Thank you everyone for joining us. I'm Bryan Roberts, Michael J. Fox Foundation patient council member and your moderator for today. You are able to submit questions throughout the hour. You should see a Q&A box near the middle of the screen, please type your questions there and we'll do our best to get to as many as possible. Also, we're providing slides from today's webinar for you to download. You should see a box called resource list on your screen. Click on the link from there and download will open in the new browser window. You can save or print from there.

There are also many common issues you may run into. If you have any technical difficulties, please try refreshing your browser. If that doesn't seem to work, please try a different browser. The boxes you see, dialogue boxes such as slides, Q&A, so on and so forth are adjustable and can collapse if they're impairing your view. Please type your questions in the Q&A box throughout the hour. We'll do our best to answer as many as possible and if we see themes arise, we will definitely try to answer many of your interesting and engaging questions.

If you have questions on another topic, we've covered everything from genetics to constipation, always popular, in our series. You can view the full library in the resource list.

Today our panelists will discuss what causes “off.” When symptoms aren’t well controlled, how to manage this often challenging time and treat these fluctuations. And I think of interest to many listeners, the therapies that are in development to smooth out these cycles.

Let's meet our panelists. Like I said, I'm Bryan Roberts, I'm on the patient council. I was diagnosed with Parkinson's disease when I was 30. Our next participant retired Associate Dean from Ithaca College, School of Business, Barbara Howard. Barb was diagnosed in 2011 at age 55. Barb also knows real pain and suffering as she's been a season ticket holder for the Buffalo Bills for over 20 years. Welcome Barb.

Barbara Howard: 00:03:41 It's actually over 25.

Bryan Roberts: 00:03:44 No one deserves that. And that's coming from a Mets fan. Glenn Batchelder is a biotechnology entrepreneur and member of The Michael J. Fox Foundation Board of Directors. Welcome Glenn.

Glenn Batchelder: 00:04:05 Thanks Bryan, glad to be here.
And our final panelist is Dr. Sarah Horn. Dr. Horn is a board-certified neurologist at the University of Pennsylvania, and an Edmond J. Safra Fellow in Movement Disorders. Thank you for joining us Dr. Horn.

Sarah Horn: Thank you for having me.

Bryan Roberts: So, we have a great, knowledgeable, and diverse range of talent to talk about “off” episodes. What we will cover today is what is “off”? Why does “off” happen? How do different patients manage “off”? And I think the devils in the details there. Some extremely interesting, innovative ways. And then finally, what are the new therapies in development? And things are quite promising for the future. And I think you want to really hear what's in the pipeline. So with that said, let's begin. Let's start with defining what is “off” time? I think once we have a definition of this, we can move forward with shared understanding. But, “off” time means something often different to each, depending on where you sit in the Parkinson's spectrum of care. Dr. Horn, why don't you start us off with, how do you define “off” time?

Sarah Horn: So, “off” episodes are whenever the benefits of Levodopa wear off and there's a return of the Parkinson's disease symptoms in between doses. The textbook definition is a levodopa dose lasting less than four hours. But practically speaking, I think of it as, whenever the Levodopa dose doesn't last until the next dose is due. These usually begin several years after diagnosis of Parkinson's disease. They're due to progressive disease combined with chronic use of levodopa. Some risk factors that we know that can contribute to developing “off” times is a younger age of onset of Parkinson's disease, longer use of levodopa and higher doses of levodopa.

And typically whenever people refer to “off” time, we're talking about motor “off.” So, that stems specifically the return of the motor symptoms of Parkinson's disease, meaning slowness, stiffness, tremors. But I think it's also important to recognize a lot of people experience non-motor “off” symptoms. Things like sensory symptoms, pain, tingling, restlessness. There can also be behavioral symptoms like panic attacks, irritability, dysfunction. And often times, the hearing loss is predictable. It happens towards the end of the levodopa dose.

Bryan Roberts: Dr. Horn, sorry to interrupt. You're breaking up a little bit. Would it be possible, I believe you were discussing.

Bryan Roberts: Huh. Dr. Horn, can you hear us now?
I'm having some trouble hearing you. I think I might call back in.

Okay, that sounds good. We'll be here for the hour. Thank you Dr. Horn.

