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'm the Vice President of Development and Marketing at the American Parkinson Disease Association or APDA for short. I am pleased to welcome you to this Web/teleconference education program designed for people with Parkinson's disease, care partners, family members, and healthcare providers. APDA is pleased to bring this program to you today.

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 educational 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.

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.

APDA is so proud to support those living with Parkinson's by helping them to 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 and their family members and through running 770+ exercise programs attended by more than 21,000 participants. These exercise programs help improve 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. These programs have been attended annually by more than 5,500 people impacted by the disease. It's programs like these that distinguish APDA as the national organization working one on one with the Parkinson's community to make each day better.

[Slide 3] And now to our program. Our presenter today is Dr. M. Maral Mouradian, who is the William Dow Lovett Professor of Neurology and Director, Center for Neurodegenerative and Neuroimmunologic Diseases at Rutgers – Robert Wood Johnson Medical School in Piscataway, New Jersey.

Today we are delighted to have Dr. Mouradian share with us an overview of dyskinesia 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 introduce Dr. M. Maral Mouradian.

Presentation

M. Maral Mouradian, MD

Thank you, Stephanie, for the introduction; and I'd like to thank the APDA for inviting me to be the speaker of this webinar and also recognize the important impact that the association has in supporting research, patient education, and in general persons with Parkinson's disease and their families.

[Slide 4] So I will begin with my financial disclosures. I receive research grants from the National Institutes of Health, the APDA, the Michael J. Fox Foundation, and other sources listed here and salary support from my employer, Rutgers University. I also receive an honorarium from the American Society for Experimental Neurotherapeutics for my role as Editor-in-Chief of the scientific journal *Neurotherapeutics*. I'm not on any speaker's bureau for pharmaceutical or device companies. I'm a founder of a pharmaceutical company that's developing a new treatment for L-dopa-induced dyskinesia, but I will not be speaking about it in this webinar because it's still in the development phase.

[Slide 5] So onto our presentation. By way of background, the primary pathology in Parkinson's disease that's responsible for the classic motor symptoms such as tremor, slow movement, and tight muscles is in a small group of brain cells or neurons in the base of the brain depicted here on the left in pink. These neurons normally contain a dark pigment and are seen as the black shape on each side of the brain stem or the base of the brain on the right pictures. In Parkinson's disease they become sick and eventually disappear. In fact, by the time Parkinson's symptoms emerge, about half of these neurons are already gone. And these neurons produce the neurotransmitter or chemical dopamine; and therefore, as they die out, dopamine levels decrease. In fact, by the time symptoms show up, already 80% of brain dopamine is lost.

[Slide 6] Therefore, the main treatment approach in Parkinson's is to replace the missing neurotransmitter dopamine. On the left here is a drawing of the normal dopamine neuron that makes dopamine from its precursor or parent compound, L-dopa or levodopa, and then dopamine is packaged in small vesicles or pockets and released out of the dopamine neuron. And then the released dopamine recognizes an X on molecules called dopamine receptors that are located on the surface of the next neuron. And on the right, is the situation in Parkinson's where dopamine neurons have degenerated, and dopamine is depleted, so the main approach to treatment is to replace this deficiency. However, if we give dopamine itself, it won't work because it does not get into the brain and is cleared quickly from the body. So, one way of replenishing dopamine is to give its precursor, L-dopa, which is taken up by the brain and changed into dopamine.

The other approach is to use dopamine agonists. These are synthetic compounds that act directly on dopamine receptors and mimic what dopamine does. Dopamine agonists in the United States used for Parkinson include ropinirole, pramipexole, rotigotine skin patch, and injectable apomorphine.

It's clear that L-dopa is more effective than dopamine agonists, with the exception of apomorphine, which is only available as an injectable. And there are few other medications that boost the system

but are much weaker than L-dopa. **[Slide 7]** In fact, L-dopa is still considered the gold standard treatment for Parkinson's.

But the problem is that the response to it changes over time. At the beginning, taking it just three times a day in most people is usually enough to improve symptoms throughout the day. But over time, the response becomes complicated with the beneficial effect of each dose becoming shorter and shorter, resulting in what's called the wearing off phenomenon. And some fluctuations can be unpredictable, referred to as on-off phenomenon. On means when symptoms are improved, and the individual is comfortable and functional, and off is when Parkinson symptoms come back. In addition to these fluctuations between on and off states, L-dopa-induced dyskinesia appears.

