Spotlight on Parkinson's Disease: What to Do When Your Medications Stop Working

Transcript

Welcome and Introductions

Stephanie Paul

[Slide 1] Welcome everyone and thank you so much for joining us today. **[Slide 2]** My name is Stephanie Paul, and I am the Senior Vice President of Development & 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. I would like to thank Sunovion Pharmaceuticals, Inc. for funding this important program and acknowledge their continued appreciation for the critical need to provide educational programs like this one to people impacted by Parkinson's disease.

APDA is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than 1 million Americans with Parkinson's disease live the best life in the face of this chronic, neurological disorder. Founded in 1961, APDA has raised and invested more than $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's community to make each day better.

[Slide 3] And now to our program. We welcome our distinguished presenter today, Dr. Un J. Kang, Founders Professor of Neurology and Director of Translational Research at the Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders at NYU Langone Health in New York, NY.

Today we are delighted to have Dr. Kang share with us the latest information about what to do when your medications stop working. 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. Kang.

Presentation

Un J. Kang, MD

Thank you, Stephanie. I'm delighted to join all of you for this APDA webinar and address this question of what do you do when the medications stop working. And I must say this is one of the more common questions I get asked. **[Slide 4]** But before I go on, let me just tell you that I have no financial conflicts of interest. **[Slide 5]** And I'm going to rephrase this question a bit, so the question I often get asked related to this is do medications stop working after a few years or several years?

And the corollary question is, should I save the medicine or delay the start of the medication for a later timepoint when I need them more? To eliminate any suspense, you saw there from the title that I label it as a misconception. My answer to these questions are no.

[Slide 6] So let's discuss why I came up with those answers. I'd like to review what the current medications are addressing, what symptoms do they treat, and to be able to understand what symptoms they are treating, it is good to know how they work. So we're going to review some of the brain and biochemical mechanisms underlying these medication therapies. And in the process, we'll be able to discuss limitations of the current medications. And then at the end, I hope to give you what's in the horizon about what new approaches are being taken to be able to address these symptoms that are not addressed by the current medications.

[Slide 7] So we're actually fortunate that there are good medications that replace dopamine, which is the basic missing ingredient in Parkinson's disease in their brain. And it treats the symptoms quite effectively in most of the cases.

On the left side of the slide, you will see that there's little cells in dopaminergic neurons in the part of the brain called midbrain; and in a small area called substantia nigra pars compacta, dopamine cells sit there, and they project long distance to the striatum where there are cells that's receiving the signal from these dopaminergic neurons. So, if we enlarge this at the cellular level, dopamine cells make the dopamine and actually it starts from a very simple compound, amino acid tyrosine, which is present everywhere, including outside the brain. What makes dopamine neurons unique is that it has two enzymes, tyrosine hydroxylase, shortened as TH, aromatic amino acid decarboxylase. It's called AADC. So these two steps makes this common tyrosine as a unique dopamine.

And the cells package it neatly into these little vesicles, and when the cells become active, they fuse with the plasma membrane, and they come out of the cell. And then there's a cell sitting next to that that has dopamine receptors that will recognize the dopamine and the message is passed on. So this is how the neurotransmitter works, and in Parkinson patients there's a degeneration of these neurons, and they're lost over time.

Before we go on, I should emphasize that there are other neurons that degenerates, as depicted in these blue-colored neurons in the brain stem; and a lot of these may be responsible for nonmotor symptoms that don't respond to dopamine, autonomics, bodily functions, and then there's also involvement of the cortical area of the brain, which will be responsible for some of the cognitive deficits that we sometimes see in Parkinson's disease.

[Slide 8] So the way I like to think about this is to use as a simple 2x2 table in my head, and we think about symptoms that responds to dopaminergic medication. And then the symptoms that's not responded, at least have a limited benefit from dopaminergic medication. And most symptoms that responds to dopaminergic medications are the motor symptoms – tremor that occurs in a resting state; slowness, we call it bradykinesia; rigidity, stiffness of the muscles; and walking problems. They usually do well, especially in early stages; but as time goes by, some of these symptoms may not responds as well, we call axial symptoms and midline symptoms – speech, gait problems, and sometimes it leads to freezing. You have to pause before you can regain and continue to walk along. And in some patients, even the rest tremor may not respond well to dopaminergic medications.