So what Dr. Horn was stating that, with the “off,” there were both motor and non-motor symptoms that occur. And we're going to delve into these throughout the hour.

So, Barb, as a patient, what is “off” time for you?

Well as Dr. Horn was saying, “off” times can be either motor related or non-motor related. And I guess “off” times are also different for everyone. I'm sure many people have heard the expression, if you've met one person with Parkinson's, you've met one person with Parkinson's. So they vary a lot. Again, as she mentioned, tremors, slowness, stiffness, gait, balance issues. In “off” times, those become more bothersome. But for me, the non-motor symptoms are actually what are my biggest Achilles’ heel if you will.

And it actually took me a while to grasp that what I was feeling was actually a part of my Parkinson's. So I do get slow and I lose some dexterity, but for me, I also get sort of foggy brained, a cloudiness, unfocused, moody and very anxious. I think Dr. Horn mentioned anxiety attacks, panic attacks kind of thing.

And it's sort of annoying from an individual standpoint because I can feel myself getting grump or feel myself getting down, but you can't start or stop it. You can't sort of just say, "Oh, just turn it "off." So that's very difficult. My voice becomes quieter and words are not as clear sometimes. Or sometimes I sound like a 13 year old boy going through puberty with my voice cracking and raspy. It's funny at our house, between my husband's sore hearing and my speech communication, we joke, it's my speech or his hearing.

The other thing to is that I think that for me the “off” times can be either very shallow and last a short period of time or they can be longer and what I call deeper. Where the symptoms seem to be more intense, there seems to be more of them. And obviously the deeper and the longer it is, the more impact it has on my daily activities.

For me, most of them happen right around my dose of medicine time. So you sort of know, with predictability. But again, it could
be ten minutes before my next dose, it could be an hour before my next dose.

And this is sometimes, it's been as much as an hour before and an hour after. So, it can be very difficult and very frustrating. When my medicine works, it works very well and I have few symptoms. So to have an “off” time is tough.

Bryan Roberts: 00:11:37 So Barb, if I could just follow up. When you say you go “off,” there's a, we'll call it different depths, you feel. Would that be the proper way to describe it?

Barbara Howard: 00:11:51 Yeah, I think in some cases, the symptoms feel very minor and you don't become as slow. I don't become as moody, if you will, kind of thing. And sometimes when, especially with the longer the “off” period lasts, the more intense it becomes, the more, sort of, noticeable the symptoms are.

Bryan Roberts: 00:12:17 Interesting. Thank you.

Glenn, as someone who's been on the therapeutic development end of, kind of the, business of bringing treatments to patients, how did you, what did you see “off” being for these individuals? What was the lived experience? How would you define it?

Glenn Batchelder: 00:16:09 Well, thank you so much. So I come from, sort of, a unique perspective having founded a company focused on developing therapies for “off” episodes. And it's probably worth noting that we sold the company. I no longer have any financial interest in it, it's just an area where over the time I was working on it, I really have become passionate about.

And so when we started the company, we had this technology that could have addressed a whole series of different disease associated challenges.

Bryan Roberts: 00:16:41 Hello everyone, I'm back.

Glenn Batchelder: 00:16:42 Hey Bryan. So I was just talking about the drug development perspective of “off” episodes.

So when we were looking for where to focus, we spoke with many Parkinson's patients and we came to realize just how impactful “off” episodes were on patient's lives. And many of them said to us, it wasn't that their underlying medications didn't work. It was really not knowing when they would let them down and sort of leave them stranded.
And we also heard that the more high pressure the situation, the more consequences if they were sort of turned “off” in the situation and worried about it, the more likely the episode would occur. And this was really at the heart of what was making patients change the way they lived.

And so we were really struck by this as an area where this uncertainty, this inability to sort of plan your life in the way that they have over time, was really something that inspired us to focus on “off” episodes and try and give patients more control of their life back.

Bryan Roberts: 00:18:14 So, now that we've talked about how we define “off,” why does “off” happen? So, Dr. Horn, how do you see the, what's the cause, the myriad of reasons, why does “off” happen in patients?

Sarah Horn: 00:18:59 Right. So, I'll start by talking about, kind of, what happens in the brains of people with Parkinson's disease. So we know that Parkinson's disease causes dopamine depletion in the brain, especially in the deep parts of the brain called the basal ganglia, which is very important in this orchestra that controls movement. And as the disease progresses, there's this loss of dopamine and that, in combination with how the brain reacts to doses of levodopa, combine to create these motor fluctuations over time.