[Slide 8] So what is L-dopa-induced dyskinesia? These are involuntary, purposeless movements that, unlike tremors, are not rhythmic. They're rather random. They're often what we call chorea-like movements, from the Greek word that means dancing. Sometimes they are more rapid and jerky. Other times it can be slower movements. These movements can be partially suppressed by the affected individual volitionally, meaning by will, but for a brief period of time.

And these dyskinesias can affect various parts of the body. They usually appear first on the side of the body that is predominantly affected by Parkinson's, as Parkinson's usually begins on one side of the body before it spreads to the other side. So, the side that Parkinson's symptoms first begin, that's also the side that dyskinesias usually appear first. And these dyskinetic movements can affect the arm and legs, hands, fingers, feet, shoulders, torso, head, neck—any part of the body—resulting, for example, in hip-body movements, body swaying movements. It can also affect the facial muscles, including lips, jaw, and others.

Now typically they start in mild form as small movements that the person with Parkinson's may not even be aware of and might be noticed only by a family member or the physician. But over time they become more noticeable and in some cases severe.

Now dyskinesias can interfere with walking, daily activities, and social life. And they can be disruptive and unpredictable; and generally, stress and excitement can make them worse temporarily, whereas being in a calm, relaxing situation can reduce these moments, again, temporarily. And a recent study reported that poor nighttime sleep is associated with dyskinesia in Parkinson patients.

[Slide 9] Now there are three main types of L-dopa-induced dyskinesia based on the temporal relation to dosing, in other words, when they appear in relation to taking a dose of L-dopa. The first type is called peak-dose dyskinesia which is the most common, shown in red in the far-left diagram. These are involuntary movements that coincide with the peak action or best anti-Parkinson action of L-dopa. And these moments occur when blood levels of L-dopa are above a certain level or threshold, Parkinson's symptoms are reduced, and the individual is in the on state.

The second type is called diphasic dyskinesia, meaning two phases, shown in blue in the middle diagram; and these occur before a L-dopa dose gives its peak full beneficial effects, or before the on period and, also, after the benefit disappears and the on period is over. So, the sequence of events with this type of dyskinesia is the person starts with parkinsonism, then the dyskinesias come, and

then the improvement or the on phase, and then dyskinesias reappear again and back to parkinsonism.

And the third type is what's called off-period dystonia, shown in gray in the right diagram. This is characterized by sustained abnormal posturing often of the foot or toes that can be painful. They look different than dyskinesia. Dyskinesias are ongoing movements, whereas dystonia is a sustained postural position. So, dystonia occurs when L-dopa levels are low, and the individual is in the off state, and it often happens in the early morning when the drug is cleared from the body overnight and is called early-morning dystonia.

[Slide 10] Now how common is L-dopa-induced dyskinesia? Actually, this complication is quite common, and it's a significant issue in the management of Parkinson's disease. On average, about 50% of people with Parkinson's develop this complication by five years of L-dopa treatment; and almost 90% do so by ten years of treatment. However, they can also emerge early, within months or even weeks, of starting L-dopa in a small minority of individuals.

[Slide 11] Now there are a number of factors that have been identified to increase the risk of developing L-dopa-induced dyskinesia. The first is individuals with young-onset disease are at greater risk than those who develop the disease at an older age. To give you some numbers, among people whose Parkinson's disease begins in their 40s, the chance of developing dyskinesia within five years is 70% compared to only 24% in individuals whose disease symptoms begin in their 70s. So, age is an important factor.

The second factor is being a woman. Women are at greater risk than men for this complication. Also, low body weight, being a small person, is a risk. More severe disease, obviously, and also higher L-dopa dose exposure. So, it's interesting to know that one possible reason why women are at greater risk is that they have a lower body weight than men; and, therefore, they're exposed to more L-dopa per unit weight.

And, finally, individuals who have what we call the akinetic-rigid form of Parkinson's, those who do not have the typical parkinsonian tremor, are at greater risk for developing dyskinesia. In other words, people with tremor-predominant Parkinson's have a lower risk of developing dyskinesia.

[Slide 12] So the question that is commonly asked is what causes these dyskinesias? Is it the disease itself or is it the treatment? Well, we think the answer is both. One needs to have significant loss of dopamine neurons as the disease progresses and also be treated with L-dopa chronically for a while, particularly taking it intermittently, which is the traditional way of taking pills several times per day.

[Slide 13] Now there are several reasons, in light of evidence, that make us conclude that disease severity is an important factor in the emergence of dyskinesia. For example, individuals who do not have Parkinson's and have a normal dopaminergic system, they do not develop dyskinesia when given L-dopa because they have the normal dopaminergic neuronal numbers.