But the majority of symptoms that do not respond to dopaminergic medications are what we call nonmotor symptoms that may include a subtle cognitive deficit, maybe multitasking, some visuospatial issues, and mood problems – lack of motivation, apathy, anxiety, fatigue, some of the sleep disturbances, and problems with autonomic bodily functions that may lead to constipation, sexual/urinary dysfunction, or dizziness when you stand up – what we call orthostatic hypotension. And it may also involve sensory disturbances and sometimes even a pain.

[Slide 9] So, what does it mean when a medication is not working? So, I'd like to take you through different stages of Parkinson's disease in discussing this issue of medication not working properly. **[Slide 10]** It could be at a time when you first start medication, and I must say and emphasize that in most people medications work pretty well, and this is the majority. But sometimes I will see patients who say, "I've been diagnosed, I took the medicine, but it didn't work." And in some of these cases, it may be because the dose was not sufficient enough, and in other cases it wasn't tried long enough. And in certain other cases it's because it was limited by side effects; therefore, they couldn't try high enough doses in a long enough duration. Sometimes it takes weeks before you really notice a benefit, and then we often titrate the medication slowly from low doses to high doses so that you can get used to the side effects and often those become tolerable.

[Slide 11] And most people do well, and actually when a patient tells me that they have to set a reminder to take medications, I know they are doing well because their medications are working smoothly enough that they don't really notice the wearing off or problems with it. And over several years though, often, and the number is usually about 50% of the people in five years and a higher proportion as the time goes on, the medication may not respond as well. And some of these take the form of dose failures. This is not as common, but just a dose simply doesn't work at some times. Most of the time it works, but once in a while it's as if you haven't taken anything.

More commonly, it's what we call motor response fluctuations; so the benefit you get, the duration becomes shorter and shorter. We call it, it wears off. The medication effect wears off too soon, and then the opposite spectrum is that you have excessive response and develop abnormal involuntary movement or what we call dyskinesia or sometimes levodopa-induced dyskinesia. And, occasionally, there may be situations where the response is erratic. Sometimes it's as if the switch has gone off, that your motor response is gone.

[Slide 12] So a good way to think about this is more graphically, and so if you just stay with the left panel, and this is depicting a response in early patients, and the horizontal line tells you how long it's

been since you took that dose. And the vertical line tells you how you're responding. So you take a medicine, half an hour, hour later, a little longer maybe, you improve and you're doing well for many hours. So if you take a medication three times a day, maybe every four or five hours, and you take the next dose and it kicks in before the first dose wears off, so you're pretty good all day; and you have to set a reminder to take medicine because you don't really notice a problem. But then over time, with the chronic use of medication, the duration becomes shorter; and it doesn't last as long. And sometimes you get an excessive response, what we call dyskinesia or levodopa-induced dyskinesia that we just talked about.

[Slide 13] So let's troubleshoot what could go wrong to give us this type of a nonoptimal response. So when you take a medication, mostly by mouth, and they go into your stomach and then it has to pass to duodenum, which is the next part of the gut that has high acidic pH, that helps levodopa to get taken up into the bloodstream, and then the vision ascend is in the brain. So it has to get into the brain, and they have to pass through this barrier called the blood-brain barrier. And it's specially designed to block off some things that go in, so it's not as common, but there are things that could go wrong and not getting properly into the bloodstream and not into the brain. So there may be delayed response to the medication. It's taking longer to get in there, and then sometimes people who have high protein-rich meal, a lot of protein gets broken down to amino acids, and amino acids competes with the levodopa in getting through these steps because they go through the same carrier. So then you may not have as good a response. So these are the problems that could potentially happen in a first step. I must say these are not very common, and I don't routinely recommend any kind of dietary changes that limits protein for this reason. But this is something we watch for.

