as carbonated drinks which sometimes help. So how can they take their medication differently?

Yasar Torres-Yaghi:

Yeah you know I'm not sure necessarily about the the true clinical trial data but you got it you know we we use strategies right we think about it like so in carbidopa levodopa's case/immediate release, maybe we tell people to chew on some carbidopa levodopa, maybe think about taking something with it like orange juice or lemonade right because maybe there's

something in terms of that acidity or citric acid that might help with absorption potentially right, maybe, so that's something that we used to try. There are different formulations like Parcopa sometimes that patients might feel, the oral disintegrating tablet of carbidopa levodopa, but again still goes down the GI tract so we're still even though we are doing those strategies with oral therapies we sometimes you know we're still reliant on that absorption in the small intestine, so our GI tract does still need to be functioning properly. Rytary is actually a medicine that's encapsulated that you can actually in patients that have difficulty swallowing you can open the capsule sprinkle that into something like applesauce and take it in patients that are having trouble swallowing but those are things that we think about you know just in clinical practice to depending on each scenario we run into.

Lauren Costantini:

Perfect. One question here, does OFF feel different if you're taking a dopamine agonist instead of carbidopa levodopa?

Yasar Torres-Yaghi:

Yeah, you know well the the answer I have is you know I don't know, you know, I know that we know the half-lives based on clinical research half-life is how long each medication administration if absorbed properly is in your system right. So we know that carbidopa levodopa might have a certain half-life and and so which means it's out of your system after a certain amount of time and so it might not be giving you benefit. We also do know that about dopamine agonists. So you can if you're taking an immediate release dopamine agonist the ones that are given three times a day orally then you actually might feel those though that dopamine agonists wear OFF too just like you would carbidopa levodopa but that's where potentially depending on each case of course we really start thinking about more extended release formulations of both carbidopa levodopa and dopamine agonists right or we think about those on augmenters or extenders those the newer COMT inhibitors, A2A receptor antagonists, those combinations of how is it that based on all the clinical research these adjunctive medications that are added to carbidopa levodopa that might extend ON time and reduce OFF time.

Lauren Costantini:

Great and the last question we'll go with today is, this is a general one get ready, please explain the three kinds of deep brain stimulation surgical treatments.

Yasar Torres-Yaghi:

Yeah, so yeah I'd love to. This is a three-hour lecture right Dr. Costantini?

Lauren Costantini:

Saved the best one for last.

Yasar Torres-Yaghi:

I can't believe it's the last question already that time flies, so thanks for making it so fun everybody and Dr. Costantini, but you got it so there are three right right now readily available in clinical practice at least that I know of we have Medtronic, we have Abbott and we have Boston Scientific and and we might think about the different technologies differently. So Medtronic has what's called a closed-loop system that can help us actually potentially understand some readings from the brain, potentially, so there might be some data that might be captured by the device. Now what that data really translates into right now that's TBD right, to be determined, but there is a capacity for Medtronic devices to actually capture some electrical information from your brain after being placed. A deep brain stimulator like Boston Scientific actually there are eight contact points so eight places to stimulate in comparison to four contact points for alternatives so that might be something that might be seen in a Boston Scientific deep brain stimulator and the Abbott device has directionality and they do remote programming that's something that's newer to them is being able to program a patient remotely through their tablet and so they do have approval to do that.

So each system has its pluses but their effectiveness really you know is tried and tested through clinical research and before anything is FDA approved of course they go through a huge vetting process of safety and efficacy, but each each device may have different pluses and minuses at any given moment but of course technology is constantly evolving right technology moves faster than this lecture right. Something new in technology might have come out just in the past 50 minutes where we've been talking and so all these all these different devices might evolve, and each company might have different things in comparison to the other at any given moment in time

Lauren Costantini:

Excellent. Well thank you so much Dr. Torres-Yaghi, this was so informative, and you made everything so easy to understand you truly have a gift for teaching.

Yasar Torres-Yaghi:

Thank you, thank you.

Lauren Costantini:

I hope everyone got as much out of it as we all did so thank you so much again and hope you all have a wonderful rest of your day

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