The second reason that we think disease severity is an important factor is in the pre-L-dopa era. When L-dopa first became available and patients were given the drug at a time that they already had

fairly significantly advanced disease. In those individuals, half of them developed dyskinesia by five months, whereas nowadays we don't wait that long for the symptoms to advance. We see 50% of patients develop dyskinesia by five years. So that is a significant difference, obviously.

In fact, the case of developing dyskinesia fairly quickly in the pre-L-dopa era was detected in a movie called *Awakenings* and was depicted by the actor Robert De Niro. There was an initial improvement, but then shortly thereafter dyskinesia set in.

Another evidence comes from a study that showed if L-dopa is started at a moderately advanced stage of the disease, dyskinesias appear earlier than if it is started at a milder stage.

And also, as mentioned earlier, dyskinesias are more prominent on the most affected side of the body. Parkinson often starts on one side of the body more than the other, so the affected side with Parkinson also has more dyskinesia.

So, all this tells us is that the degree of dopamine neuron loss or disease severity is an important factor in developing L-dopa-induced dyskinesia.

[Slide 14] Now there are certain properties of L-dopa itself that contribute to these motor complications as well. First, L-dopa does not stay in the body very long. It is cleared relatively quickly, so about three-quarters of the dose that one takes is gone by about three hours. In addition, food in the stomach and how fast or slow the stomach empties its food content affect its absorption from the gut into the bloodstream.

In addition, dietary proteins interfere with the access of L-dopa from blood into the brain where it acts.

And the graph here shows in the lower white curve how blood levels of L-dopa go up and down as an individual takes L-dopa, carbidopa pills repeatedly during the day. And the red curve shows how the symptoms shift between on and off state. So, this is motor fluctuation because of the unstable nature of L-dopa levels in the blood.

[Slide 15] Now in addition to the properties of L-dopa itself, the fact that it stays in the system for a short time, the ability of the brain to handle and to respond to L-dopa changes as the disease progresses. In a normal brain, or in early Parkinson disease, shown in the upper panel, L-dopa is processed in a way that allows its delivery from dopamine neurons to the next neuron in a steady, continuous manner.

But in advanced disease, shown in the lower panel, when most dopamine neurons have already degenerated, dopamine is released in an intermittent or interrupted manner which is not optimal. Now there is evidence to suggest that delivering dopaminergic drugs intermittently contributes to the development of dyskinesia because in laboratory experiments repeated injections of a dopaminergic drug produced dyskinesia whereas continuous delivery of the same drug does not.

[Slide 16] In addition, in people with Parkinson's disease, dyskinesias are more commonly induced by L-dopa than by dopamine agonists drugs given alone. But remember dopamine agonists generally stay longer in the body than L-dopa does and, therefore, provides a more steady stimulation of the

dopamine circuitry. In addition, dopamine agonists are also generally much less effective as anti-Parkinson drugs than L-dopa, except for apomorphine which is injectable. So, there are two possible reasons why dopamine agonists cause less dyskinesia. It's because they are weaker, but they also stay in the system for a longer time.

[Slide 17] Now as mentioned earlier, L-dopa does not stay in the blood for very long. After taking a pill, levels go up and then most of it is cleared by about three hours, as shown in the wide curves. But early in the disease process, as shown on the left, improvement of symptoms is still felt in a steady manner because the window of benefits, as shown in green, is wide. But in advanced disease, this window becomes narrow, so that when blood levels of L-dopa go above the upper limit of the window, dyskinesias appear; and when the levels go below the lower limit of the window, the person turns off and Parkinson's symptoms return. And, optimally, the effect of L-dopa is felt only briefly when the levels are within the green zone.

[Slide 18] Another way to look at this is shown in this slide. In early or mild disease, depicted on the left, the window of benefit or what we call therapeutic window between the top red line and the bottom green is wide and the ups and downs in blood levels of L-dopa are not felt by the person who experiences the benefit throughout this period.

We call this having a smooth response. But in advanced disease, the window of benefit or the therapeutic window virtually disappears in some individuals; and the red and green lines become almost the same. So, when drug levels go up in the red zone, dyskinesias appear. And then when levels go down into the blue zone, Parkinson's symptoms return, and the individual turns off.

[Slide 19] So now moving out to the management of L-dopa-induced dyskinesia. For peak-dose dyskinesia, adjusting individual L-dopa doses and their frequency is generally the first step because sometimes the patient may be overtreated with too much L-dopa; and simply reducing the dose will do the trick. But it has to be done judicially to make sure that the Parkinson's symptoms do not return as well.