[Slide 14] So there have been new developments to see if we can bypass this whole thing and deliver it in some other way without relying on our gut. So you can put a tablet under your tongue, and then it goes into the epithelial and then go right into the brain. There's a new medication that was approved so that you can inhale, like asthma drugs, and then it goes into respiratory epithelium and right into the brain. And then there's an injection formulation that you can inject under the skin as if you're using insulin; and then it gets right into the bloodstream as well. And these help medications to act more quickly, but these are usually kind of a supplementary adjunct rescue medication, not the mainstream.

[Slide 15] There are other ways to bypass the gut. You can put patch medications that you can use as a transdermal preparation. This is more of a synthetic dopamine that mimics dopamine effect, L-dopa effect, or the subcutaneous injection can be combined with a pump so that it can continuously supply. So these bypassing methods can give you a quicker delivery or more sustained delivery if that's what's necessary.

[Slide 16] In addition, I'm sure you're aware there are a lot of different formulations of the main carbidopa-levodopa medication so that it'll be released slowly in the gut. And there have been formulations of sustained, they call it different names, continuous release, extended release, and so on, but they all talk about the same thing. And there have been preparations available for some time, but they have not been too effective.

Recently, a new formulation has been combined with immediate release and sustained release together, and it came out as a brand named Rytary™. As you can see on the right-hand side, they seem to do a pretty good job of sustaining the blood level after taking the medication. And then there's another way that is, levodopa is available as a solution, and it can be infused directly into the gut, in the duodenum, and that's called Duopa. So there's different ways of sustaining the L-dopa effect.

[Slide 17] Now the last step is since everything in the body gets broken down by enzymes, there are two main enzymes that break down L-dopa and dopamine, and one is MAO (monoamine oxidase). The other one is a COMT (Cacechol-O-methyltransferase). So there are lots of inhibitors of different formulations that inhibits these steps and, therefore, make the dopamine last longer.

[Slide 18] And another way to make medications last longer is producing a synthetic dopamine. Instead of levodopa that becomes dopamine, the natural compound in the brain, there are many synthetic dopamine medicines. We call them, as a category, dopamine agonists. And this is the same diagram that I showed you talking about how the dopamine is produced, so you basically bypass all this, the step of making them, and just go right to the receptor by using this synthetic dopamine and that's dopamine receptors, sitting there in the striatum on the left-hand side. And they have a longer half-life, so they last longer; and they're also extended formulations that make it last longer even more or the patch preparations that you can put it on top of the skin.

Dopamine receptors, there are like five different types. Actually, it's a bit complicated; and these synthetic dopamine agonists mostly hit a D2 type of receptor, not like the natural dopamine that hits all the receptors. So, it has a somewhat limited efficacy and has a different side effect profile, but they do their job of producing slow release.

[Slide 19] Now there's a whole different approach of treating Parkinson's disease. I'm sure you're aware of this. There are brain surgeries. I think may be too big a word for this, but these are stereotactic functional surgeries where you specifically target small areas of the brain; and in the '60s, '70s, and '80s, used to be that you would take a small area and destroy them with the electrical lesions and that had a pretty good functional effect of improving symptoms.

Nowadays, we use deep brain stimulations mostly, which is an electrode, very thin electrode that gets passed into the brain. You can see the trajectory. This is an MRI (magnetic resonance imaging) picture, and you can see some of the structures are outlined; and these dotted lines represent some of the electrode tracks and gets to the structure that we want to get to and then electrically modulate the function of the neurons and achieve a quite effective way. But the best way to think about this is, and that's why I titled it as modulation of neurons, to make levodopa work better. They're not completely replaced, but they make the medication work better.

And more recently, there have been the application of ultrasound, which we usually think about as a diagnostic tool. Everybody gets sonograms for this and for that, but you combine MRI with the ultrasound and noninvasively modulate or destroy some of these structures. Right now, it's mainly approved for tremor and targeting thalamus that I just outlined.

[Slide 20] So we talked about what happens when medications do not work as optimally as before, and the corollary question though that I mentioned at the beginning is that there is reason to delay the start of the medication for later because the implication the use of medication is giving us all these problems. So why not save it later when we really need them?

[Slide 21] There have been a lot of experimental studies and clinical studies, anecdotal observations that seems to have a consensus that we don't have to worry about it. This is the combination of the disease itself and the medication, but most likely, the complication is driven by the disease itself.

