Spotlight on Dyskinesia and Off: Feeling Good Every Day

Transcript

Welcome and Introductions

Cathi Thomas, RN, MS, CNRN

[Slide 1] Welcome everyone and thank you so much for joining us today.

[Slide 2] My name is Cathi Thomas, and I am the Program Director of the Parkinson Disease and Movement Disorder Center and also the coordinator of the American Parkinson Disease Association Information and Referral Center at Boston University Medical Campus.

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 Adamas for funding this important program and acknowledge their appreciation for the critical need to provide educational programs, like this one, to people impacted by Parkinson's disease.

The American Parkinson Disease Association, or APDA for short, is the largest grass-roots 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 $185 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 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 the latest information about dyskinesia and off in Parkinson's disease. 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 and other programs.

It is now my pleasure to turn the presentation over to Dr. Gilbert.

Presentation

Rebecca Gilbert, MD, PhD

Thank you so much, Cathi, for that introduction. Today I am pleased to be talking about Parkinson's disease, dyskinesias and off and try to lend some insight into why dyskinesias happen, why off time happens, and to try to help our community feel good every day.

[Slide 4] Here are my financial disclosures. I have salary support from both APDA and from NYU (New York University) Langone Medical Center.

[Slide 5] So, the outline of my talk today is as follows. I'll start by talking about levodopa treatment and then discuss what are motor fluctuations and what are levodopa-induced dyskinesias before I talk about current and future solutions to these difficult problems.

[Slide 6] So let's begin by talking briefly about Parkinson's disease itself. Now most of our listeners who have joined us today are very familiar with this disease. They either have it or love someone who does. By way of introduction, Parkinson's disease is due to a lack of a chemical in the brain called dopamine. And dopamine is a chemical in the brain needed for normal movement. The substantia nigra is an area deep within the brain that communicates with other brain areas using this chemical dopamine. The cells of the substantia nigra degenerate in Parkinson's disease.

Now other types of nerve cells in the brain also degenerate in Parkinson's disease, and this can lead to a variety of symptoms such as changes in mood or sleep or gut function. But for the most part, the symptoms of Parkinson's disease that affect movement – that is slowness, stiffness, tremor – these symptoms are caused by a lack of dopamine. **[Slide 7]** And so, if there's a lack of dopamine in the brain, how do we correct for this and help the movement symptoms of Parkinson's disease?

Now dopamine itself, unfortunately, if given as a pill or even if given as an infusion directly into the bloodstream is not able to cross from the blood into the brain. It's not able to cross the blood-brain barrier. And so, giving dopamine itself is not an effective treatment for Parkinson's disease. The chemical levodopa, however, is a precursor of dopamine, and that means it gets converted into dopamine once it's in the brain. Levodopa can cross the blood-brain barrier and enter the brain; therefore, levodopa can be potentially used as a treatment for Parkinson's disease.

Now carbidopa is added to levodopa to allow for even more efficient entry of levodopa into the brain. And so, carbidopa-levodopa in a pill form is ingested by mouth, absorbed in the small intestine, and is able to cross into the bloodstream and finally cross the blood-brain barrier into the brain itself.

[Slide 8] After the carbidopa-levodopa is absorbed from the small intestine, crosses into the bloodstream, and then crosses into the brain, enzymes in the nerves themselves can convert the levodopa into dopamine. **[Slide 9]** Once the levodopa has been converted into dopamine within the nerves, the dopamine can then enter the space between the two nerves and bind to the dopamine receptor on nerves that allow for the continued propagation of the message from one nerve to another. And in this way giving levodopa, which then converts into dopamine, can allow the normal

signaling between nerves to occur. And in this way levodopa can mimic what dopamine does naturally.

[Slide 10] However, levodopa is taken at particular times during the day, so the brain levels of levodopa vary throughout the day depending on how far a person is from the last pill they took. So, a dose is taken, the levels of levodopa in the brain rise, after a time they fall again, and then rise again with the next dose. Early on in levodopa therapy, this is usually not a problem, probably because there is normal dopamine being made by surviving cells and the peaks and the troughs of levodopa levels are not bothersome and a person feels good throughout the day with a whole variety of different levodopa brain levels. **[Slide 11]** However, as Parkinson's disease progresses, there is a smaller window of levodopa brain levels that result in good symptom relief. At the lower levodopa brain levels, a person may not feel that their symptoms are well-controlled, and these times are referred to as off times. And this fluctuation of feeling good for part of the day and then feeling that the symptoms are not controlled for part of the day is called motor fluctuations.