In addition, we can also add the drug amantadine, which our group showed 20 years ago that it can partially reduce the severity of L-dopa-induced dyskinesia. It also improves Parkinson motor symptoms to some extent. And recently, extended-release capsules of amantadine became available under the brand name Gocovri™. It is taken once a day at bedtime and reduces severity of the dyskinesias partially, by about 30%, and increases on time without too much troublesome dyskinesia by about two to three hours per day.

Now amantadine should be used with caution, particularly in older individuals because one of the more common side effects is hallucinations, in addition to a drop in blood pressure upon standing and dizziness. And if medical treatment is unable to manage dyskinesia, the surgical procedure of deep brain stimulation or DBS is considered, which can be very effective and reduces the dose requirement of L-dopa if the stimulator is placed in a particular part of the brain.

Now it's important to note that it's not essential to treat every mild dyskinesia if the person is not bothered by minimal extra movements and may not even be aware of them. And these movements can be watched until they become bothersome.

[Slide 20] Now diphasic dyskinesias are the most difficult to treat. General approaches for managing these include adjusting L-dopa dose and schedule, adding amantadine, deep brain stimulation, and also L-dopa-carbidopa intestinal gel infusion, known with the brand name Duopa™ in the US and Duodopa® in Europe can be considered. So, this delivers L-dopa directly into the gut through a tube inserted in the stomach and connected to a portable pump. So, this continuous delivery system maintains L-dopa in the blood steadily above a certain level in order to avoid diphasic dyskinesia. And the graph on this slide here shows the variable blood levels of L-dopa in red when the individual takes oral L-dopa-carbidopa tablets compared to the steady levels with Duopa infusion shown in blue.

[Slide 21] So as a result, Duopa increases on time without troublesome dyskinesia and also decreases off time. And for off-period dystonia, again, the main goal here is to minimize off time by adjusting the L-dopa dose and also using extended-release carbidopa-levodopa capsules known with the brand name Rytary™ or with L-dopa-carbidopa intestinal gel infusion or Duopa.

In addition, for abrupt off-period dystonia that comes on quickly, one can use subcutaneous injection of apomorphine that can be useful, and it acts quickly.

And, in addition, in some cases, botulinum toxin injection in the appropriate muscle can be helpful in minimizing off-period dystonia if other options failed.

[Slide 22] Now here are options that are not specifically approved for L-dopa-induced dyskinesia but can improve on time without troublesome dyskinesia or without worsening dyskinesia. I mentioned approaches to provide continuous drug delivery through intestinal infusion with Duopa, also extended-release carbidopa-levodopa capsule or Rytary provides more on time without troublesome dyskinesia.

And, in addition, apomorphine infusion may also reduce dyskinesia. This is available in Europe but not in the United States at this time. And recently a drug named safinamide became available in the US with the brand name Xadago® and is used in conjunction with L-dopa. So, it's added onto L-dopa, and while it's not specifically indicated for dyskinesia, when it's added to L-dopa for someone who has significant off time, the drug can increase on time without worsening dyskinesia.

[Slide 23] Another common question that comes up is when one should start L-dopa, and the answer is that treatment should be individualized for each person, depending on the severity of the symptoms, the age of the individual, and also presence of the other associated symptoms.

So, generally, L-dopa is needed when symptoms are at a stage that they interfere with daily activities, job performance, and quality of life in general. So, if someone has enough symptoms that are bothersome, L-dopa should not be withheld. Also, there are other medications that I mentioned, such as dopamine agonists, that may be sufficient for milder symptoms early on in the disease.

[Slide 24] And now what's on the horizon for treating L-dopa-induced dyskinesia? New compounds that target different chemical systems or transmitters in the brain are being tested, both in clinical trials and in the laboratory. And also new ways to deliver L-dopa continuously in addition to the Duopa or the intestinal formulation I mentioned. There is also being tested a subcutaneous delivery

system with a small needle under the skin attached to a pump to deliver the drug continuously. That's in the development stage, not available yet.

Plus, subcutaneous infusion of the dopamine agonist apomorphine can be an option, which I mentioned earlier, is available in Europe. It provides continuous delivery of the drug subcutaneously under the skin. And finally, since advancing disease severity is an important factor in the generation of dyskinesia, then treatments that flow or stop progression of the disease are expected to minimize the risk or severity of dyskinesia. There are currently no treatments yet proven to modify the disease process, but a number of approaches are being tested; so that will be an interesting question to look into in the future.