I think this diagram from a paper I took from Italian Parkinson's experts illustrates this point very clearly. So they compared response of patients in Italy versus patients in Ghana in Africa. So if you look at Italian patients, this seems pretty similar to the US. You get diagnosed here, and then within a year and a half you start taking the medicine. And then maybe about four years pass by on the average – obviously, this is an average phenomenon – and then you start having problems like wearing off and dyskinesia. But I should actually take this opportunity to say most of these problems are actually, it's not major problems but is really something to deal with. So it takes about four years.

So, patients in Ghana, Africa, they have less access to a ready diagnosis, so it may take them longer, almost five years for diagnosis from the onset of symptoms; and then it may take another year before they start medication. So this was kind of delayed, so the question was answered by a natural experiment here. Then do we delay the appearance of complications? And the answer is pretty clear, no. It comes pretty quickly. So, it seems like the onset of complications are driven by duration, meaning the severity of disease, rather than as much from the medication. Obviously, both do contribute.

[Slide 22] So we talked about what does it mean when medication is not working, at the beginning, after several years of the complications. But there are times where we really have to sit and think are we taking the right approach? Is this the right disease and right medications because it seems like things are not working?

So, obviously, I think one of the first things we have to think about is, is this really Parkinson's disease because there are many disorders that look like Parkinson's disease, but they are slightly different disorders. There are various names for this, and I won't go through all of that, but I'm sure you heard about multiple system atrophy, MSA; progressive supranuclear palsy, PSP; and so on. So some of those disorders look like Parkinson's disease. They even respond to the medication for a while, and then they stop responding altogether.

And then even in Parkinson's patients, I talked about even some of the motor symptoms. They may respond some, but then don't respond any more, particularly gait, freezing, and some of the speech problems and so on.

And then there were symptoms, actually looking back, that never really responded or partially responded to dopaminergic medications. So mostly those nonmotor symptoms. They're not likely to be dopaminergic. Therefore, they didn't respond to the dopaminergic medicines; but they've become more noticeable. So that's the only reason that comes up is "I was doing fine." So if you're not thinking about specific symptoms, "I was doing fine, but then I'm not doing so well. I'm still taking

medicine," the reason is because they were not the kind of symptoms that medication was designed to treat.

[Slide 23] So let me come back to this 2x2 box table and put this kind of in a summary form. So we talked about that there are symptoms that responds to dopamine. Most of them are motor symptoms, and they do respond well. But then there was a little bit of a complication of wearing off, dyskinesia, and so on. And some of the problems, especially speech, gait, and freezing, they may respond early on in mild cases; but then the major problems as time goes by, they're not really dopaminergic and doesn't respond well.

And most of these symptoms that do not respond to medication are the ones that never really responded to start with, but it wasn't as noticeable, and it becomes more noticeable as time goes on – some of the cognitive deficits, depression, anxiety. We talked about all of these before.

And the interesting question is are there nonmotor symptoms that respond to dopamine? And it's not as obvious, but over time some of the symptoms fluctuate just like the motor symptoms in response to medicine – anxiety, some of the apathy, fatigue. So you're better when you take the medicine. When the medicine wears off, you're more anxious, you have more symptoms.

So, there may be some dopaminergic component to this, and this type of insight may help us to come up with a better treatment for these symptoms. And then medication can produce hallucinations, and especially in young people with the dopaminergic agonists, the synthetic dopamine, may develop impulse control disorders over time, gambling, excessive shopping, hypersexuality. Some of these problems are associated with the use of dopaminergic medications over time.

[Slide 24] So how do we deal with these symptoms that are not responding to the usual medication? So the nonmotor symptoms, although they're not typical dopamine-dependent motor problems, we have symptomatic treatments for many of those. You take antidepressants for depression, you take medications that relieve anxiety for anxiety, and so on. Sleep, autonomic problems, there are lots of different ways of dealing with the symptomatic management and symptomatic medications, just like, let's say, depression from any causes or anxiety from any causes. These will be treated by the same kind of approach.