Bryan Roberts: 00:19:41 So, when a person is going “off,” is there a typical amount of time it takes? Or is it very individual?

Sarah Horn: 00:19:57 So like most things in Parkinson's disease, it's very individual. But, commonly, whenever people are first starting to notice that they're experiencing “off” times, it'll happen toward the end of their dose. They'll notice if maybe they're a little bit late on their dose, they'll notice their Parkinson's starting to reemerge.

And then as time goes on, that'll happen earlier and earlier.

Bryan Roberts: 00:20:24 Great. And I think you also said something that many Parkinson's patients kind of realize in just about everything is very individualized with Parkinson's. There are some commonalities, but the lived experience tends to be different for everyone.

Now Glenn Batchelder, what about the gut? What role does that play in this?
Glenn Batchelder: Yeah, so it's interesting. So, from somebody who works with trying to make better drugs, levodopa is remarkable drug, partially because it, in the end, replaces exactly what your brain is missing, the dopamine. But one doctor said to us as we were sort of beginning this journey of trying to figure this out was in terms of maintaining those consistent level of dopamine, L-DOPA, not too high so you don't trigger the potential dyskinesia, and not too low so that you turn “off,” is that you really couldn't come up with a more challenging oral drug or a more challenging disease in Parkinson's disease for this situation.

So, the reason is because L-DOPA is what you call a neutral amino acid. Amino acids are the things that make up proteins, these little blocks. So, because of that, L-DOPA only goes from your gut, or your intestines, into your blood in a very small part. It's called a jejunum. Otherwise, it just sits within the intestine, and therefore, in contrast, many of the drugs out there, any time they're in your stomach or along the way, they're going into your blood. So it gets hung up there, and as Parkinson's disease progresses, for example, your stomach with, what they call, empty more radically.

It may push the L-DOPA through very quickly, or it may hang it up there for a long time, and it doesn't get in. When it does go down along the way, and it reaches the jejunum portion of the intestine, it competes with all the other amino acids. So, if you've ate some meat or other proteins, those are going through the same pathways and can keep the L-DOPA from getting in. All of this creates this situation where, in terms of time and how much gets in, it's a real challenge to predict.

If we come back to what Dr. Horn was just talking about, having a consistent level is extremely important, and the further along you are with the disease, the more sensitive people get to that level and hence, part of the hypothesis, why people have these “off” times. We in the drug development business call that oral delivery of L-DOPA the oral gauntlet. It's just a very, very challenging thing to do, and so a lot of what people think about in terms of developing drugs is how do you create that more consistent level.

Bryan Roberts: Great. Very interesting. We want to take your questions as we go through the hour, I think now might be a good time to take our first question. This question will go to Dr. Horn. Dr. Horn, does exercise help decrease “off” periods, and Dr. Horn, if you could please speak up? The mic may be a little low.

Sarah Horn: Okay, can you hear me better now?
Bryan Roberts: 00:24:10 Yes, that's better. Thank you.

Sarah Horn: 00:24:14 So exercise in general is really great in Parkinson's disease. I recommend pretty much all of my patients to pick up a regular exercise routine whenever they're diagnosed with Parkinson's disease, and then to continue it really for the rest of their lives. We have some research that's been done on exercise and Parkinson's disease, and we know that it helps in a lot of areas, including mobility, walking, activities of daily living, mental health, mortality.

I don't know of any specific studies that have been done looking at “off” time, specifically, but I think that in Parkinson's disease, people who exercise regularly generally feel better and may be able to better tolerate their “off” times. The caveat is that sometimes people notice that stress, be it emotional stress and anxiety, or physical stress like exercise, can actually trigger “off” times, so that's one other consideration to think about when thinking about “off” times in exercise.

Bryan Roberts: 00:25:22 Barb, as someone who exercises with a regularity, does it sometimes make you feel more “off” while you're doing it?

Barbara Howard: 00:25:36 I generally try to plan my exercise when I think I'm not going to be “off,” but yeah, there are times when I have a particularly ambitious program at hand, as I complete the program, whether it's on the elliptical or whether it's doing some running or whatever, I will start to feel myself going “off” and it's not unusual for me to sort of have to counter that with, again, the timing of it. So, it does have again, as Dr. Horn pointed out, it's not every time that I exercise, so it's different now from person to person, but even from day-to-day.

