Spotlight on Parkinson's Disease: Enhancing Communication About Off

Transcript

Welcome and Introductions

Stephanie Paul

[Slide 1] Welcome everyone and thank you so much for joining us today. **[Slide 2]** My name is Stephanie Paul, and I am the Vice President of Development & Marketing at the American Parkinson Disease Association or APDA for short.

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 would like to thank Acorda Therapeutics for funding this important program and acknowledge their continued appreciation for the critical need to provide educational programs like this one to people impacted by Parkinson's disease.

APDA is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than 1 million Americans with Parkinson's disease live the best life in the face of this chronic neurological disorder. Founded in 1961, APDA has raised and invested more than $170 million to provide outstanding patient services and education programs, elevate public awareness about the disease, and support research designed to unlock the mysteries of Parkinson's that will ultimately put an end to this disease. APDA distinguishes itself as the national organization working one on one with the Parkinson's community to make each day better. And now to our program.

[Slide 3] Our presenter today is Dr. Rebecca Gilbert who is APDA's Vice President and Chief Scientific Officer. Today we are delighted to have Dr. Gilbert share with us an overview of how to enhance communications with your doctor about your OFF periods. After the presentation, we will open the program for questions from both telephone and Web participants. 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 one and other programs.

It is now my pleasure to introduce Dr. Gilbert.

Presentation

Rebecca Gilbert, MD, PhD

Thank you so much, Stephanie. Good afternoon everybody. I am delighted to be giving today's webinar entitled, "Enhancing Communication About Off." I'm going to give my financial disclosures. **[Slide 4]** So here are my financial disclosures, and we'll begin right away.

[Slide 5] So today I will be discussing the clinical phenomenon of ON and OFF time in Parkinson's disease, and I'll be touching on these five main topics, which I have listed here in my first slide. The first is pretty straightforward, what is meant by ON and OFF time in Parkinson's disease? This may be very apparent to some people listening, but others may not really be sure when am I ON, when am I OFF? Do I have ON and OFF time at all?

The second is why does this phenomenon occur? What is the scientific basis for the presence of ON and OFF time? Now what if I know that I have good times of my day and bad times of my day, but I can't really discern any pattern to when I feel good or when I feel bad. How can I work to improve that type of situation? And we'll try to give some practical help to discerning that pattern. And what are the current strategies to try to get rid of OFF time, and what are future strategies that are being investigated to solve this problem?

[Slide 6] So ON and OFF time in Parkinson's disease, this is defined as a clinical phenomenon that some patients with Parkinson's disease experience in which the Parkinson's medication, and that's typically levodopa, may work at certain times of the day and do not work at other times of the day. The times where the medication works, the patient feels ON. The times where the medication is not working, the patient feels OFF. This cyclical change throughout the day tends to occur as Parkinson's disease progresses.

Now I want to emphasize here that this phenomenon occurs only in some patients with Parkinson's, many patients with Parkinson's but not all. And if so, it could be your experience that you do not have this ON and OFF cycle throughout the day; and that's fine, that's good. But it's definitely something that affects many people, and it should be addressed as formally as possible.

And so, looking at the bottom of the slide, we have a graph that you may have seen before which gives a pictorial vision of what ONs and OFF look like. So, in the X axis is time and in the Y axis is the clinical response. So, at time zero, a dose is given; that's the blue arrow. And I take my dose, my clinical response improves, my Parkinson's disease symptoms lessen, and I turn ON, and I'm over the top of the graph.

And then, as time goes on, the effect starts to wane, the clinical response starts to dip, my Parkinson's disease symptoms return, and I turn OFF. Just about at that point, I take another dose, there's another blue arrow, and my symptoms, again, improve; and I cycle throughout the day.

Well what happens to a person during ONs and OFFs? **[Slide 7]** Now the symptoms that may occur in these two periods of the day can be motor symptoms, and they can be nonmotor symptoms. So,

motor symptoms include slowness, stiffness, difficulty walking, tremor may return, there may be dystonia. Dystonia is abnormal posturing of a limb. For example, toe curling, and this can be even painful. And then there are nonmotor symptoms which are very important to highlight. Examples may be anxiety, depression, or pain; and these may be symptoms that actually fluctuate throughout the day and may be in response to changes in medication levels. Definitely important to have a handle on both the motor and the nonmotor symptoms that may occur.

[Slide 8] What's also important to note is that in some people with Parkinson's disease, the clinical response to a dose may lead to extra movements or dyskinesias; and this can happen at the peak of the dose response.

In the dyskinesias, they may be tolerable to people. They sometimes may not even be noticed by a patient experiencing them. But at other times, dyskinesias may be bothersome; and so, it may be important for a patient to avoid getting those dyskinesias and staying in the good ON time, ON time without dyskinesias.