And then for these symptoms that are more resistant, but motor symptoms like gait and freezing, there is lots of research going on trying to understand maybe we should deal with a different neurotransmitter other than dopamine. For example, acetylcholine, so cholinergic agents are being explored. Glutaminergic agents are being explored, and then there is lots of research looking at a novel way of modulating brain – maybe perhaps different structure other than what we've been dealing with or different methodologies. Some of these may include gene therapies into a specific part of the brain. So there's lots going on trying to address these dopamine medicine-resistant symptoms. But at the end of the day, what we really like to do is treat the disease so that it doesn't get any worse rather than just treating the symptoms once they become symptomatic.

So there have been lots of clinical trials looking at medications that may modify the disease and slow down the progression. We don't have any one that works yet. I think one of the simplest ways is

actually SSRIs [sic] (selective serotonin reuptake inhibitors). There's growing evidence that SSRIs [sic] may modify disease, and it's good for the patients with Parkinson's disease.

And then among the agents that's been tried, isradipine is almost wrapping up. We don't have the answer yet, but this is a calcium channel blocker used for blood pressure. And we'll have the answer for the effect of isradipine fairly soon, I think.

And then there are new approaches, and one of the newer approaches is attacking alpha-synuclein. I didn't talk about this very much, but alpha-synuclein is the protein that clumps up within dopaminergic neurons and other neurons I talked about that degenerates in the brain, that's responsible for some of the nonmotor symptoms, and form a little inclusion called Lewy bodies and probably lead to the demise of the cells.

So currently there are at least a few alpha-synuclein antibodies that's attempting to reduce the burden of alpha-synuclein protein so that this clumping does not happen or reverse or reduce the degeneration that's going on. So that's actively being tested at this point.

And there are a couple medications that are used for other disorders, like exenatide for diabetes, nilotinib for cancers, which is a c-Abl inhibitor that's being repurposed and tested to see if it works to slow down the degenerative process of the Parkinson's disease and actually modify the disease. And there are lots more going on in research understanding what leads to degeneration.

[Slide 25] So to summarize what we just discussed, we talked about what the current medications are addressing when we say the medicine's not working anymore. What are the current medications addressing to start with and the fact that most of the current medications are dopaminergic and they're good at treating motor deficits?

And we talked about the limitations of current medications. Those motor symptoms improve well, but you may develop fluctuating responses; and we talked about how to deal with it, lots of different things that have come along to deal with this issue. And then we talked about the fact that nonmotor symptoms may not be fully addressed with these dopaminergic medications, because many of them may not be related to dopamine. And how do we address these symptoms? We said some of the nonmotor symptoms, like depression, and anxiety, can be treated just like any other depression, anxiety with the symptomatic medications that are available. And there are lots on the horizon in using a nondopaminergic approach to come up with new medications to treat some of the motor symptoms like gait and freezing that are not responding to current medicine, different way of modulating brain, and ultimately a new way of stopping the disease or at least slowing down or preventing it from progressing any further.

So I thank you for staying with me through the last half an hour, and I'm sure we'll be happy to, with the remaining period of time, answer any questions.

Question & Answer

Stephanie Paul

[Slide 26] Dr. Kang, thank you very much for this very detailed and informative presentation today. It is now time for the Question & Answer session.

Let's start with a question from the Web; and this question comes from Richard. "At which point do you switch to levodopa when a dopamine agonist is working well and is well-tolerated?"

Un J. Kang, MD

Yes, I think that's a very good question that commonly is encountered. I don't think it will be a simple question to answer in a general way because it really depends on individuals. For example, the patient's age, their other symptoms that could potentially predispose them to have more side effects, and so on.

So, most of the times, almost always, a dopamine agonist is not sufficient to treat symptoms beyond the first phase of the disease. So eventually most people end up adding or replacing it with a carbidopa-levodopa. So the time will come, and I think this is a very individual decision between the patient and kind of considering all the aspects of the patients with the patient's neurologist.

Stephanie Paul

We have a question coming on the phone. If we could go to the Operator and answer that phone question.

Operator

Our next call is from Steven of New York. Please state your question. Your line is now live.