Bryan Roberts: 00:26:17 For those of you listening to the webinar, you may be seeing a theme of unpredictably, and I would argue that is probably one of the hardest things about “off.” When it comes, it's often hard to schedule life around it. But, one advantage of having Parkinson's is you have a long timeframe to learn to manage many symptoms, I think. I think exercise is one. I've started skateboarding, which I would not recommend, because when I go “off,” I really go “off” the board.

Like my seven-year-old said, "Dad, this was not a good idea," so lesson learned. If you don't have a seven-year-old to manage your “off” time, there are other ways to do it. Let's talk about how individuals manage “off” and perhaps how we talk about it as well. So Barb, give us a little context. What is your day-to-day
like now verse, let's say five years ago and how does that impact your “off” times? Does it impact it? What is life like?

Barbara Howard: 00:27:56 Well, five years ago, I was an associate dean of a school of business and I was in 40 to 50 hour work weeks. They were very stressful positions, and that's been pretty much my standard throughout my career. It wasn't long after my diagnosis that I could tell that this stressful environment was not a good environment to have Parkinson's in, and vice versa. I found the more stressful the situation, the more my PD symptoms impacted my daily life.

Now that I've retired, I still get very dizzy, but I have more control over my schedule. I volunteer 8 to 12 hours a week at a local hospice house. I sit in on a zoning board of appeals for the town. I'm active in the local United Way, women's leadership council, and I travel, both with my husband and to see my one-year-old granddaughter. So, I haven't become housebound or not willing to do some things, but I try not to fill my days with too many activities.

I don't make appointments too early in the morning when I know it's going to be tough for me to get up and get going and be there. I recognize that there are certain times during the day that I have a higher probability of an “off” time than others, and so I try to work around those. Again, as I mentioned, I try to exercise at a time during the day when I'm generally in a good position.

One of the things that, for me, and recently just in the past few months, I have been more apt to tell my family and friends when I was actually experiencing an “off” time, but I made sure to tell my husband and say to him, “I'm ‘off’.” That sort of has been good because sometimes it's not physically obvious to somebody. It's physically obvious to me. My brain is foggy. I can feel myself being moody. I can feel all those kinds of symptoms, but they're not necessarily visible to everybody else. The fact that they now understand, that's been very helpful because they've been able to support me through those tough times.

Another thing, I take my medicine on schedule. We've heard previously that the meals, the eating, and the combination of eating and the food sometimes doesn't work well, so I try to make sure that I stay on a, not rigid but sort of an accommodating schedule for not taking medicine and eating food basically at the same time. Then, one of the things that I've had to do over the past few years is to adjust the timing and the dosage of the Parkinson's medication itself.
Working with my doctor, we've made adjustments to both the timing and the medication a couple of times and it has minimized my “off” times. Obviously, anything else that keeps the stress out of your life is good.

Bryan Roberts: 00:31:02 Barb, I just want to get back to what you were talking about with communication. Can you talk a little bit more about when you decided to tell your close friends, your husband, so on and so forth, that you were going “off”? Did that lessen the severity? Did it lessen the time? What was the outcome?

Barbara Howard: 00:31:24 It's hard to tell because I still have relatively minor “off” times right now, but I hadn't really had a period of time when it has been really “off.” It's more comforting and it's less stressful for me, so my guess would be that in this period of time, they probably are shorter. Unfortunately, it's hard to tell. We did a medication adjustment at about the same time, and so the combination of the two certainly has been helpful. The fact that I can turn to my husband and say, “I'm 'off','” and him sort of understand what that means to me, and potentially means to him, because usually he's the bear or the grumpiness kind of thing, so I think just the fact that they understand and that support, I think it's helped a lot.

Bryan Roberts: 00:32:17 Thank you, Barb. For disclosure to everyone listening, Barb and I worked together at Ithaca College, both as associate deans. I couldn't tell when she was “off” because school of business deans are always grumpy and irritable, but thank you for the clarification Barb.

Barbara Howard: 00:32:39 Oh, anytime. Thank you, Bryan.