[Slide 12] Now off time in Parkinson's disease, when a person feels that their symptoms are not well-controlled, can have a number of different manifestations. A person may feel that their motor symptoms return. They feel slow, stiff, they may have difficulty walking, and they may have a lot of tremor. In addition, a person may feel that nonmotor symptoms can be very prominent in this off time, and this may manifest as anxiety, depression, and pain. And so off time can be a very, very difficult period of time for a person who has motor fluctuations.

[Slide 13] So what are the solutions? How can off time be managed? So, on the left, we have the varying levels of levodopa brain levels which correlate to the good time, the on time, and the bad time, the off time. How do we keep a person in the on state for longer? And there are two main strategies. One is to figure out how to deliver a drug, either levodopa or a different medication, that has a more continuous delivery and doesn't have those falls back to the off period. And that's a continuous drug delivery strategy. The second strategy is to give a medication between doses to keep a person on the on period, and that's called an as-needed strategy.

[Slide 14] In terms of allowing for drug delivery to be more continuous, what are the possibilities to achieve this? One is to give a longer-acting levodopa formulation. So, researchers are developing ways in which levodopa is more longer acting in a person's brain and the levodopa levels remain elevated. The second is to add another medication with a different mechanism of action to lengthen the effect of a dose. And the third is deep brain stimulation (DBS), which is a surgery for Parkinson's disease and is a talk in and of itself, and I will be talking about it a little bit further on in the talk. The second possibility of how to manage off time is to use an as-needed strategy. Either one can take levodopa doses more frequently or use another medication, a quick-acting medication, as needed if a dose wears off.

[Slide 15] Now I focus on this chart on various levodopa formulations that can achieve either the continuous or the as-needed strategy, but you should be aware that there are other medications with other mechanisms of action not in this chart that can also be used to implement these two strategies. Now the standard formulation of carbidopa-levodopa, its brand name is Sinemet®, that's the first line;

and then there are a number of other carbidopa-levodopa formulations that can help to achieve either a more continuous on time or to be used as needed. There is a carbidopa-levodopa extended release. There is a formulation called Rytary®, and there is an intestinal gel that is infused directly into the gut. And all these are carbidopa-levodopa formulations that allow for more continuous on time. Then we also have two levodopa formulations that can be used as needed. One is called Parcopa®. It's an orally disintegrating pill. And one is Inbrija®, which is an inhalation powder.

[Slide 16] We will now turn to a discussion of a related problem, a problem also associated with fluctuations in levodopa brain levels and one that often accompanies this problem of on and off time or motor fluctuations. And that problem is levodopa-induced dyskinesias. Levodopa-induced dyskinesias are movements that are involuntary, uncontrolled, and purposeless and they are a side effect of levodopa. **[Slide 17]** Now in order to get levodopa-induced dyskinesias, you need two things. You need progressive loss of dopamine neurons. That means you need to have Parkinson's disease. And you also need intermittent exposure to the drug levodopa. Without both of these conditions, a person will not ever develop levodopa-induced dyskinesias. So, if a person without Parkinson's disease takes a lot of levodopa, they will not develop dyskinesias.

[Slide 18] Now here is a schematic to demonstrate where in the cycle of on and off in levodopa brain levels dyskinesias tend to arise. They tend to arise in two prominent places. One, at the peak dose when levodopa brain levels are at their highest. But in addition, levodopa-induced dyskinesias can occur as levodopa brain levels are rising at the steepest point and as they're falling at the steepest point. And those dyskinesias are called diphasic dyskinesias and they're very common and probably more common that people realize. So, it's important to know that levodopa-induced dyskinesias do not only happen when levodopa brain levels are at their highest.

[Slide 19] Now a couple of facts about levodopa-induced dyskinesias. First, is that they typically affect the more Parkinsonian side first. What I mean by this is that a person with Parkinson's disease can typically tell you which side of their Parkinson's started first and which is worse. That is the side that typically develops dyskinesias first. Dyskinesias, of course, could migrate to the other side as well as to other body parts including the neck or the face, the shoulders or the torso. Dyskinesias typically start in mild form and they can become more noticeable over time. And sometimes they can become so bothersome that they interfere with walking or daily activities and certainly can interfere in a social situation as well. Stress and excitement can exacerbate levodopa-induced dyskinesias and, interestingly, the movement associated with levodopa-induced dyskinesias can contribute to weight loss that is associated with Parkinson's disease.