Now we have a full webinar archived on the APDA website which is dedicated to a discussion of dyskinesias, and I definitely recommend those who are interested in dyskinesias to get that webinar and to view it. It will give much more information about dyskinesias.

[Slide 9] Now why do ONs and OFFs occur at all? Now this is a very, very complicated and complex issue; and many factors play into why this phenomenon happens at all. But we do know that as the disease progresses, there are fewer healthy neurons that are able to release their own dopamine and that are able to convert the Sinemet®, levodopa that's ingested by mouth. They're not able to convert it to dopamine, and they're not able to release it properly.

And so, what this means is with the fewer healthy neurons in the brain, the release of dopamine becomes less reliable. So, in the beginning of the Parkinson's disease course, all brain dopamine levels lead to a good clinical response. And this is pictured in the graph in that bluish-greenish area. So, the entire range of levodopa levels give a good clinical response.

But as the course of the disease progresses, there is a smaller and smaller window in which this blue-green area is shaded. And what happens is as the dopamine levels in the brain rise high, instead of getting a good clinical response, you get dyskinesias. And as the levels dip low, you get OFF time. Too high is no good and too low is no good. And as the disease progresses, this window narrows and narrows.

[Slide 10] And so what if I know that I have good times during the day and I have bad times during the day? But they seem to be random, and they do not seem to be related to my medication doses. What do I do then? The graphs that I've shown so far have been very simple and seemingly very easy to follow. But this often is not the experience of patients. It is very common for patients to feel this way. It is very common for patients to feel that there is no rhythm or reason to their ON and OFF time. What happens then? So, the best thing to do in my experience is to keep a medication diary, and I'll show you examples of what those diaries look like and how they can be used by your physician to help tailor your medication treatments.

Now, very importantly, to keep an accurate diary, you must be able to tell the difference between whether you're experiencing tremor or whether you're experiencing dyskinesia. Now, again, this may be obvious to some people listening, but it may not be obvious to some. And so, what do you do if you're moving, you're having some extraneous movements, and you don't know whether this is a tremor or dyskinesia? It's really important to know the difference, and that is because tremor implies that you don't have enough medicine in your system. Dyskinesia implies that you have too much medicine in your system, and so we need to know which way it is. And so, one thing to do is to videotape your movements and bring that video to your doctor's visit, and the doctor will likely be able to distinguish between tremor and dyskinesia for you.

Another option is to come to a prolonged doctor's visit. Some doctors will allow you to do this, to sit in the doctor's office for many hours and have the doctor or whoever's in the office look at you periodically and be able to see what kind of movements you are experiencing.

[Slide 11] And the final way to help you distinguish is a wearable technology which has become a very big sort of buzzword in the Parkinson's field today. It's a very hot topic. The general idea of what wearable technology is, is a group of different technologies that are worn on the body in some way that gives clinical feedback about all sorts of conditions.

In our situation, there are wearable sensors that are being developed to tell whether a patient is ON or OFF throughout the day. And one is this example that I show here, which is Kinetigraph™; and this technology is able to distinguish whether a movement is a dyskinesia or a tremor. Now this is yet to be sort of widely available in clinical use; but some day, and I think someday soon, this will be part of clinical care, and it will be very, very helpful for many patients.

[Slide 12] Now if a particular person with Parkinson's is not able to discern a pattern in medication adjusting to clinical response, it could be because of erratic medication responses which are very common in people with Parkinson's disease, especially as the disease progresses. And there are many types; here are three that I pull out, which we'll discuss. One is a dose failure. So, a dose is ingested, but it fails to work. The second is a delayed ON, so a dose is taken, but it takes longer than usual to work. And the third is a sudden or unpredictable loss. So, a patient that, I'm sorry, the medication efficacy stops working suddenly or stops working unpredictably.

[Slide 13] Now why does this happen? There are many reasons, but one thing to really think about, if the medication doses simply do not correlate to the clinical response is to think about the GI tracts, the gut. Now as many of you listening know, the gut in Parkinson's disease can be very abnormal. Many people with Parkinson's disease have constipation, for example. Another problem that many people with Parkinson's disease have with their gut is something called delayed gastric emptying; and that means that the time from when food or medications move from the stomach into the small intestine takes a long time, much longer than it should and much longer than people without Parkinson's.

So, what potentially can happen is a patient ingests the medication, and the medication hangs out in the stomach for a lot longer than it needs to, and it then makes its way more slowly into the small intestine. So, the result of that could be a delayed ON. You take the medicine at one time, but it doesn't actually be seen by the small intestine where the medication is absorbed for a while, and so

you do not turn ON during that period; and that can, of course, interfere with how the medication is then absorbed into the blood and then transported into the brain.