Bryan Roberts: 00:32:42 Dr. Horn, you've worked with a myriad of patients at different times of the disease. How do you work with them to manage “off”?

Sarah Horn: 00:32:56 Right. There are numerous options to help reduce the amount of “off” time a person is having a day. An “off” day, I'll use multiple different strategies in combination to really help optimize the symptoms. One of the first strategies I usually recommend is decreasing the time in between levodopa doses. So, for example, if somebody is taking two tablets of carbidopa/levodopa three times a day, I may have them try one and half or two tablets four times a day, trying to be particular with how they're spacing it, so maybe four hours in between every single dose.
The downside to this is that you have to remember to take four pills a day, and higher doses of levodopa can cause side effects like hallucinations, dyskinesia, sleepiness, nausea, but the main benefit with sticking with carbidopa/levodopa is that it tends to be predictable and effective. There are newer formulations of carbidopa/levodopa on the market that sometimes I'll use as well. Rytary is a newer extended release version of carbidopa/levodopa, and each dose lasts longer, so people don't have to take it as many times a day, and then it can also reduce “off” time.

However, there are some downsides. It can be difficult to convert to Rytary and the process can sometimes take weeks, and it can also be expensive. Duopa is a gel form of carbidopa/levodopa that's infused continuously into the gut. This requires a surgery to place a tube, which is similar to a feeding tube, into the stomach that then is advanced into the small intestine. This can be a good option for people who have more severe “off” fluctuations that aren't well controlled with oral medications and who also are not good candidates for something like deep brain stimulation surgery.

Since it's a continuous infusion of levodopa, it can really help smooth out those on/“off” fluctuations, but the downsides are that it requires surgery and there's a pretty high complication rate in people who have tried Duopa, such as infection and clogged tubes. Then, the device is external to the body, so people who have Duopa have to carry around and manage the device all day. Another option besides using different strategies of carbidopa/levodopa is to add on a different type of medication to carbidopa/levodopa.

These generally reduce the total daily “off” time by around one to two hours. MAOB inhibitors decrease the breakdown of dopamine and COMT inhibitors decrease the breakdown of levodopa, so they both kind of act to give a boost to the carbidopa/levodopa that you're already taking. These meds are generally pretty well-tolerated, but they can worsen dyskinesia, hallucinations and other side effects from carbidopa/levodopa.

Then, there are some things to consider with these medications, so for example, MAOB inhibitors can't be mixed with many over-the-counter cold medications and have to be stopped before surgeries. COMT inhibitors sometimes cause explosive diarrhea and orange urine, so those are just things to be aware of. Dopamine agonists are another class of medications that can added to carbidopa/levodopa to reduce “off” time. These can
be easy to take because they come in once-daily pill formulations, and then there's also a patch formulation.

However, there are some caveats. This class of medication tends to have a higher risk of side effects than other medications for Parkinson’s disease, so they’re not right for everybody. Some side effects that people experience include compulsive behaviors, like excessive gambling or shopping sprees. It can also cause sleepiness, including sleep attacks, and increase the risk of hallucinations. The risk of these side effects increases with age, so I generally avoid prescribing these medications in people over 65 or so.

Bryan Roberts: 00:37:10 Well, there's certainly a range, and we're going to continue talking about the ways we can manage “off” in a few minutes, but I think it may be a good time to take a few more questions. We have one that many of you have asked, it's trending, so panelists, this one just came in. Do treatments treat the non-motor symptoms of “off” too? Do any or all of these treatments treat the non-motor symptoms of “off” too?

Sarah Horn: 00:37:47 That’s a great question. In people who have non-motor “off” symptoms, meaning that their non-motor symptoms fluctuate with their levodopa doses, then these treatments can help with that. There are some treatments that do not help with non-motor “off” symptoms. The main one that I think is worth noting is deep brain stimulation surgery. We commonly use that to treat people with Parkinson’s disease who are having a lot of on/“off” fluctuations, but that one really helps with the motor fluctuations and not the non-motor fluctuations.

Bryan Roberts: 00:38:28 Great. Thank you. We have another question. How important is it to take your medication at the exact interval times? Barb, how important is it?