[Slide 20] About 50% of people with Parkinson's disease develop levodopa-induced dyskinesias within five years of their levodopa or after five years of their levodopa therapy. Unlike tremor, levodopa-induced dyskinesias are not regular and rhythmic, so it should be clear to a person whether they're experiencing tremor or dyskinesias. But sometimes it's not clear and a person themself may have a hard time distinguishing whether in that moment they're tremoring or having dyskinesias.

Now it's actually very important to be able to make this distinction because if a person misidentifies levodopa-induced dyskinesia as tremor and tells their doctor at their doctor's visit that they're having tremor, the doctor may increase the levodopa and inadvertently make the dyskinesias worse. So in

this situation where a person is not sure what type of movement they're having, I would recommend to videotape the movement and bring the videotape in to the doctor so that that doctor can see what movement they're talking about and make a decision about medicine management.

There are some people that may not even be aware that they're having dyskinesias at all. The same exact movement in two different people, one person may not notice they're moving, and the other person may be very bothered by it. And so, there's a lot of variability in a person's reaction to their dyskinesias. But it must be noted that if a person is not bothered by their dyskinesias, if they don't notice that they're doing them, that's completely fine. They do not need to be treated. Dyskinesias are not dangerous and so if they are not bothering a person with Parkinson's, they can be left alone.

[Slide 21] Now probably the most common question that I get asked about dyskinesias are can they be prevented? So, a person is let's say diagnosed with Parkinson's disease for the first time and at some point in their course, levodopa is suggested. And a person would rather not have dyskinesias and they say to their doctor, "I would like to delay starting levodopa because I do not want to get dyskinesias." And the question is does delaying taking levodopa affect the presence of levodopa and dyskinesias down the line? And so, this question has been a difficult question to answer, and it was addressed by the study that I have here on this slide.

In this study there were two groups of people with Parkinson's disease. One in Italy and one in Ghana. And the main difference between people with Parkinson's disease in Italy and Ghana is the rapidity that the person gets medical attention. So, in Italy the system is a very western medicine system very similar to the United States. In Ghana there is less access to healthcare and people with Parkinson's disease in Ghana tend to see doctors later on in their symptoms and tend to get treatment further along in their disease.

In Italy, which is a surrogate for the United States for the purpose of my talk now, patients tend to go to doctor's kind of early on as their symptoms develop and they start medication for their symptoms early on. And according to this chart, if you look at the top bar, the light blue bar represents the period of time where the patient had symptoms but didn't yet get any treatment. The darker blue represents the period of time where they were on levodopa but did not have any problems with levodopa. And then the pink bar is the development of wearing off. That's the development of the period of time when the levodopa does not reach, the effects of one levodopa does not reach to the next dose and there is a period of time where symptoms return. And then the dark red is the period of time when dyskinesias start.

You can see the group that received levodopa toward the beginning of their course they had a good five years of levodopa without any complications. And this five years is reminiscent of what people think of in the United States as the honeymoon period; the period of time where levodopa can be taken, symptoms are resolved without any complications at all. And then the wearing off starts. So that timeframe is very familiar to us.

In Ghana, however, the same patients are not seen by doctors early on. They have symptoms. They do not get any treatment so that light blue and slightly darker blue period is longer. And then levodopa is started significantly later. As you can see when a person receives levodopa later, that is levodopa

was delayed, not because of a decision but because there was a delay in getting to see a doctor, the amount of time that levodopa works without any complications is extremely short. It's a number of months and then wearing off and dyskinesias start.

So, this study implies that the clock to levodopa-induced dyskinesias starts ticking when Parkinson's disease starts, not when levodopa is started. And so, if a person delays taking levodopa, all that does is shorten the amount of time that levodopa works well. Dyskinesias and wearing off will come and will come very soon because levodopa-induced dyskinesias correlate with degree of Parkinson's severity and not from when levodopa is started. So, this is a very important point that needs to be understood by all people who are afraid of starting levodopa.

[Slide 22] So another study that addressed the same question, can dyskinesias be prevented, was a study which looked at patients who were first diagnosed and what medications they were put on. And this study followed two groups of people: one that were started on levodopa immediately when they needed medication and another group that were put on what was called a levodopa sparing strategy. They were given medications but were not given levodopa. They were given other medications. And these two groups are followed over time. And after seven years, the number of patients with levodopa in both these groups were pretty much identical. So, it did not matter whether a person was started on levodopa or started on another medication because over time the patients tended to need to be switched to this levodopa anyway in order to treat their symptoms. And so, following these patients over time with the natural history of how their Parkinson's was treated they ended up in the same place at year seven. And so, avoiding initially starting levodopa did not affect emergence of levodopa-induced dyskinesias.