[Slide 25] And with respect to nondrug approaches to managing dyskinesia, there are attempts to optimize the DBS procedure, technical aspects of the DBS procedures and the stimulator and the leads. Also, being tested is transcranial magnetic resonance guided focused ultrasound that creates a small lesion in a specific region of the brain to repress dyskinetic moments. Now this is a fixed lesion and cannot be adjusted and it cannot be reversed, contrary to what DBS does, which does not produce a lesion and is adjustable. And the third approach being tested is transcranial magnetic field stimulation. So, these last two approaches focus ultrasound and magnetic stimulation. They do not require brain surgery, no holes in the skull or implants in the brain that are required for DBS.

So, in summary, L-dopa and dyskinesia is a significant problem for the quality of life of people with Parkinson's disease and also a challenge to manage in some individuals. We have a few therapeutic options now and more are on the horizon.

So, I will stop here and I'm happy to address questions.

Presentation Question & Answer

Stephanie Paul

[Slide 26] Dr. Mouradian, thank you so much for this very informative presentation. It is now time for the Q&A session.

Stephanie Paul

Okay, Dr. Mouradian, we have our first question. It comes from Martha, and her question is, "Is there a connection between Parkinson's and vasculitis or Parkinson's and pure autonomic failure?"

M. Maral Mouradian, MD

Well, Parkinson's is what we call a neurodegenerative disease, which I mentioned the group of brain cells or neurons degenerate whereas vasculitis is inflammation of the vessels or the arteries, for example. So, there is no real evidence that there is a vasculitis in Parkinson's. There is an inflammation in Parkinson's, but it's of a different nature. There are inflammatory or immune cells in

the brain which we call microglia. Those are activated in Parkinson's, but it's a completely different nature than vasculitis that targets vessels.

With respect to pure autonomic failures, that is, as the name indicates, it only affects the autonomic nervous system. It does not affect the dopaminergic system. It is a progressive condition, and it's treated differently. Although I should say many patients with Parkinson's also have an element of autonomic dysfunction. In other words, their blood pressure drops when they stand up; they have symptoms related to their GI tract, the bladder, sweating changes and so on. So, there's different conditions, but with respect to the autonomic symptoms, there are some of those symptoms in Parkinson's also.

Stephanie Paul

Terrific. Thank you, Dr. Mouradian. We have several callers on the phone, so I'd like to go to our first phone caller please.

Operator

Our next call is from Laun from Boston. Laun, please state your question. Your line is now live.

Laun from Boston

Hi, doctor. My husband was diagnosed with Parkinson's a few months ago, and he's 70 years old. The doctor had prescribed Sinemet®, which is carbidopa-levodopa, .25. So, do you think he should have been in the dopamine agonist instead of going directly to this medication?

M. Maral Mouradian, MD

Well, as mentioned earlier, choosing a drug should really be individualized by the physician because it depends on many factors that a physician has to take into consideration. So, without evaluating a particular patient, it's really impossible to make a recommendation. We generally look at factors, for example, the general health of the individual, the memory and cognitive status of the individual, the age, and how severe the symptoms are. So, in general, it's important to individualize and have the treating physician who saw the patient to make that determination.

Stephanie Paul

Okay, thank you. Now we're going to go to one of our Web questions. This comes from Eric, and the question is, "What percentage of control release carbidopa-levodopa reaches the brain as compared to fast-acting or regular carbidopa-levodopa?

M. Maral Mouradian, MD

Well, actually, the old controlled-release carbidopa-levodopa that's been available for a very long time has a lower, what they call, bioavailability. Only about two-thirds of it gets into the system, and only a very small fraction of L-dopa actually gets into the brain. So, the difference between short-acting versus long-acting, it really depends how much of it is really taken up by the gut, what we call the

bioavailability. But once it gets into the bloodstream, only a very small fraction gets into the brain. But it's, obviously, sufficient to have a beneficial effect.

Stephanie Paul

Okay, terrific. We have another phone caller, so let's please go to the next phone caller.

Operator

Our next call is from Mark from Philadelphia. Mark, please state your question. Your line is now live.

Mark from Philadelphia

Doctor, thank you. I've heard about a new medicine called Gocovri for dyskinesia. Can you tell me a little bit more about that?

M. Maral Mouradian, MD

Yes, as I mentioned, Gocovri is extended release amantadine. Amantadine we've been using for quite some time, and we know for 20 years that it has ability to suppress L-dopa-induced dyskinesia.