Steven from New York

Hi, how you doing? The first question I have is you are perfectly normal, and you never had Parkinson's and you took Parkinson's medication, would the synthetic medication you were taking take over from the natural secretion of dopamine in the body and you can actually get Parkinson's disease if you never had it? That's question number one.

Question number two, can you actually go abroad, I never heard of anything beyond deep brain stimulation, like you were talking about, what was it called again?

Un J. Kang, MD

Focused ultrasound.

Steven from New York

Yes, focused ultrasound. Is that in trial or is that used a lot now?

Un J. Kang, MD

So it's mostly used for tremor at this point, and there are investigations going on trying to see if it'll be as useful for other symptoms of Parkinson's disease.

But let me ask you, with respect to your first question, let me understand the question a little bit better. So are you asking if a normal person takes dopamine agonist, can you develop Parkinson's symptoms? Is that what you're asking?

Steven from New York

Yes, let's say you were misdiagnosed, and somebody gave you a Parkinson's medication when you didn't have Parkinson's disease, would the synthetic dopamine take over for the natural dopamine which was being secreted in your body, and then can you actually get Parkinson's disease by taking a medication if you didn't have it?

Un J. Kang, MD

The simple answer is no, but this is a very, very interesting, thoughtful question. The dopamine, in most of the cases, if you're a normal person who doesn't have a loss of dopaminergic neurons, levodopa or dopamine agonist, the synthetic dopamine, doesn't produce much effect, especially the levodopa. And when you take it, there is a possibility that there's actually an effect of dopamine agonist on the dopamine neuron itself. It's called presynaptic receptors. They detect it, and they can shut down the production of the dopamine a bit, but it's all pretty well-regulated. So people don't develop parkinsonism, the symptoms of Parkinson's disease. Often the case where you develop Parkinson symptoms from the medication is dopamine receptor blockers rather than dopamine receptor agonists. And then, so that's just a symptom by modulating dopamine levels. The actual disease is very unlikely that it'll actually produce a degeneration of neurons.

Stephanie Paul

Okay, Dr. Kang, we're going to move onto another question from the Web. This comes from Kate. The question is, "Is it the levodopa or carbidopa that over time cause hallucinations and delusions? Does this mean the medication is becoming ineffective?"

Un J. Kang, MD

So I think the first part of the question is does levodopa-carbidopa produce hallucinations? Yes, it can, and many of the dopamine medications can produce hallucinations, particularly visual hallucinations. Somehow that seems to be more dopamine-related, so it can happen. But there are people who are more susceptible to this, maybe people with some cognitive problems, people with

older age. So it is possible, but it really depends on what stage they are and what kind of dose they are using.

I think just because it's producing hallucinations doesn't mean that it's not treating the motor symptoms, for example. So if we think about it in terms of what symptoms medication is addressing, what are the dopamine responsive symptoms, what are the dopamine nonresponsive symptoms, we have to sort of look at it as not as just a global response and global am I better, am I worse, but, yes, it may produce hallucinations; but it may still treat the symptoms of tremor, rigidity, and bradykinesia. So we can't say lost efficacy, you know.

Stephanie Paul

Okay, thank you, Dr. Kang. We do have another phone caller. Let's go to that question.

Operator

Our next call is from Larry from Massachusetts. Please state your question. Your line is now live.

Larry from Massachusetts

Thank you for taking my question, but I'm calling about the, starting out when I try to walk, I freeze sometimes; and I have problems with turns. Is there any way to treat that or is that just part of the Parkinson's or could it be something different?

Un J. Kang, MD

Yes, those are probably the two most common situations where freezing occurs. And do you, so patients may experience freezing when the medication effect wears off. So if that's the case, it's called off-freezing. Then it's a matter of regulating the medication schedule and the dose, just like other symptoms as I talked about, the wearing off. But later on, the freezing may occur despite the use of medication and despite the fact that your other symptoms are improving but you're freezing is not.

In those cases, there are no good, easy, simple ways of treating with a medication. But often freezing can be treated with physical therapy, little tricks. So Parkinson patients have trouble sometimes executing kind of automated tasks like walking without thinking. And let's say you freeze, but if you change your mindset and change the walking task into, let's say, I'm going to step over this little dot on the floor or shine a little laser light that crosses in front of you and try to step over or use a little cane inverted way and you want to step over the handle of the cane that's on the floor. So there are other tricks that you can use, some people, you can use to overcome freezing. And some people will, let's say, listen to a tone, music, to try to get over it. So there are nonmedical ways of treating freezing as well.