[Slide 23] The next question is does introduction of levodopa in a more continuous manner as opposed to giving Sinemet, which is a shorter-acting levodopa, does that affect development of levodopa-induced dyskinesias? That is if we started everybody on a longer-acting levodopa, would that mean that there was a difference in levodopa-induced dyskinesias down the line? The answer to this is we don't quite know the answer because there has been no clinical trial looking at levodopa-induced dyskinesias comparing those receiving a long-acting versus a short-acting levodopa as their first treatment. So, we don't know how this would affect levodopa-induced dyskinesias.

[Slide 24] So once levodopa-induced dyskinesias are there, what treatments are available? So, as you might imagine from the talk up till now, changing levodopa dosage, changing levodopa timing could help control levodopa-induced dyskinesias. Converting to a longer-acting levodopa formulation may help, and we'll look at some data about that. And then we have a treatment called amantadine which can be introduced. And, finally, deep brain stimulation can be helpful for levodopa-induced dyskinesias as well.

[Slide 25] So converting to a long-acting levodopa does this help? There was a study called the ADVANCE-PD clinical trial and it examined the effects of the extended-release capsule, which also is known as Rytary®, to see whether its helped in reducing dyskinesias. So in this study, patients with at least two and a half hours of off time that were on immediate-release carbidopa-levodopa or Sinemet were randomized to either staying on Sinemet and having their doses maximized, shortened, lengthened, changed in any which way versus a group of patients that were switched to Rytary

longer-acting carbidopa-levodopa and the two groups were compared. And this table shows that overall a person treated with Rytary could expect about one hour more of good time without dyskinesias than someone who stayed on Sinemet. So, a bit better with the longer-acting version versus the shorter-acting version.

[Slide 26] Another strategy for a long-acting levodopa is the levodopa-carbidopa intestinal gel. And here's a schematic of how that works. There is tubing that is inserted directly into the small intestines and emerges from the abdominal wall and is connected to a pump which is connected to a cartridge of levodopa-carbidopa intestinal gel. And the gel is pumped continuously into the gut throughout the day or the waking day.

[Slide 27] And there was a study that showed or that analyzed patients who were on Sinemet, carbidopa-levodopa immediate release, and were converted to the levodopa-carbidopa intestinal gel and compared to see which group had fewer dyskinesias and better on time. An analysis of the two groups of patients, the one that remains on the immediate release and the one that was converted to the intestinal gel, showed that the patients on the gel had less time with bothersome dyskinesias and more good time during the day without bothersome dyskinesias. And so, this, again, is a potential strategy for reducing dyskinesias.

[Slide 28] Another strategy for reducing dyskinesias is using the medication amantadine. This is a medication that has been around for decades and has been used to treat levodopa-induced dyskinesias for a long time. There have been some small clinical trials a number of years ago which showed that indeed it did reduce levodopa-induced dyskinesias. And it's also interesting that this medication has some anti-Parkinsonian effects as well, so it doesn't just treat dyskinesias but can help motor symptoms of Parkinson's disease. Can be used for tremor and the slowness and stiffness of Parkinson's disease.

[Slide 29] So recently, there has been a development of amantadine extended-release capsules, brand name Gocovri®. And this is a medication, the only medication that is specifically approved by the FDA (U.S. Food and Drug Administration) for treatment of levodopa-induced dyskinesias. Amantadine that's not extended release never got the specific indication by the FDA for levodopa-induced dyskinesias and has been used off label for this purpose. But this medication, Gocovri, is approved by the FDA for treatment of levodopa-induced dyskinesias. And in clinical trials, there's a number of them that have been published, it improved dyskinesias and reduced off time. And so that is a very good combination.

Now the formulation that's in this extended-release capsule provides for an initial lag in amantadine concentration so the levels of amantadine do not rise immediately upon taking the pill. And the pill is recommended to be taken before bed. Then there is a slow rise in the amantadine levels during the night and the concentrations reach their normal level or the level that will give clinical effect in the morning, and it stays elevated throughout the waking day.

Now additional clinical trials are necessary to directly compare the efficacy of these extended-release amantadine to immediate-release amantadine for control of levodopa-induced dyskinesias. There have been attempts to determine if the extended release is better than immediate-release

amantadine for levodopa-induced dyskinesias. And a recent paper followed patients on Gocovri for over two years. And within that analysis of those results, the study identified a subgroup that had been switched from immediate-release amantadine to Gocovri and studied that group individually and showed that there were improvements in that group when they switched from immediate release to Gocovri. So, this could suggest that extended release may be better controlling dyskinesias than the immediate release, but, again, additional clinical studies would be needed for a direct comparison.