So Gocovri is a new formulation that delivers amantadine for a longer time and with a particular profile. It's given at bedtime, and the levels gradually go up overnight and reaches its expected level by the morning. So, it is the same chemical, amantadine, that's available generically; but it's longer acting and its release profile is different. It does suppress the dyskinesias partially, but what we don't know is how it compares to the generic formulation because that comparison was not done.

Stephanie Paul

Okay, we have another question from the Web. This is coming from John, and the question is, "Can dyskinesia be stopped or slowed for someone with bilateral DBS?"

M. Maral Mouradian, MD

Okay, that's an interesting question. Well, obviously, DBS is very effective in reducing dyskinesia, also motor fluctuations between off state and on state with dyskinesia are greatly improved with DBS. And with DBS placed in a small brain region, as I mentioned earlier, called the subthalamic nucleus or STN, the dose of L-dopa that's needed to ease Parkinson's symptoms is reduced substantially. And that, in and of itself, can contribute to influence dyskinesia.

So, while a person has DBS and the stimulator is on, dyskinesias are greatly improved. Now most DBS procedures in Parkinson's are done in individuals who have motor fluctuations and dyskinesias that are not manageable by medications.

So, at the start of DBS, these people already have dyskinesia. But whether DBS slows future worsening of dyskinesia, it's hard to know because these people will not be taken off of their DBS as long as they're doing well. But all I can say is that theoretically it's conceivable that DBS might have a

positive impact on these moments because it provides a steady stimulation of the brain circuitry that's closer to the normal state than taking pills intermittently.

As mentioned earlier, in laboratory settings, we know that stimulating this system intermittently is associated with dyskinesia, whereas stimulating it continuously is not. So overall, while DBS is on, dyskinesia is greatly reduced. And whether DBS stops or slows the worsening of dyskinesia, it has not been proven in clinical testing; but it's conceivable that's the case.

Stephanie Paul

Okay, terrific. We had another phone caller. If we can please go to the next phone caller.

Operator

Our next call is from Alan from New York. Alan, please state your question. Your line is now live.

Alan from New York

You had mentioned in this rebuttal that there was a way of reducing some of the off time by adding another drug. My wife has significant off times, freezing spells if you will, and I think you did mention quickly a drug that could be given in addition to the carbidopa-levodopa that may help reduce that freezing or off time.

M. Maral Mouradian, MD

Well there are several approaches to treat someone who's having a lot of off time or freezing time. The drug I mentioned is only one of them. The first approach is to try to review the overall medication schedule of the individual to see what improvements and adjustments can be made to minimize that. So, there is more than one way of doing that. The drug safinamide is only one of them. If the person has too much off time, a dopamine agonist can be added, and other drugs can be added. For example, drugs that block the degradation of dopamine such as entacapone and others. So, the doctor has various ways of doing it, but it starts by reviewing the whole list of medications and timing and dosages of what the patient is taking.

Stephanie Paul

Terrific. Thank you, Dr. Mouradian. We'd like to now go to another Web question. This comes from Jerry, and the question is why would dyskinesia appear on some days and not on others if medication is taken consistently?

M. Maral Mouradian, MD

Well, that's an interesting question; and, actually, it's not an uncommon situation. Frequently doses of L-dopa do not get exactly the same degree of benefit or dyskinesia on different days, and there are several factors for this variability from day to day, including the timing of taking carbidopa-levodopa in relation to food because food in the stomach slows down absorption of the drug from the gut into the bloodstream and, therefore, eventually into the brain. Also, what kind of food the person may have

consumed. We mentioned protein interferes with access of L-dopa into the brain and, therefore, taking L-dopa close to consumption of a high protein meal may make it less effective and also produce less peak-dose dyskinesia.

In addition, variations in stress level or mood conditions from day to day might impact the response to L-dopa. So, the response to this drug from day to day is frequently not identical; and as the disease progresses, this becomes more of a problem, and the response becomes more and more unpredictable.

Stephanie Paul

Okay, terrific. We have some more people who are on the phone, so if we could please take the next phone caller.

Operator

Our next call is from Stephen from New York. Stephen, please state your question. Your line is now live.

Stephen from New York

I have dyskinesia. I just developed it. I've had Parkinson's for five and a half years. I actually have a few questions, but I don't want to take up too much time. I have 30 first cousins, and 4 of us have Parkinson's disease. So, actually, one question is, is it hereditary? I'm the last one alive. My third cousin just died three days ago, and he was perfectly fine three days before Christmas. He was lucid, he had no problems, and all of a sudden, he passed away. So is the Parkinson's hereditary, number one. And does it skip a generation?