Another thing to keep in mind is the ingestion of dietary protein. Dietary protein is found in things like chicken, meat, eggs, dairy; and that protein can interfere with absorption of levodopa. The reason for this is both protein and levodopa are absorbed in the small intestine, and they actually use the same transporter to cross the small intestine wall into the bloodstream. And so, if there's a lot of protein present in the small intestine, the levodopa won't have a chance to be absorbed; and it will just be passed through the small intestine and not be absorbed to be used by the brain.

The third thing to keep in mind is that other gastrointestinal pathologies may coexist in a patient. For example, *Helicobacter pylori* infection. This is the infection that causes ulcers. And there is an entity called small intestinal bacterial overgrowth. This is a condition in which there is too much bacteria in the small intestine, and it's being recognized as a condition that affects many people with Parkinson's and not, but in Parkinson's disease can interfere with levodopa absorption. So, these things can really play a role in why medication efficacy is so erratic.

[Slide 14] So let's have some examples of medication diaries. Here's medication diary number one. This is a pretty straightforward case. We have a patient who takes their dose at 7:00 in the morning. They take one tab of levodopa, and they also have some cereal; and it takes about a half an hour for the medication to work. And then the medication works quite well for a number of hours.

But the patient is meant to take their dose at 11. That's the scheduled dose, according to their physician, but they turn OFF early. They turn OFF at 10:00, so the dose really lasts three hours and not four. And the patient sort of muddles their way through that last hour, takes their dose at 11 as they're supposed to, turns ON at 11:30. Then the patient has something that is a protein-rich food for lunch, and the medication doesn't last very long, and they turn OFF.

[Slide 15] So the patient brings this medication diary to their next doctor's appointment, and then the doctor makes two observations. One, that the patient wears OFF before their dose is due. There are many potential fixes to this problem, and we're going to go through many of them. But the general principle is that we want to even out levodopa delivery. We want to give even distribution of the medication throughout the day. So, one simple solution is to move the 11 AM dose to 10 AM, and that way you don't have those dips that can cause the OFF problem.

The second issue from this medication diary is that the patient may have protein effect. Their medication does not last well in the presence of dietary protein. And so, one solution to that problem is to move the protein intake to the end of the day, and that can be suggested as a way to get around that issue.

[Slide 16] Sometimes the medication diaries are a lot harder to figure out, so here's an example of one like that. So here the medication diary starts at noon. They take their first dose at noon. They have some soup and salad, so no protein with that meal for lunch. But they do not turn ON from that noon dose. So, they don't turn ON, and at 1:30 it's been an hour and a half. The patient's getting really frustrated that they haven't turned ON, so they take another dose. They've been instructed by

their doctor to take an extra dose should their medication not make them turn ON. And so now they've taken the dose at noon and a dose at 1:30.

By 2:00, they have some trouble, some dyskinesias, because, probably, the first dose potentially was held up in the stomach, got slowly released into the small intestine just as the second dose was appearing, and the medication levels rise. And so there might be some dyskinesias at that point. The patient then may be ON for a while, takes their dose as scheduled at 3:30, but then is OFF again for a while. Then they turn ON at 5.

So, as you can see, this seems a lot more random; and if you're a patient making this medication diary, you can get really frustrated because you don't know what to expect, you don't know what result a medication dose will have, and you can't plan for a day which is so erratic.

[Slide 17] So you bring this medication diary to the doctor's appointment; and, again, the pattern is much harder to discern. But it does seem, now that we understand the concept of having these erratic medication results, it does seem that there are some dose failures, there's some delayed ONs. It does not seem related to protein intake. So, in this situation, it may be worthwhile to have a gastrointestinal workup and to see if there's a gastrointestinal reason for all this erratic response. In such a situation, you may consider rescue doses for the times when the medication doesn't kick in; and we'll discuss that strategy for OFF time as well.

[Slide 18] At this point, I want to bring your attention to a tool on APDA's website called, "The Healthcare Communication Graph." And this can be found at the website (apdaparkinson.org/healthgraph) listed right here on this slide, and this tool allows you to track a series of Parkinson's disease symptoms over time to share at your doctor's visit. And this type of strategy where you're chronicling your Parkinson's symptoms every day over time, it may be a very useful addition to something like the medication diaries that we've discussed before.

[Slide 19] So now let's turn to some strategies for treating OFF time. The major principle that we're aiming for is not to let dopamine levels fall below a certain point. We are aiming to even out the valleys, to not have the valleys at all.

[Slide 20] And here in a pictorial graphic sense is what I mean. So, on the left is a graph I've already shown you, the cyclical ONs and OFFs. But what we're aiming for is we want to make drug delivery more continuous. So, you take your dose, your clinical response improves, and it stays improved for a while. That's really what we're aiming for.