[Slide 30] Now I've mentioned deep brain stimulation a few times. Deep brain stimulation is a system that has been approved for use in Parkinson's disease since 1997. It involves the placement of a lead or electrode deep within the brain. The electrode emerges from the brain and the wire that connects the electrode gets tunneled under the skin and attached to an implantable pulse generator which sits in the chest, much like a cardiac pacemaker does. It's sort of a brain pacemaker. And this implantable pulse generator in the chest contains a battery, which fuels the system, as well as a little computer that can be programmed. And it can be programmed remotely by a programmer. Either the doctor and, in some cases, the patient themself can program the system for certain parameters in terms of the electricity that's placed within the brain. And this system can help both Parkinson's disease symptoms as well as dyskinesias. And DBS or deep brain stimulation can reduce dyskinesias probably in two ways. First, by improving the Parkinson's disease symptoms themselves, it allows for reduction in levodopa dosage. And when levodopa dosage is reduced, that will reduce dyskinesias. In addition, it may directly affect electrical activity in the brain which improves dyskinesias.

[Slide 31] Now there are a number of treatments of dyskinesias in the research pipeline, and this is a lot of words and a lot of chemicals and names that we don't necessarily have to go through in detail, but suffice it to say that there are a number of products in clinical development at various stages of the clinical trial process. And that is very exciting because levodopa-induced dyskinesias are still a major problem and it is always good to know that pharmaceutical companies are working on this problem to try to come up with additional solutions. The final point on this slide is focused ultrasound. And this is a procedure that is being developed to help control dyskinesias with a phase III clinical trial underway.

[Slide 32] And I'd like to talk for a minute about focused ultrasound. In this procedure, there are focused beams of ultrasound energy that are sent through the skull into the brain from outside the brain. And these focused beans of ultrasound energy converge within the brain on a very, very tiny, small area to form a small lesion. So, this lesion is created without actually cutting into the brain or opening up the brain in any way.

By creating this small lesion, this interferes with the electrical activity of the brain. It has been approved for treatment of tremor both in Parkinson's disease and in another condition called essential tremor. And it's being studied in people with dyskinesias as well as people with more advanced Parkinson symptoms in general. So eventually, I do believe that this treatment will be approved for the treatment of dyskinesias and so that is another exciting development that is under way.

[Slide 33] So, in summary, levodopa-induced dyskinesias and off time can adversely affect the quality of life of patients with Parkinson's disease. Levodopa-induced dyskinesias may be treated by altering the levodopa dose, the timing, or the formulation; amantadine, now also available in extended

release, can be used to treat levodopa-induced dyskinesias; deep brain stimulation may reduce levodopa-induced dyskinesias; and a number of other medications as well as a procedure called focused ultrasound are being researched for treatment of levodopa-induced dyskinesias.

[Slide 34] And on that note, I would like to open up the discussion to questions that I will be happy to answer along with the help of Cathi Thomas as well.

Cathi Thomas, RN, MS, CNRN

Okay, thank you, Dr. Gilbert, for your very detailed presentation today.

Question & Answer

Cathi Thomas, RN, MS, CNRN

It is now time for the Question & Answer Session.

We will take our first question from the Web audience. “Dr. Gilbert, do all PD patients eventually develop dyskinesia?” This was submitted by Marianne.

Rebecca Gilbert, MD, PhD

Right. So that’s a great question. The answer is no. Although they are quite common, about 50% of people will develop dyskinesias on levodopa. So, there are definitely people who take levodopa for many, many years and do not develop dyskinesias. In addition, there are people who have very mild dyskinesias that are not bothersome to them at all and so the 50% includes sort of all comers, the ones that have the mild form and the ones that may have a more bothersome form of dyskinesia. So, I don’t want to leave the impression that everyone has the same degree of dyskinesias. There can be quite a variety.

Cathi Thomas, RN, MS, CNRN

We will take the next question from the telephone audience, please.

Operator

Our next call is from Marie from Pennsylvania. Please state your question; your line is now live.

Marie from Pennsylvania

Yes. You had mentioned that amantadine would be helpful in controlling dyskinesia. Do you have to take amantadine continuously or when you experience the dyskinesia?