Barbara Howard: 00:38:46 Well, from my viewpoint, it’s critical. I actually use the alarm feature on my smartphone to remind me when it's time to take my meds. As Dr. Horn mentioned, one of the options is to take them more frequently, and so for me, that’s four, five times, six times a day kind of thing. I really do think it’s very important. My friends and family members are accustomed to my smartphone beeping on an irregular basis kind of thing, and they're good about reminding me.

If I forget to take my medicine within a very few minutes, the likelihood of an “off” time for me is considerably higher. It’s exponentially higher, and the “off” time is usually longer and deeper if I'm more than a few minutes off my schedule, so to
me, it's a good thing to do. The thing is, too, if you stick to your schedule, I think it's easier for the doctor to suggest modifications. If you're consistently coming “off” it three and a half hours, or you're consistently coming “off” it two and a half hours, or whatever it is, that helps them decide what the next step might be for you in terms of changing your medications. So the short answer is, take your medication on time.

Bryan Roberts: 00:40:05 Yes. As admittedly the world's worst Parkinson's patient, I can speak to the other end. I frequently miss doses. I don't ever set a regular schedule, and I fully understand that life would be much easier for me if I played by the rules. One day I will, but I'm also a Mets fan, and I remain one so life is hard by choice. Thank you, Barb. It's funny, the patients I work with, even individuals on the patient counsel, those who are disciplined, and I think discipline is important with this disease, they simply do better at every stage.

All right. Let's go back to talking about “off.” Glenn, we often hear that language matters when describing “off.” From your experience, what is a shared, let's call it an “off” vocabulary, and why is it important for all of us to speak about “off” the same way?

Glenn Batchelder: 00:41:28 Well, I think as everybody has highlighted, this is a complicated disease in terms of each patient being different. So the more, when we talk about things, they can use a common vocabulary and it makes, I think, our hearing from patients, it really made a difference in terms of the communications with the doctor. For example, when we started ... I started focusing on this area back in time and learning about it, there wasn't a real clear vocabulary.

Some people would call it just wearing “off” at the end of a dose and some people would take these episodes to be that their medicines weren't potent enough. And then they would start to describe something different to the doctor and other people would talk about an “off” episode, and sometimes the fact that physicians weren't entirely clear what they were talking about. So I think one of the things actually that The Michael J. Fox Foundation has been helpful with, from my perspective over this time is helping to clarify that language which is these. Because these “off” episodes are often this very unpredictable event. And that unpredictability is such a critical component of what makes them important to address. So I think the clearer the patient and the doctor are with each other, and the more they can use the language of an “off” episode as opposed to
how the medication is performing overall, it seems to make a big difference from what we've heard from patients.

And one of the ways one of the doctors in the field had helped me visualize it, he said, "You know, there's really two things we do. We try and pave a smoother road, which is this notion of keeping everybody in a very stable condition, and the second, is filling in the potholes. Finding ways when the medication starts to fail, finding ways to quickly fill up that pothole. And for me, that visualization has really been helpful over time.

Bryan Roberts: 00:43:44 That's an excellent way to talk about it. I hadn't heard that, but it makes a lot of sense. Thank you. So there are many different ways to manage "off." We covered multiple. Dr. Horn, can you just touch upon one other? I'm going to move this slide forward. The injectable apomorphine. Can you just talk about that option please?

Sarah Horn: 00:44:20 Right. So I think of Apokyn an injectable form of apomorphine as a way to fill in a pothole, like Glenn was mentioning. So this is usually used on an as-need basis. And it is medication that's in the class of dopamine agonist. And it is injected into the stomach, upper arm or upper leg, similar to somebody would inject insulin. And it acts very quickly. Onset can be as soon as ten minutes. It's pretty short acting, so it needs to be used in combination with the other Parkinson's meds that a person is using.

Bryan Roberts: 00:45:35 Hm. Great. Thank you. Before we move forward, we have another popular question coming through. Let me take a look here. Do - sorry, let me fix my glasses. Do "off" times happen with each dose, or at a specific time during the day? I'm sorry, I'll reread that. So if we're talking person to person, and again, we know about the variability of this disease, are there times of the day where "off" is more likely? Again, does the likeliness, is that really more individual-specific experience with "off"?

Sarah Horn: 00:46:41 Things can be individual, experience are different between patients, but it's not uncommon that "off" times can be bad in
the morning, because it's been a while since the last dose, and then also sometimes people find that toward the end of the day, their “off” periods are worse. So there are some relationships that some people notice as the day goes on.