Second option, if we can't get that, is to give doses in a rescue manner. So just as a patient may turn OFF and their clinical response dips, we're going to give another dose and keep that response in the ON section. And so, the two solutions, two possibilities to attack this ON and OFF problem is either making drug delivery more continuous or implementing rescue strategies. And, frankly, we can take all the help we can get; and sometimes both these strategies are thought of simultaneously.

[Slide 21] So here are the current solutions available for OFF time in the continuous category. The first two we've talked about, trying to smooth out levodopa dosages by giving smaller doses more frequently; and that would be the concept of moving a dose earlier to try to cover OFF time. Another,

as we discussed, paying attention to GI issues and protein intake. But there are other medication manipulations that can be done. One would be to add a MAO inhibitor, a monoamine oxidase inhibitor, like selegiline, rasagiline, or the newly approved safinamide. Another option would be to add a dopamine agonist. The ones available in the United States are pramipexole and ropinirole. Those two are available in pill form in a short- and long-acting version. And then there's the rotigotine patch which is a long-acting version that you wear as a patch.

Sometimes the long-acting versions, the medication you take once a day, like the pramipexole ER, ropinirole XL, or the rotigotine patch can be helpful in this type of situation because you're getting medication evenly spread throughout the day, in addition to your levodopa dosages.

In addition, we can add a medication like a COMT (catechol-O-methyltransferase) inhibitor, entacapone or tolcapone. These medications inhibit the breakdown of levodopa and allow for a more continuous and smooth efficacy of the medicine.

There is a longer-acting levodopa formulation known as Rytary™, that's a carbidopa-levodopa extended release. This medication is actually a pill containing small little bubbles of medication, and this medication dissolves. The smallest spheres dissolve first, and then the middle-sized, and then the bigger ones. And there's a slow release of the levodopa from the stomach in that way. And this can be helpful to some people. Other people don't find it helpful, I should say, but some people do find it helpful to kind of smooth out their medication response.

There's also a form of carbidopa-levodopa in an intestinal gel, and this is called Duopa™, and the method of delivery is inserting a tube from the stomach into the small intestine, and this tube is then attached to a small pump that is worn on the outside of the body. And this pump pumps the intestinal gel into the small intestine continuously throughout the day, and that is another method of giving continuous levodopa.

And, finally, deep brain stimulation (DBS). This is a topic all in of itself and, in fact, will be the topic of the next APDA webinar. But for our purposes here, deep brain stimulation can be an alternative to medication adjustments when a patient is having a lot of ON and OFF phenomenon. And what happens in this type of surgery is a wire is inserted in the deep parts of the brain which delivers electrical stimulation continuously to the brain and in that way jumpstarts the circuitry that's abnormal in Parkinson's disease. And since the stimulation is given to the brain continuously, it can mimic a more smooth release of levodopa than medications can.

[Slide 22] Some current solutions to OFF time in the rescue category are two. We have Parcopa®; this is carbidopa-levodopa that is dissolved in the mouth. Since it doesn't need to be broken down in the stomach in the same way, it can provide a quicker boost of medication than some of the other formulations of carbidopa-levodopa can. And we also have apomorphine injections. Apomorphine is a very powerful dopamine agonist which is not available in pill form or patch form. It's available only in injections, and it can be used when a patient feels that they're turning OFF. They can give themselves an injection, and they can turn back on.

[Slide 23] Now what are future solutions to ON and OFF time? And, again, we have the strategies that are aiming for more continuous drug delivery, and we have the strategies that are aiming for rescue.

[Slide 24] So here are the continuous strategies that are under development now, and we'll go through each of these. There's the subcutaneous levodopa infusion, the subcutaneous apomorphine infusion, the Accordion Pill™, opicapone, and focused ultrasound.

[Slide 25] So the subcutaneous dopamine infusion, this is a proprietary formulation of carbidopa-levodopa. It's actually a liquid, and the idea is that instead of being pumped into the gut, which is how Duopa works, this is going to be pumped into the subcutaneous tissue, more in line with an insulin pump than the Duopa. And this is being tested in these two versions that you see here, the belt pump version and the patch pump version, and clinical trials are investigating whether this mechanism will allow the levodopa to be absorbed properly and to give a smooth response.

[Slide 26] A similar setup is being investigated with apomorphine, the dopamine agonist that we talked about as the rescue injection. In this setup, the apomorphine is infused slowly and subcutaneously; and this apparatus is approved in Europe and is used in Europe, and it is undergoing clinical trials now for the United States.

[Slide 27] The Accordion Pill. This is a type of pill that's being designed not just for levodopa. It's being designed for any pill that needs to be absorbed slowly throughout the day. The idea is that the Accordion Pill is made up of thin films on which the medication is embedded. These films are then layered and then folded and put into a capsule. And the idea is that the patient ingests this medication; and because the folding is very, very complicated and intertwined, it takes a while for this unfolding to happen. And this unfolding then allows for slow release of this medication.