Rebecca Gilbert, MD, PhD

That's a really good question. So, amantadine is typically given every day. The assumption is that dyskinesias will be a problem every day and is not typically given as needed. If somebody has a pattern where they take levodopa much more on Mondays than they do on Tuesdays and they only have dyskinesias on Mondays, would it make sense to only take amantadine on Mondays? That kind of thing. I'm not sure. I would think that that could be discussed with your doctor as a possibility.

Cathi, do you have anybody in your practice that takes amantadine sort of as needed?

Cathi Thomas, RN, MS, CNRN

No, it's pretty consistent. The physicians order it on a regular basis. Obviously, the dose varies from person to person but not as needed.

Rebecca Gilbert, MD, PhD

Yes, that's my experience as well.

Cathi Thomas, RN, MS, CNRN

Okay. Thank you. I'd like to ask another question that was submitted by Rita. "Why, when my dyskinesias occur, do I also have extreme pulling in my neck and head that is painful?"

Rebecca Gilbert, MD, PhD

That's a great question, and that's not something I addressed, which I probably should have addressed because it is a common problem. So dyskinesias often look, as I described, they are dance-like sort of flitting movements that can occur in the face or the neck and they kind of look like somebody's a little fidgety. That's one type of dyskinesia that you may recognize.

But there is another movement that can be a dyskinesia equivalent, which is dystonia. Dystonia is a more sustained twisting of the muscles and can involve the neck, it can involve limbs, the arms or the legs and can be painful. And so, there are some people who experience what's called dystonic dyskinesias and that's I think what Rita is describing.

So, the principles of treatment would be the same whether the dyskinesias are sort of more flitting and not sustained or if they're more dystonic. And so, the treatment portion of this talk would be helpful for Rita as well.

Cathi Thomas, RN, MS, CNRN

Thank you so much. We have a great question from William. "Do levodopa induced dyskinesias affect the ability to drive a car safely?"

Rebecca Gilbert, MD, PhD

That is a very, very good question. They can. They most certainly can. Again, dyskinesias are varied and there's some people with mild little fidgety movements and there's certainly some people with movements of all types not related to Parkinson's who drive. But the dyskinesias can be more prominent than that and can certainly affect a person's ability to perform activities with their hands and their legs and drive a car.

What I typically tell people, if a person is concerned about their ability to drive a car, that is a huge red flag for worrying about it. You want to worry about these things before something happens. And so, if that thought has entered your mind, then I would strongly consider whether driving is a good thing to be doing until the dyskinesias are under control.

Cathi, do you have anything to add about that one?

Cathi Thomas, RN, MS, CNRN

No, I think it's certainly on target, and I think individuals oftentimes will bring that up and sometimes not. So, communication is so important between the person, the family, as well as the physician or provider of healthcare. Most definitely.

Rebecca Gilbert, MD, PhD

Yes, absolutely. Absolutely.

Cathi Thomas, RN, MS, CNRN

So, we have one more question from Reiner. "Will dyskinesia continue if you stop taking your carbidopa-levodopa?"

Rebecca Gilbert, MD, PhD

The answer is no. It is a side effect of medication and so dyskinesias are present when, as I showed in the graph, they're either present at the high doses of levodopa brain levels or as the levodopa brain levels are rising quickly or falling quickly. Once a person's levodopa levels are low and in the off period, there will not be dyskinesias. And so, somebody who is firmly in their off time will not have dyskinesia. If a person does not take levodopa for a while, they will not have dyskinesias. So that's, of course, the balance that we try to strike. Levodopa is very effective in treating Parkinson's disease symptoms and being off or not taking levodopa is very distressing to a person. They have a lot of trouble moving and so that isn't the solution. The solution is finding a way to tolerate the levodopa and not switch into bothersome dyskinesias. And that's what researchers are trying to harness because stopping levodopa is not the answer.

Cathi Thomas, RN, MS, CNRN

Okay, thank you. We will take the next question from the telephone audience.

Operator

Our next call is from Deeta from Colorado. Please state your question; your line is now live.

Deeta from Colorado

Yes. Does the altitude affect Parkinson's, either the symptoms and/or dyskinesia?

Rebecca Gilbert, MD, PhD

That is an incredibly good question. Not practicing medicine in a high-altitude environment, I do not know the answer to that question. But it's definitely something I will investigate.

Cathi Thomas, RN, MS, CNRN

Great response. We also have a question from Lori. "Can exercise or lifestyle changes play any role in managing dyskinesias?"