M. Maral Mouradian, MD

Okay, all right. So, the answer, is it hereditary, it certain can; and there are many, many genes that have been identified that can cause hereditable Parkinson's disease. And it's complex because different genes have different patterns of inheritance. Some are what we call dominant. In other words, it goes from one generation to the next without skipping and some are recessive, which sometimes skips. So, there are many different types of genetic inheritance of Parkinson's, and it's very complex; and without doing gene testing, it's difficult to make any prediction. Even with genetic testing, if we don't know what gene to look for, it will be difficult to make a prediction. But it certainly can be hereditary, and the list of genes that now we know because Parkinson's is expanding rapidly.

Stephanie Paul

Okay, thank you, Dr. Mouradian. That's very helpful. We have another question from the Web. This comes from Robin. The question is, "Are there kinds of protein that do not affect Parkinson's drugs so much, plant protein versus red meat, etc.?"

M. Maral Mouradian, MD

That's a very interesting question. Generally, patients report that red meat tends to be more of a problem when taken in close proximity to L-dopa, whereas fish, for example, is less of a problem. But it's generally the specific amino acid components of a protein that is the culprit. The kind of amino acids that use the same transporter system from the blood to the brain. So, anecdotally, generally speaking, most people think red meat is more of a problem, but one has to test and try for themselves to see which one works or doesn't work for them.

Stephanie Paul

Okay, thank you. We have another caller on the phone, so if you could please take that question.

Operator

Our next call is from Allison from Ruskin. Allison, please state your question. Your line is now live.

Allison from Ruskin

Hi, good afternoon. My father was diagnosed with Parkinson's in his late '30s, early '40s. We tried levodopa and all those medications, and they were counterproductive. The hallucinations were out of control. Nothing seemed to work. We later were told he was diagnosed with parkinsonism. In five years he's deteriorated to the point where he can't get out of bed. Is that common with parkinsonism? Is there a big difference between Parkinson's disease and parkinsonism?

M. Maral Mouradian, MD

All right, so what you're describing, it's not unusual for somebody to develop symptoms that look like Parkinson's disease at the beginning. But then over time the disease evolves, and additional manifestations show up and becomes more complicated that doesn't fit the diagnostic criteria of Parkinson's disease itself and then perhaps the physician may say, "It doesn't look like Parkinson's disease anymore. It's a more atypical form of parkinsonism.

That happens. In fact, at the beginning of symptoms, about 15% of the diagnosis, even by experts, prove to be the wrong diagnosis when eventually one looks at their brains. So, there is some clinical overlap, and things change over time.

So, Parkinson's disease we define as the typical presentation, typically with slow, uncoordinated movements, plus tremor and tight muscles. And also, we like to see a good robust response to L-dopa.

The atypical Parkinson syndromes, there are a few of them that have some features similar to Parkinson's disease but in addition have other manifestations. And those individuals or the conditions don't respond to L-dopa as well as Parkinson patients do.

Stephanie Paul

Okay, Dr. Mouradian, we have a question from the Web. This comes from Greg and the question is, "Can strenuous activity induce dyskinesia? I have experienced this."

M. Maral Mouradian, MD

Oh, that's an interesting question. Obviously, exercise has been looked at. We looked at the possibility whether exercise, such as getting on a treadmill, affects how the body handles L-dopa; and we found no such effects. Generally, it's also variable from one person to another, I think, in this case that you're describing excessive exercise making it worse.

Some other patients may report that it actually improves. There have been some studies looking at exercise or a sort of multidisciplinary program of physical therapy and exercises may even improve dyskinesia. So, there may be some variability; and, again, as mentioned earlier, Parkinson's, there are more than one type of Parkinson's, what we call Parkinson's, and there is a lot of variability from person to person.

Stephanie Paul

Okay, great. We have another question from the Web. This comes from Eric. The question is, "Rytary can be expensive. Can a combination of regular and controlled release be used and be just as effective?"

M. Maral Mouradian, MD

Not really. The old controlled release L-dopa-carbidopa is not as effective. It's not as controlled as we think it is. And, also, as mentioned earlier, its bioavailability, in other words, how much of the pill you're taking actually gets in the system is low. And because it's controlled-release, stays in the stomach, in the gut for a longer time and, therefore, more susceptible to variations in absorption. The Rytary has a unique combination of an immediate release and an extended release in a certain proportion that allows an improved profile compared to taking just existing generic L-dopa-carbidopa standard release and extended release.