[Slide 28] And in clinical trials, it was seen that the pill is retained in the stomach for way longer than a regular Sinemet pill, which tends to stay two to three hours in the stomach. This stays in the stomach for eight to 12 hours, slowly releasing the medication into the small intestine. A phase II trial showed some promising results, and currently it is undergoing phase III trial; and that is available for patients to participate in.

[Slide 29] Opicapone, this sounds like tolcapone and entacapone because it too is a COMT inhibitor, the newest developed COMT inhibitor. **[Slide 30]** This is a medication that inhibits the breakdown of carbidopa-levodopa, but it's seemingly better, a better compound than entacapone. And that's why it's being studied.

A phase III trial has been completed, and it did show a decrease in OFF time that was much better than of the control group. And this also is continuing to be evaluated to see whether it will be approved by the FDA (United States Food and Drug Administration) for use. So, stay tuned for more on that.

[Slide 31] And then we have focused ultrasound. Focused ultrasound is a really fascinating new technology, again, available in Europe for many conditions, available in the United States for some conditions, but not yet for Parkinson's disease. The idea for focused ultrasound is that there's focused

beams of ultrasound energy that converge within the brain tissue on a very specific point in the brain to form a small lesion in the brain. So, all the energy, each beam of energy itself is not able to create any damage. But when all the energy converges on that one spot, it burns a little hole in the brain without having to cut into the brain at all.

This small lesion then interferes with the brain circuitry and can improve Parkinson's symptoms. So, this is undergoing clinical trials for Parkinson's disease. It is already approved by the FDA for another brain condition known as essential tremor, and now we are most likely going to see its approval for Parkinson's disease as well; and that will be something to be in line with deep brain stimulation. Patients will have to choose between one of those two procedures if that's what their doctor recommends.

[Slide 32] Now let's discuss future drug delivery systems in the rescue category, and there are two. One is the levodopa inhalation powder, and the other is apomorphine sublingual film.

[Slide 33] So levodopa inhalation powder is the idea that it's used for rescue doses – patients either dose didn't turn ON or for some reason they have erratic medication response and may be able to give themselves a boost of the carbidopa-levodopa inhaled; and, therefore, the absorption takes place through the pulmonary tract and not through the gastrointestinal tract. So, this is kind of a new mechanism of delivery.

Positive results of the phase III trial were announced in February 2017, and a new drug application has been submitted and is awaiting FDA decision. So, this is actually close to being approved.

[Slide 34] And, finally, the apomorphine sublingual film. So currently as we discussed, apomorphine can be injected by a patient. That isn't a very pleasant experience for some people. They'd rather not inject. And so, a sublingual film has been developed, placed in the mouth with absorption in the mouth, through the walls of the mouth, and positive results of a phase III trial of this type of rescue dose were announced in January 2018. And, again, a new drug application has been filed for this; and, again, FDA decision is awaiting.

[Slide 35] And so to summarize, ON and OFF time in Parkinson's disease can adversely affect the quality of life of people with Parkinson's. And so, it's really important for people with Parkinson's to try to keep track of the timing of their medications and their clinical response, maybe through a medication diary, to help inform their doctor about how to adjust their medications to help their ON and OFF time.

And as I went through, there are many, many strategies to help ON and OFF time and many additional strategies that are currently under development. And so, there's a lot that can be done now, and in the future, we're going to have a lot more strategies as well.

And now I'll be happy to take questions.

Question & Answer

Stephanie Paul

Dr. Gilbert, thank you very much for this really informative presentation today.

[Slide 36] It's now time for the Question & Answer Session.

Stephanie Paul

Okay, let's get started. Our first question is coming from the Web. It's coming from Michael, and the question is, "My doctor does not focus on my questions about OFF times. What is the best way to discuss this strategy for control?"

Rebecca Gilbert, MD PhD

That's a great question; and, obviously, it's very, very key to bring up these issues in your physician's visit or else you won't get anywhere. You won't have any improvement.

So, what I would suggest is maybe of your own accord, making a patient diary, making a medication diary over a week. Every day write out the time of the day, whether you're awake, medications, food that you've taken, and what your response is and bring those to your next doctor's appointment. And then I think that will open up the conversation.

Stephanie Paul

Okay, terrific. Here is a question from the Web again, from Allen. "What is the best way to deal with fatigue associated with OFF episodes?"

Rebecca Gilbert, MD PhD

All right, so that's a good question. If we do think that fatigue is an OFF symptom and that the fatigue really is fluctuating with the medication, then the best way to handle it is to decrease OFF time through any of the strategies that we mentioned.

Now there are a lot of options, as we mentioned, all the different medication adjustments that can be made, either changing the timing of the medication you're taking now or adding another medication, and those are all things to consider.