Rebecca Gilbert, MD, PhD

That is a great question. We, obviously, encourage exercise tremendously to maintain as good a response to or keeping the body as fit as possible to help our Parkinson's disease symptoms. So theoretically, by keeping fit, by maintaining one's self physically as best as possible, one could theoretically minimize their dependence on levodopa which would, therefore, decrease dyskinesias. However, that is a theoretical situation. There are plenty of people who do their best with their exercise and still need to take levodopa and still get the dyskinesias. So, while we encourage exercise as much as possible, it may not be the ultimate solution to dyskinesia specifically. And, again, Cathi, I don't know if you want to add anything there.

Cathi Thomas, RN, MS, CNRN

Yes. So similarly, whether it impacts dyskinesia, we don't fully understand. However, if a person does have motor fluctuations or dyskinesias throughout their day, oftentimes when they exercise can be very, very important. So that they can get in a good workout and do it safely, we rely often on our personal trainers and physical therapists to help people figure out how they may exercise or do other activities around motor fluctuations.

Rebecca Gilbert, MD, PhD

Yes, that's a really good point because in order to maximize your workout, you want to be on. You want to be in that on state and so you need to time your activities as best as possible.

What I should mention that's sort of along those lines when people approach a healthcare provider sort of concerned about their staring levodopa and delay levodopa because of that, I showed a couple of studies that provide evidence that delaying levodopa is not the answer and actually does not delay dyskinesia at all. Despite that, some people do tend to want to push it off. But what that

ends up doing is that you end up being in an off state when you could be taking medication and make yourself less rigid and more able to exercise.

Now if we're saying that exercise is a wonderful thing for Parkinson's disease but you're keeping yourself in the off state by not taking levodopa, then you're kind of shooting yourself in the foot. And so that's why we do tend to encourage people maximizing their ability to function as early as possible so that they can exercise and get all that benefit in the face of the fact of delaying levodopa does not, in fact, delay dyskinesias.

Cathi Thomas, RN, MS, CNRN

Thank you. And here is another question submitted by Carol. "Are there any studies on the effect of CBD oil on dyskinesia?"

Rebecca Gilbert, MD, PhD

So that's a great, great question, and it's definitely something that needs to be studied. There is some anecdotal information that CBD can be good for dyskinesias but there, as far to my knowledge, has not been a large enough well-designed study to really understand whether that is something that we should be recommending to everyone. And that's definitely research that needs to happen.

Cathi Thomas, RN, MS, CNRN

Here's another question related to an intervention. "How can you manage eating protein with taking medication?"

Rebecca Gilbert, MD, PhD

Right. So that's a great question. So, as I discussed in various parts of the talk, the levodopa is ingested in the mouth, gets absorbed in the small intestine, and ends up in the bloodstream and finally into the brain. But within the small intestine, it actually can compete with dietary protein to cross into the bloodstream. So, there are these little transporters on the walls of the small intestine that are normally there to transport protein from where your food is in the small intestine into the bloodstream and the levodopa sort of hitches a ride on that transporter. And so, if there is a lot of protein in the small intestine, the protein will cross, and the levodopa may not. It may stay in the small intestine and then you don't absorb it. And so, you may take a levodopa pill and you don't feel the effects of it because it never actually passes into the blood and then into the brain.

And so that's where this concept of not eating so much protein around when you take a levodopa pill comes from. However, a person needs protein because if you don't have protein, you don't have the building blocks of your cells and you don' have energy and you can't sort of sustain your muscles and it's not something that you can continue to do. Everyone needs protein. So how do you manage eating the protein and getting your effect of the Sinemet?

So, there are two main strategies. The first one I think is a little easier to do and that is to take your protein meals and eat them at the end of the day. And so, you have your carbs and your vegetables

during the day for your first two meals. And then when you don't need to be as mobile, that's when you have your protein. That's one possibility. The other is to evenly divide your protein throughout the day. So, you're always eating small amounts of protein, so there's always the same amount of protein in your gut and so you're never going to fill up your transporters and you allow Sinemet to cross. That's a little harder to actually manage to keep your protein intake consistent throughout the day. It requires a little more work and it's not something I've seen practically implemented that easily.

So, what I should mention, however, is not everybody has this protein effect. It actually usually affects in later stages of Parkinson's and not even majority of patients. So, you need to test yourself whether that's true, so you can take a pill with some protein and see if it's less effective than if you take it without. But you shouldn't assume that you have the protein effect if you don't because that can be very limiting. So, you want to make sure that this is a problem for you before you try to solve it.

Cathi Thomas, RN, MS, CNRN

Thank you. And let's take another call from the telephone audience.