Stephanie Paul

All right, thank you for that. We have another question from the Web. This comes from Beth, and the question is, "How can you tell the difference between dyskinesia and the advancement of PD?"

M. Maral Mouradian, MD

Well, that's an interesting question also. Obviously, dyskinesia are the involuntary movements that we discussed, be it like dancing-like movements, chorea-like movements, or less commonly dystonia, the sustained posturing. And these certainly advance also as the disease advances, and they become more severe, and they last longer and become more difficult to manage.

So, these are extra movements. Again, these are not the tremors described earlier; they're not rhythmic. But one of the signs that the disease is advancing is how severe the off periods are, and how long they are, and to what degree the stiff muscles and the tremor and the slow movements or the incoordination are. Those are the Parkinson's symptoms or the symptoms of the underlying disease itself.

So, we see these when L-dopa wears off, and the off symptoms are apparent, both to the person with Parkinson's and to the physician. In the off state, we see the disease, sort of the baseline disease.

And also, the need for more and more medications is another sign of advancing disease, meaning there are fewer dopamine neurons left and also the individual needs to take more of L-dopa in order to replenish that deficiency.

Other signs of advancing disease include problems with balance, falls, difficulty with daily activities such as eating and dressing independently. Other manifestations may show up including swallowing difficulty and memory and cognitive difficulties, hallucinations. So, it's a whole spectrum of symptoms that may show up as the disease progresses.

So, although worsening dyskinesia and advancing disease often go hand in hand, in other words, as the disease advances, so do the dyskinesias, telling the difference between the two, between dyskinesia and advancing disease is not difficult for a trained neurologist or a movement disorder specialist.

Stephanie Paul

Okay, thank you. We have time for one more question. This comes from Marjorie, and the question is, "Does dyskinesia contribute to weight loss?"

M. Maral Mouradian, MD

That's another good question. Weight loss, actually, is common in Parkinson's disease itself, even early on in the course of the disease without L-dopa. And there are many factors that can contribute to weight loss throughout the course of the disease, including burning more calories because of dyskinesia. But also, the rigidity or tightening of the muscles and the tremors, these are all adding up to burning more calories that can contribute to weight loss.

Other reasons for weight loss include nutritional intake because of difficulty swallowing perhaps in some people and decreased sense of smell and decreased appetite, maybe nausea because of medications, and also reduced absorption due to slow stomach emptying. All can contribute to weight loss.

So, burning extra calories can be viewed, two factors, both the off state having more tight muscles and tremors, but also the onset with dyskinesia and since often people when they're fluctuating respond, switch between these two states, both can contribute to weight loss.

The other side about this relation between dyskinesia and weight loss is that patients with lower initial body weights and those who lose weight have a higher risk of developing dyskinesia. And part of it is probably because people with lower body weight are getting more L-dopa per unit weights; and as I mentioned earlier, low body weight is a risk for dyskinesia, so that can explain if somebody starts with a low body weight or losses weight, they're at higher risk of dyskinesia.

The other interesting thing about weight and dyskinesia is that weight gain can occur after DBS, perhaps because there is less energy consumption because of decrease in muscle activity as both tremor and muscle tightening and dyskinesias are reduced. So, several factors, including dyskinesia, can contribute to weight loss in Parkinson's.

Closing Remarks

Stephanie Paul

[Slide 27] That's great, Dr. Mouradian. Thank you so much. This has been really terrific information, so my thanks to you and my thanks to everyone for participating in today's telephone and Web education program.

[Slide 28] I do apologize that we couldn't get to all of the wonderful questions, but we're pleased to let you know that APDA has partnered with Smart Patients. This is a forum where people with Parkinson's, their care partners, and families learn from each other and support each other and offer you the chance to continue the conversation with others in the PD community.

Immediately following this program today, please join us for a moderated chat at www.smartpatients.com/apda. If you have any questions or would like to speak with someone in our Scientific and Medical Affairs Department, I do encourage you to visit our website or call 1-800-223-2732 and you can ask your questions there.

I want to thank Dr. Mouradian for her presentation today. 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 that was in the confirmation email you received.

APDA is so proud to invest in patient services and education and to have been a funding partner in most of the major Parkinson's disease scientific breakthroughs that are improving the quality of life today. To do all of this, we rely on the support of the entire Parkinson's community. If you are interested in supporting APDA or want to learn more about how you can get involved, please visit our website at www.apdaparkinson.org.

Our thanks, again, to Dr. Mouradian and to all of you for joining us today. 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.