Stephanie Paul

Okay, we have another question from the Web. This comes from MaryAnn. If someone is taking Nuplazid® (pimavanserin) but still has hallucinations, is this a reaction to the meds?

Un J. Kang, MD

It wouldn't be a reaction to Nuplazid, but I guess you could call that as an effectiveness of the Nuplazid in this particular situation. But it's very difficult to say without knowing the details. Maybe the dose is not enough. Maybe you haven't tried long enough. But often one of the first things you could do when there's a hallucination is to reassess the whole medication status of can we reduce the parkinsonian dopaminergic medications? What are the mix of medications? Is that a combination of dopamine agonist, the synthetic dopamine as I talked about, and levodopa?

Then you may be able to make the medication adjustments to reduce the chance of having hallucinations. And also there are other medications that can be tried for hallucinations.

Stephanie Paul

Okay, the next question comes from the Web. This comes from Cindy. "What are your thoughts on taking CBD (cannabidiol) for tremor control?"

Un J. Kang, MD

So this is a very popular question nowadays about the CBD. So far, there's really no evidence that CBD treats any of the parkinsonian symptoms. It's actually interesting because it hits the receptors in the striatum that interacts with this whole dopamine circuitry. But there isn't any clinical evidence that any of them treats parkinsonian symptoms.

Stephanie Paul

Okay, another question from the Web comes from Shahriar. And the question is, "What are the impacts of PD on sexuality," and you mentioned hypersexuality.

Un J. Kang, MD

So let's go back to what we talked about as in these nonmotor symptoms. The PD itself, it may accompany autonomic dysfunction; and sexual function is part of the autonomic nervous system-mediated function. So you could have a problem with a sexual function because of the autonomic involvement of Parkinson's disease.

Now the opposite end I was talking about is often seen as a part of the impulse control disorder where you use, especially younger people using dopamine agonist, the synthetic medication. We think it may have to do with the particular type of dopamine receptors and other neurotransmitter receptors that it's acting on. And it can lead to excessive impulse control disorder, including hypersexuality. So it sort of, we're talking about, I guess, two different ends of the spectrum – one

due to autonomic involvement in Parkinson's disease, the other one due to this excessive response to dopamine agonist medication.

Stephanie Paul

Okay, we have another question from the Web. This comes from Barbara. "What actions are taken if meds do not work after DBS (deep brain stimulation)?"

Un J. Kang, MD

Yes, again, I think the reason I went through different aspects of what symptoms are improving, what symptoms are not improving with the medication, and DBS is a little difficult to answer questions in a very general way without knowing what symptoms are not responding. So this is a little difficult question without really talking to the patient and having detailed information.

Stephanie Paul

Okay, let's move onto the next question, coming from Michelle. "Why does Sinemet® make me sleepy in daytime but make me anxious at night?"

Un J. Kang, MD

Yes, that's a very interesting question. This sleepiness from Sinemet, carbidopa-levodopa, is not an uncommon side effect. And when that happens, I try to take measures that will blunt the high peak of blood levels that can occur after taking medications. So sometimes slow release or taking with a food can slow down that aspect of it.

Now it may also be Parkinson's patients have sleep problems, and so when they don't have a good night's sleep, in the daytime there's excessive daytime drowsiness and falling asleep. And on top of that problem, and adding the sedating effect of carbidopa-levodopa, can exacerbate the problem.

Now the anxiousness at night, I guess what I will have to know would be is this happening like as soon after the medication or is this happening when the medications are wearing off? As I discussed, these nonmotor symptoms can also fluctuate through the dose cycle, so people often get anxious, actually when the medication is wearing off, and it can be relieved by medication after let's say half an hour, an hour after the medicine. So I suspect that maybe the medication is not, this anxiety may be occurring during the off period of the medication at night.