Operator

Our next call is from Deeta from Colorado. Please state your question; your line is now live.

Deeta from Colorado

Once you're in dyskinesia during the day is there a treatment to get you out of dyskinesia quicker or is it just you've got to wait it out?

Rebecca Gilbert, MD, PhD

Okay. So, if you have dyskinesias, this is kind of harkening back to the other question, is there an as-needed treatment? Like you feel the dyskinesias, you take a pill, and the dyskinesias go away. The amantadine that we have that can counteract dyskinesias doesn't really work that way. It's not usually given as needed. It's given every day and it sort of cuts the overall amount and intensity of the dyskinesias or throughout. So, it really isn't used as an as-needed treatment as you're describing. So, we don't really have that yet what you're hoping for.

Cathi Thomas, RN, MS, CNRN

Great question. And we'll take another question from the Web, and this was submitted by Romain. "I see a lot of confusion between patients and physicians, miscommunication resulting in inadequate therapy. What is the best way to provide symptom information to my neurologist?"

Rebecca Gilbert, MD, PhD

Right, that's a really, really good question. So, the problem, of course, is that you go to your neurologist once every three months, once every six months and you're living with yourself every minute of every day. So how do you translate all that information into a once in three-to-six month 20-minute session? And that can be really, really tricky to do. One thing I sort of said earlier, which I think

can be very helpful, is videotaping anything that you're concerned about. That's a really good way to cut to the chase and the doctor feels really confident about what they're seeing, what they're doing if they can really see it with their own eyes. So, I like using that strategy a lot.

Another strategy is to try to keep a diary a couple days before your visit to get a sense of when you take your medications what the effects are, what the timing is, and whether food affects it and whether sleep affects it. Whatever you can think of to include in the diary to try to come up with a pattern that will help your doctor understand what's going on because it can be very, very difficult to translate what you feel into something that can practically change the medication. So, you want to really capture these elements because that's what's going to help the doctor make the decisions.

Cathi, do you have anything to add to that really good question?

Cathi Thomas, RN, MS, CNRN

Yes, I do. Yes, and I do. And sometimes in the moment too, which you mentioned, dyskinesia can increase in certain stressful situations. So sometimes your physician or healthcare provider may notice more dyskinesia when you come to the office or if they're visiting you on rounds just because you're engaging and discussing your health. So most often people will volunteer and say, "I'm having more dyskinesia and it's because I'm here and I'm a little bit nervous." So, it's important not only to keep diaries for your day or two before, but also kind of think about certain situations where dyskinesia or other motor fluctuations may occur. In addition to arriving to the physician office and having more dyskinesia, sometimes spouses or partners will share that the person is doing perfectly well right now and it's a little bit different at home. So, it goes both ways.

Rebecca Gilbert, MD, PhD

Absolutely, yes.

Cathi Thomas, RN, MS, CNRN

Communication is really, really important and we love the idea of taking some notes a couple of days before. Don't make it into days and days of keeping track but just taking a look at how you're doing and use a tool that can help you do that.

Rebecca Gilbert, MD, PhD

Yes. You make an excellent point. I ask a patient to walk up and down the hallway and the daughter will say, "He has not walked like this in six months." That it's being at the doctor that either makes them better/worse and you have to take that into account because what you want to treat is the everyday stuff and not the what happens in that 20-minute visit.

There are wearable devices that are being developed. There's a couple on the market already that can be worn and can gather data about whether dyskinesias are happening or tremors happening and try to give the doctor some more real-time information. I think those are going to become more popular with time as well.

Cathi Thomas, RN, MS, CNRN

Yes. And we have one more question from Joy from the Web. “Does Dyskinesia progress from the lower to the upper body?” Is there any pattern?

Rebecca Gilbert, MD, PhD

Not necessarily. Certainly, dyskinesias can happen in the arms first and then the legs. I’d say it’s probably more common for the upper body to be first, but, certainly, they can happen in the legs first as well, so there’s a lot of variability.

Closing Remarks

Cathi Thomas, RN, MS, CNRN

[Slide 35] Okay, at this time I would like to thank you so much, Dr. Gilbert. And my many 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. 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 at apdaparkinson.org or call 1-800-223-2732 and you can ask your questions there. I also want 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.

[Slide 36] APDA has introduced an easier way to track your symptoms and manage your care through the APDA Symptom Tracker mobile app. Download to your mobile device today to keep track of your symptoms, create your reports, and share them with your care team or your doctor for more personalized care and support. This app is available through the App Store or Google Play.

[Slide 37] 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 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.