You also would like to consider whether, in fact, the fatigue is not necessarily related to OFF time but is a phenomenon you may experience regardless of your medication levels. And if that's the case, then that opens up a different sort of avenue of thinking about it. So, I think that's the first question. And, again, you can get at that question with a medication diary to see if the fatigue really does have a correlation with the medication doses.

Stephanie Paul

Okay, thank you. Here's a question from Debbie, and the question is, "How many people with Parkinson's disease are actually protein sensitive? I thought the number was 20%."

Rebecca Gilbert, MD PhD

So that's a great question, and I'm not sure we know exactly what percentage are protein sensitive. But it's not everybody. It's definitely not everybody, and I think that's very important to highlight because very often this concept of having to avoid protein is all over the literature; and everyone feels that they need to not have protein. And protein is very important. Protein is the building block of life, and you need to eat protein to have energy.

And so, if you don't need to manipulate your protein during the day, then you shouldn't. And so, you should not assume that's what's happening. So, if you are not sure whether you have a protein effect, the best way is experimentation. So, you spend a couple of days keeping a medication diary and having your protein at the end of the day and seeing if you have a more smooth response to your medication and less erratic responses to your medication. And then you will know. I mean there's no blood test to tell you whether you do or do not have a protein effect. You need to actually just experiment, and that's what I would suggest if you are not sure.

And, again, don't assume because it is a very, it's much easier not to have to worry about the protein effect. And if you don't need to worry about it, then you don't need to worry about it.

Stephanie Paul

Okay, great, thank you. Here's a question from Catherine. And her question is "What is the difference between levodopa and dopamine?"

Rebecca Gilbert, MD PhD

Okay, great question. So, levodopa is what is present in the pills that are given. So, all the formulations that we've talked about so far contain levodopa, and the reason is because that dopamine does not cross the blood-brain barrier. It must be in the levodopa formulation to get into the brain and then be converted into dopamine once it's in the brain. And so, all the medications we've talked about so far are levodopa. However, dopamine is what actually does the work once it's in the brain.

Now what's important to know about that is that the dopamine is a drug, meaning if you go into the ICU for some other unrelated cause, low blood pressure may be a problem, and they will give you an infusion of dopamine to raise your blood pressure. That dopamine is not a Parkinson's medication and does not enter the brain. And so that can be confusing even for doctors who say, "Oh, we have dopamine." But that's not the dopamine that a person can ingest to make it into the brain to affect Parkinson's symptoms. So, hopefully, that answers your question.

Stephanie Paul

Yes, that's very good. Okay, I have another question from Jeffrey, and he asks, "If I do not experience OFF episodes, does that mean my medication is working effectively?"

Rebecca Gilbert, MD PhD

Okay, that's a great question. It means that, yes, so one of two options. Yes, it means that your medications are working optimally, and you should be very pleased. There're two major categories of people with Parkinson's. One is people who have what we call motor fluctuations, so that's another way of saying ON and OFF time; and there are other people who we call smooth responders. They take their medication. The medication works. It lasts a long time. It lasts well into when they take their next dose. They never experience a period of time in the day where their medications wane. That's great. We love smooth responders. So, if you are one of those people, then fantastic, and none of what we talked about is necessary for you. You are a smooth responder.

Stephanie Paul

Okay, great. And here's a question that follows after that. This comes from Marjorie, "Why is OFF so unpredictable day to day?"

Rebecca Gilbert, MD PhD

Okay, that's a great question. So, one option may be protein effect. You may be eating different amounts of protein in different days or the timing of your food may be different in different days, and that could be responsible for some of the erratic nature of the responses from day to day.

In addition, the delayed gastric emptying problem can be variable. So, a patient who has that problem where the stomach does not unload their contents into the small intestine in the normal rate, that may be very erratic. One day the stomach may hold onto the contents for longer than another day, and so the erraticness of medication response may be linked back to the erraticness of delayed gastric emptying as another possible option.

And the other thing to keep in mind is that Parkinson's symptoms in general can vary widely, not just because of protein or the gut, but things like fatigue, whether you slept well the night before, whether there's depression, all sorts of things, whether you're constipated and feel lousy from that, whether your blood pressure is low. There's so many different reasons that a person with Parkinson's may have a variable experience from one day to the next, and that all feeds into how the Parkinson's symptoms will be felt that day.

And so that's one of the most frustrating things about Parkinson's is how variable the symptoms are, and there's just so many reasons why that variability is present. So, thanks for that really good question.

Stephanie Paul

Okay, terrific. I believe we have a telephone caller, so, Operator, could we please take that phone call?

Operator

Yes, our next call is from Kayla from Maryland. Kayla, please state your question. Your line is now live.

Kayla from Maryland

Hi. My physician has suggested using Duopa, but I am concerned about the surgery for the PEG tube placement. Does this usually cause problems?