Stephanie Paul

Okay, the next question comes from Jared; and Jared asks, "I am taking a multivitamin that contains iron. Is it true that iron can block the carbidopa-levodopa from reaching the brain?"

Un J. Kang, MD

No, I don't think there's any evidence that iron that you take will have any interference with the carbidopa-levodopa reaching the brain.

Stephanie Paul

Okay, here's a question from Angie. "My mom now has issues with orthostatic hypotension. Blood pressure drops when she sits up or stands and passes out for a few seconds. How can this be treated or can it?"

Un J. Kang, MD

Yes, this is one of the common problems in Parkinson's disease, contributes this autonomic problem that leads to orthostatic hypotension, blood pressure dropping when you stand up. Ordinarily, if you lie down or sit and then stand up, your heart needs to pump harder to work harder to get the blood into the brain. But there's a failure for the autonomic system to properly adjust to this, and the medications, Parkinson medications, both levodopa-carbidopa and dopamine agonists can make this problem even worse.

So there are many things that can be done symptomatically. First thing, we make sure is that the simplest is to, when you stand up, we always ask the patients to go slow. From lying, you sit for a while and maybe you half-sit and then stand up, instead of jumping out of the bed. And the other thing we make sure is that by taking the blood pressure and pulse at the same time, we make sure that there's enough fluid intake evidence for any kind of dehydration. So that's one common problem also is that not taking enough fluid.

And then we take some conservative measures such as using a compression stocking to make the blood go back to the heart from the leg, the venous pool in the leg, so that it doesn't pool there, but let it return to the heart faster. And then often when patients sleep at night, I advise them to elevate the head of the bed. You can get a little block, plastic block from hardware stores and put it under the bed post, just over the head, not in the legs, so the whole bed is a little tilted. So you get used to this, a little bit of an upright, the head high, leg low position even when you sleep, which can help to adjust to the orthostatic upright postures when you wake up. And then there are medications that can be used to either increase the blood volume or constrict the blood vessels so that your pressure can be maintained when you stand up.

Stephanie Paul

Okay, we have one final question, and that will come from a caller.

Operator

Our next call is from Donna of New Jersey. Donna, please state your question. Your line is now live.

Donna from New Jersey

Hi, doctor. If an elderly patient is being treated with Nuplazid and it's helping for hallucinations but increasing the tremors dramatically, where it's really affecting the quality of life, is there anything that can be done to help with the tremors?

Un J. Kang, MD

I guess did the tremors respond to carbidopa-levodopa?

Donna from New Jersey

In the beginning it did.

Un J. Kang, MD

In the beginning it did, yes. This is a very interesting phenomenon, yes. The tremor is a combination of a dopaminergic and perhaps nondopaminergic. Some people think maybe serotonergic which Nuplazid is. It kind of modulates the serotonergic system or maybe some other neurotransmitters, and sometimes anticholinergics will for the tremor.

So it looks like you're modulating neurotransmitters in a way that tremor is getting worse. So this will be, I think it'll be something that has to be tried in a trial and error basis one at a time. So I guess I'll have to know what the details of what other dopaminergic medication the patient's on, has the patient tried other medications for the tremor, and what was the dose of Nuplazid and so on. So it'll be a little bit hard to say in generality what should be done, but this will be something that really has to be worked out individually, depending on the details of the circumstances and medications.

Closing Remarks

Stephanie Paul

[Slide 27] Thank you so much, Dr. Kang, and my thanks to everyone for participating in today's telephone and Web education program. We 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 & Medical Affairs department, I encourage you to visit our website at www.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 you complete the program evaluation form.

[Slide 28] APDA is proud to support those living with Parkinson's disease by helping them live life to the fullest every day. We do this each year by providing more than 1,700 support groups that serve more than 75,000 people with Parkinson's disease and their family members and through running 770+ exercise groups attended by more than 21,000 participants.

These exercise programs help improve the symptoms of Parkinson's and lesson 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 Parkinson's.

And we rely on the support of the entire Parkinson's community to accomplish all of this. To join us in the fight against Parkinson's and to learn more about the support APDA provides across the country

through our network of chapters and information and referral centers, as well as our National Research Grant Program and Centers for Advanced Research, please visit us at apda.parkinson.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.