Barbara Howard: 00:47:08 Yeah, I concur with that. That's very typical of my - if I'm going to have an “off” period, it's more likely that it will happen in the morning than early afternoon or early evening. And the later the day gets, the more likely that I will have an “off” period. So I think that's probably a pretty typical pattern.

Bryan Roberts: 00:47:30 It does seem it's quite individual-specific. But I do hear that, mornings, late afternoons. For me, it's predictable when I exert myself for physical activity. I'm an active baseball player. In the seventh inning, I always start to go “off.” I really can't explain why, but I would imagine I'd be playing professionally if that didn't occur. Let's talk about the future. What new therapies are in development to help us with these “off” periods? Glenn, you were on the vanguard of this. What do you see coming down the pipeline?

Glenn Batchelder: 00:48:39 So I think it's actually a pretty exciting time for this issue in Parkinson's. There's a good deal in development and I'll touch on the things that are in later-stage development. There's some even earlier things, there's still more ideas and looking like they're going to be products. But it comes back to what we were talking about a little before, which is really two strategies – this paving the road smoother or filling in the potholes.

The first with the filling in the potholes concept is it allows patients, if they start to feel they're going “off,” which often we hear they do know it’s coming. And the technologies that are able to, in large part, bypass that oral gauntlet. So they don't have to take a drug, whether it's L-DOPA or some other drug orally. But they can get the drug into the blood in a very quick and reliable way. So that's the first strategy people are pursuing.

The second is this sort of paving the smoother road, which has to do with maintaining L-DOPA or in some cases the dopamine levels in the brain, right where you want them, and finding ways to hold it there so you have fewer and less severe “off” episodes.

So with the first strategy, there's two potential therapies. They're actually filed with the FDA, which is pretty exciting. So toward the beginning of next year, the FDA will decide whether to approve them and make them available to patients. So one is
this idea of inhaled L-DOPA. So full disclosure, this is the one that I worked on. And what it allows, is patients, when they start to feel like they're going “off,” they can inhale the L-DOPA. And because the lung is a great transport mechanism, its whole purpose is to transport oxygen, CO2, in and out of the body, it actually does a great job of transporting L-DOPA right into the blood in a very predictable way, and boost the L-DOPA levels enough to carry to the next dose. It's not replacing oral L-DOPA, it's just when it fails, when you don't get enough in, it gives the necessary boost. So that's the first one.

The second one goes back to what Dr. Horn was talking about apomorphine. So instead of it being an injectable form of apomorphine, they have developed what looks like a Listerine strip that you put below your tongue. And rather than swallowing it, it actually goes in through the mucus membrane and gets absorbed rather rapidly. And because apomorphine to your brain kind of looks like dopamine. It stimulates similar things in the brain. It then can also diminish or abort an “off” episode. So those are the filling in the potholes therapies that are relatively soon we hope, are going to be available for patients. The other side is really around this paving the smoother road. And there’s sort of three relatively late stage therapies in development. One is a pill that when it gets to the stomach, expands. And it stays there. And it has L-dopa/carbidopa and it creates a sort of constant stream into the intestine. So it takes at least a part of the oral gauntlet and makes it a little more predictable. So it's something that then would allow you to take an oral pill and then ideally, hold your blood levels in that range of not too much, not too little, more effectively.

The second one I'll talk about is kind of an injection patch. So it's a patch, but it has small needles involved so that it actually allows you to have a pump that slowly meters L-DOPA and carbidopa in below the skin which then diffuses into the blood and sort of creates a continuous stream going around that oral gauntlet and allowing the blood levels of L-DOPA to be held in a very consistent and steady fashion. Again, reducing the frequency and severity of “off” episodes.

And the final one to talk about is a gene therapy. So this is something where genes that produce a particular protein, it's called DOPA decarboxylase. But simply what that means, is it produces a protein that takes L-DOPA and converts it to dopamine and what has been found, is that as patients progress over the disease, not only do they make less dopamine in the brain, but they make less of this enzyme necessary to break L-
DOPA down into dopamine. And by implanting this gene therapy in there and having your body create essentially a new machinery for producing this enzyme, patients are able to take whatever dopamine is in the brain, and their brains are able to more quickly and efficiently and predictably convert it into dopamine.