Rebecca Gilbert, MD PhD

So, it is true that insertion of a PEG tube is required. It's actually a tube that enters through the stomach and sits in the small intestine where the medication is absorbed. That process can have some side effects and some complications that you need to be aware of. It can result in infection at the site. There can be kinking or breaking of the tube, which can result in problems.

In general, if there are problems from the system, from the actual hookup in the system, so then you don't use the pump for a short while, you take your oral doses that you have readily available knowing this may be a problem, and you go to the gastroenterologist and get it fixed. So, the problems are not usually that dire. There may be a little infection around the insertion. You may have to take some antibiotics. In general, beside it may be an annoyance that you need to have the system fixed, but it isn't necessarily a really dangerous set of things that can happen. And so, it's a risk-benefit analysis. You definitely have to be aware that these things may happen, and they may interrupt your life, and they may have to be dealt with; but the positive results may outweigh the possibility of those things happening.

And so just like anything, you want to have all the information, really understand the good that can come of it, the bad that can come of it, maybe talk to patients who've had it done and get a sense on the ground what it feels like to have that system in place, and then make an informed decision with you, your family, and your doctor.

Stephanie Paul

Terrific. Thank you, Dr. Gilbert. We have another question coming from the Web. This comes from Diana. The question is, "Are there ways to get the levodopa absorbed more quickly, such as chewing it?"

Rebecca Gilbert, MD PhD

Okay, great question. So, the Parcopa that I mentioned, this is carbidopa-levodopa that gets dissolved in the mouth, so you don't swallow the pill and then it gets broken up by the stomach

churning, but it gets dissolved in the mouth itself. So that is a way of increasing the quickness of how the medication can give its effect.

You can actually mimic that by chewing a pill. So, you can take a regular carbidopa-levodopa pill, chew it up, grind it up, and it should sort of mimic what a dissolvable pill will do. Some say that if you chew up your medication and drink it with sparkling water, something with carbonation, that's the sort of fastest way to turn a carbidopa-levodopa pill into a pill that's more like the dissolvable pill. And so, you can definitely experiment with those things as rescue doses.

Stephanie Paul

Okay, thank you. I believe we have another caller. Operator, if you could please take the phone call.

Operator

Yes, our next call is from Jodi from Tennessee. Jodi, please state your question. Your line is now live.

Jodi

Thank you. How do I know if my anxiety is related to OFF time or just a symptom of the disease?

Rebecca Gilbert, MD PhD

Right, so that's an excellent question. Anxiety, again, is exactly like the question about fatigue earlier. It could definitely be a phenomenon that fluctuates with medication doses, but it could also be a nonmotor symptom that you have regardless of medication doses. And sometimes that's hard to tease out. And the best way to try to get a feel for it is, again, a medication diary where you would have the time of the day and when you take the medicine and when you experience the symptom, and then try to correlate the symptom to the medication doses.

If the anxiety is an OFF phenomenon, and it does seem to peak when the medication is at its lowest in your brain, the solution would be, again, to even out the levodopa delivery and make the delivery smoother and to not have those valleys where the anxiety would kick in.

If the anxiety is not related per se in a time-linked fashion to the medication doses, then attacking the anxiety sort of independently would be the way to go with a medication that would treat anxiety or other nonmedical interventions to anxiety.

Stephanie Paul

Okay, thank you, Dr. Gilbert. We have another question from the Web. This comes from Dwight. And the question is, "If you feel you are protein sensitive, is it an option to keep your protein intake consistent and adjust the medication instead?"

Rebecca Gilbert, MD PhD

Okay, that's an amazing question. The answer is yes, that would be a very reasonable way to approach it, if possible. The flip side is true. So, if patients have too much medicine in them and may have a period of time where they have troublesome dyskinesias, some people would eat proteins at that point to try to bring down their level. So, manipulating your protein to try to achieve the optimal clinical response is not a crazy idea, and if you can aim for that, that may work.

Stephanie Paul

Okay, thank you. We have another question from the Web. This comes from Beth. The question is, "How is the choice made between a MAO inhibitor and a COMT inhibitor for rescue therapy?"

Rebecca Gilbert, MD PhD

Okay, that's a good question. MAO inhibitors are typically less powerful than COMT inhibitors. And so, if you're experiencing any significant amount of OFF time, you may need a COMT inhibitor to be added. That's a bit more powerful a medication, and that would be a decision that you would make with your doctor. Of course, there are side effects to each of these medicines that have to be weighed as well. COMT inhibitors, for example, can cause diarrhea in a small percentage of patients. So, if you are one of those patients who experience that from the COMT inhibitors, then that may not be an option for you, and you may have to choose a different method of prolonging the ON times.

Stephanie Paul

Okay, thank you. Here's another question from the Web. This comes from Roger. "Would being on a time-released form of levodopa rather than regular Sinemet be a better choice for me? I have to take seven pills a day."

Rebecca Gilbert, MD PhD

So that's definitely something to consider. Now what I should add, however, is that if you take seven pills a day, and ON the schedule that's been created for you, your Parkinson's is well tolerated or there isn't a lot of OFF time, then one may consider keeping you just the way you are. We don't like to fix what's not broken. So, taking seven pills a day, in and of itself, it is not convenient, for sure, and that may be a reason to change; but if that can be handled and the seven pills a day are doing their job, then one may consider keeping things as they are.

If you're taking seven pills a day and you're still getting a lot of OFF time and there really isn't a good, smooth response to the medication, despite all those doses, then, yes, I would definitely consider some of the other strategies that we talked about today including a long-acting or the extended-release carbidopa-levodopa that I mentioned during the talk.

Now, that does not mean that this will be a panacea. There are many people who switch from seven doses a day of the regular carbidopa-levodopa and they take the extended release instead, and they don't find that it's as good, and they might switch back.

And another thing to mention is that when you're switching from the carbidopa-levodopa seven pills a day to the extended release, you're not going to necessarily go to three times a day or one time a day, certainly not. You may go to five times a day. So, the number of pills can still be significant. The number of doses can still be significant. So, the amount of benefit that you get may not be as great as you're imagining, but certainly it's worth a try. If your current situation is not ideal, definitely worth trying some of these other options that we talked about.

Stephanie Paul

Okay, here's another question from the Web. This comes from Robert, and his question is, "Does exercise affect the OFF periods?"

Rebecca Gilbert, MD PhD

Oh, that's a great question. So, it very well might. I mean some people definitely experience that an exercise regimen or a period of time doing exercise can improve their motor symptoms. And so, one could extrapolate from that that if exercise is thrown into the day, it could definitely boost the motor response to a point where you don't feel as OFF. And so, there's never a time when a Parkinson's doctor says no to exercise. And if exercise can feed into the variability of the day that we talked about and enhance your day in any way, then I would say to go ahead and to use that to the full potential.

Stephanie Paul

Okay, we have one final question today from the Web, and this comes from Rajiv. And the question is, "Is a lack of sleep a typical symptom? I sleep less than three to four hours a night but do nap around three to four hours during the day."

Rebecca Gilbert, MD PhD

There's many things that are true about what you just said. One is that people with Parkinson's can have a very difficult time with sleep. Typically, they fall asleep okay, but then wake up either once and then can't go back to sleep or wake up frequently throughout the rest of the night, and then they may be totally exhausted during the day and take a nap during the day. So that is a pattern that we see.

As I said before, people have been asking about the variability of the days in Parkinson's. And certainly, being fatigued and not having a good night's sleep can feed into why one day might be really not as good. If the sleep wasn't as productive, that next day may be a worse day in terms of Parkinson symptoms than a day where the sleep was better. And so, getting good quality sleep is really vital to maximize ON time. That's definitely true.

And also, something to add is that if a person does a lot of sleeping during the day, that may be part of the reason why they're having a lot of trouble at night. And there may have been sort of a flipping of the day and the night. This is not necessarily happening to you, but something to keep in mind. Like what's the chicken and what's the egg? Why am I not sleeping? Well, maybe I'm not sleeping because of my nap. I know that I'm napping because I haven't slept, but how do you break that cycle?

And that may be something to work on to try to get more consistent sleep at night, and that may make the days in general better.

Closing Remarks

Stephanie Paul

[Slide 37] Okay, Dr. Gilbert, thank you so much for this wonderful information. And my thanks to everyone for participating in today's telephone and Web education program. I do apologize that we couldn't get to all of the wonderful questions, **[Slide 38]** but if you have a question or would like to speak with someone from our Scientific and Medical Affairs Department, I encourage you to visit our website or call 1-800-223-2732, and you can ask your questions there.

Stephanie Paul

I'd like to thank Dr. Gilbert for her presentation. I would also like to emphasize to everyone on the phone that we really do appreciate your feedback and comments and want to make sure that you complete the program evaluation form. APDA is so proud to support those living with Parkinson's disease by helping them live life to the fullest every day. We do this each year by providing more than 1,700 support groups that serve more than 75,000 people with Parkinson's disease and their family members and so running 770 plus exercise groups attended by more than 21,000 participants. These exercise programs help improve the symptoms of Parkinson's and lessen the impact of the disease. We also offer educational symposia across the country on living well with the disease, and these programs have been attended annually by more than 5,500 people impacted by Parkinson's.

We rely on the support of the entire Parkinson's community to accomplish all of this. To join us in the fight against Parkinson's and to learn more about the support APDA provides across the country through our network of chapters and information and 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 everyone.