So those are kind of the three paving the smoother road therapies. And all of them have real promise, as everybody has said, different patients will respond differently to them. So one tool isn't going to solve all of this, but I think they all contribute to the mission.

Bryan Roberts: 00:55:00 Well sounds like the future is bright. And I think it gets back to, Glenn, when I hear you describe these, is predictability of life. And basically a state of normalcy, however you want to define that. So again, individuals being able to live well and have confidence that they can manage their safety. And it sounds exciting.

Glenn Batchelder: 00:55:34 Maybe one sort of point of that is exactly what you highlighted, is it's not just the unpredictability, but it's the worrying about the unpredictability. So by giving patients things that will make them more confident, that they won't have them, it probably will reduce the severity and frequency itself. To be determined, but that's a hope and a possibility.

Bryan Roberts: 00:55:56 That is exciting. And as a patient, I look forward to the next few years. Because I think we're really going to see some impact. So looks like we have about five minutes left. So I think at this time, we'll take some more questions. I also want to mention that almost all the therapies we've discussed, the ones that are coming down for the future, they've all been funded in some way by The Michael J. Fox Foundation. So good people, and the hard work they do there really do make an impact on all of our lives. And I'm really appreciative for all their efforts.

Okay. Let's go to some questions. So, sleeplessness. Many medications cause it. Is there a way to manage it? Barb, did you experience this when you were working?

Barbara Howard: 00:57:07 Sleeplessness? Or sleepiness?

Bryan Roberts: 00:57:13 I guess they're both related.

Barbara Howard: 00:57:14 Okay. I was going to say, actually both. And even since I've worked, I went through a pretty long period of time where if I
slept for four hours a night, that was a good night kind of thing. And then I would be sleepy during the day and would have daytime sleepiness which would sometimes come on unpredictably unannounced. I would be very sleepy. And the more stationary I was, for instance in a meeting or riding in a car, those kinds of things would actually increase the sleepiness.

The sleeplessness and not being able to sleep through the night, it was a little bit more difficult to address. About the last month or so, I actually modified my evening dose of levodopa and that seemed to help. I've been getting a pretty consistent six to seven hours of sleep. Still shy of what they recommend for someone, but it does help. And that helps the daytime sleepiness. So it's something you definitely want to check with what your doctor is doing and have a conversation. Because sometimes there is something they can do to adjust the medicine.

Bryan Roberts: 00:58:32 And Barb, just following up on that, is that a good reason to be specific in choosing a neurologist? Not a general neurologist, but someone who specializes in movement disorders?

Barbara Howard: 00:58:52 Having experienced both, I started out with a general neurologist and very quickly was changed to a motor disease person. And there's a big difference. You really want to have someone who is up to date and focused on the treatments and the therapies and those kind of things related to Parkinson's. Versus someone who is more of a generalist. So yeah, I would say it's very important.

Bryan Roberts: 00:59:32 Looks like we have time for one more question. This one is pretty straightforward. Does stress cause “off”? I think I could answer this one. At a very stressful job where Barbara works 40-50 hours a week, I work 70-80 because I'm not as talented or smart as she is. But the job itself is very stressful. We have donor issues, we have administrative issues, a lot of issues. And I can tell you that it does create perhaps more frequent “off” times or sometimes deeper “off” times. But also in a way, in a kind of odd way, I've learned to handle “off” better. And handle stress better. So there is a silver lining to it. The repercussions of “off” have kind of given me perspective, which those of us in communications don’t often have. So I'm able to prioritize what's an emergency, what's not. And I think I just have a better view on my life.

Well looks like we're just about at the hour. Thank you everyone for joining us today. And thank you Barb, Glenn, Dr. Horn, for sharing your expertise. We'll be sending a link of the webinar so
you can listen on demand again as you'd like and you can hear the sheer panic in my voice when the power went out. Enjoy a good laugh there. Please mark your calendars for our next webinar which is November 15. That's right, we're already into November. We will play a webinar on research year in review. It has been a very exciting year. So you won't want to miss that. We'll have staff behind the scenes at The Michael J. Fox Foundation there to answer any questions you may have live. I look forward to listening to that. Panelists, thank you so much for taking part in this today, and everyone listening, stay well. We'll see you in November. Bye.