Spotlight on Addressing Motor and Non-Motor Symptoms

The Changing Landscape

Transcript

Welcome and Introductions

Stephanie Paul

[Slide 1 – Title Slide] Greetings everyone and thank you so much for joining us today. **[Slide 2 – Welcome and Introductions]** This is Stephanie Paul, and I am the Vice President of Development and Marketing at the American Parkinson Disease Association or APDA for short. I am so pleased to welcome the more than 1,300 people who registered for today's telephone and Web education program for people with Parkinson's disease, family members, and care partners. Healthcare providers will also benefit from this program.

I'd like to say a special thank you to Joan and Ross Collard for generously supporting this program. I would also like to thank AbbVie for funding this important program and to thank them for their continued appreciation for the 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 one million Americans with Parkinson's live life to the fullest 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 and ultimately put an end to this disease. To join us in this fight against Parkinson's and to learn more about the support APDA provides nationally through our network of chapters and information and referral centers, as well as our national research program and eight centers of advanced research, please visit us at apdaparkinson.org.

In 2016, APDA was proud to support those living with Parkinson's each day by providing more than 1,700 support groups that served 74,000 people with Parkinson's and their family members, running more than 770 exercise groups, attended by 21,000 plus participants. These exercise programs help improve symptoms of Parkinson's and lessen the impact of the disease. We also offered educational symposia across the country on living well with the disease. These programs were attended by more than 5,500 people impacted by Parkinson's. It’s programs like these that distinguish APDA as the one national organization working one on one with the Parkinson's community to make each day better.

[Slide 3 – Presentation] And now to our program. I am pleased to introduce our presenter today, Dr. David G. Standaert, who is the John N. Whitaker Professor and Chair of Neurology at the University of Alabama Birmingham School of Medicine in Birmingham, Alabama. Dr. Standaert is also the Chair of the APDA Scientific Advisory Board.

Today we are delighted to have him share an overview with us about how to address motor and non-motor symptoms of Parkinson's disease. After the presentation, we will open up the program for

questions from both telephone and Web participants. We sent an email reminder to everyone registered for the teleconference that includes a link to a program evaluation. We encourage everyone on the line to complete that 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. David Standaert.

Presentation

David G. Standaert, MD, PhD

Thank you, Stephanie, and good afternoon. My name is David Standaert, and I'm going to take the next few minutes to try and give you an update on some exciting advances in Parkinson's disease, changing therapies affecting both motor and non-motor symptoms. My goal here is to give you a view of what's new, what's exciting, what's coming down the road in Parkinson's disease, and then to leave some time at the end to try to answer some of your questions.

[Slide 4 – Disclosures] Before we begin just a few brief disclosures; I've spent much of my career developing new treatments for Parkinson's disease, and in the course of this, I do work with various companies. These are three companies that I served as a consultant for in the last year, and I just want you to be aware of that.

[Slide 5 – Parkinson's Disease: 200th Anniversary] So we are at the 200th anniversary of Parkinson's disease. Dr. James Parkinson's described this condition in 1817, and 200 years later his description is still a very sound and valid one. This picture on the lower left here is from the faceplate of his book. It's a very short book. It's about 40 pages long, and it was titled, "An Essay on the Shaking Palsy." And this was the original name for Parkinson's disease. It was actually renamed as Parkinson's disease some years later.

He described this here, if you can read this small print. It says, "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported, with a propensity to bend the trunk forward, and to pass from a walking to a running pace." A bit flowery, but still a very good description of the symptoms of Parkinson's disease that we recognize today.

Of course, Parkinson's has a human side, and these photos on the right are just some of the public figures who have really exemplified Parkinson's disease to the world and the community. Many of you will recognize the Pope, Davis Phinney, Linda Ronstadt, Michael J. Fox, Muhammad Ali, Robin Williams, and Mo Udall. But these are really representatives of the worldwide community of Parkinson's disease, which affects millions.

[Slide 6 –Age and Parkinson's Disease] One important thing to appreciate about Parkinson's disease is that the main risk factor for developing Parkinson's is getting older. The older you are, the greater the risk is. And this changes in a very dramatic way. So if you look at the graph on the right, this plots along the bottom, age, starting with below 29, and then 30 to 39, 40 to 49, 50 to 59, and so on. And then on the vertical access, it has incidence per 100,000, the number of people who will develop Parkinson's in a given year per 100,000 people of that age. And as you can see, if you're below the age of even 50, it's not very common. We do see patients who develop Parkinson's earlier than that; I have seen patients who were less than 20 years old who have developed Parkinson's. But that's quite rare. On the other hand, when you turn the corner and cross to the 60 to 69 or 70 to 79, Parkinson's becomes very frequent, about 3% of people over the age of 65 are affected by Parkinson's disease. So that's really a large number.

One of the major accomplishments, of course, in medicine is that we're all living longer. Most people who are alive today can expect to live to be at least 80, at least on average. That would be the expectation. But you can see if we all live to be 80, there's going to be a lot of Parkinson's disease among us; and this is really a challenge that we have to confront with better therapies and, ultimately, finding a cure for this condition.

[Slide 7 – Classical Features of Parkinson's Disease] Let me talk a little bit about the features of Parkinson's disease that we recognize and give you a little sense of how physicians and scientists think about this disease. So in terms of the symptoms of Parkinson's disease, we really think of four major symptoms of Parkinson's disease. One is tremor. It's a resting tremor, so it's a tremor when the limb is still, when it's not doing anything. Often this comes out when people are watching TV, reading a newspaper. An interesting thing about the tremor is most patients can make it stop if they think about it. So if they focus on the tremor, it goes away. But as soon as their mind is off on something else, the tremor returns. And this is the characteristic tremor of Parkinson's disease. There is bradykinesia, which is a fancy term for slowness, slowness of movements. There is rigidity, which is stiffness in the limbs. And the last symptom we look for is postural imbalance, which is being unstable on your feet, having a tendency towards falling.

And these four features are what we teach our medical students, and our neurologists in training, and our movement disorder specialists in training. This is what we teach them to look for when they're looking to make a diagnosis of Parkinson's disease.

Now there are some images here that show different aspects of this. The top right, the figures that look like little butterflies there, these are actually sections from a human brain. So these came from an autopsy. The one on the left is normal, and you can see it has these black areas in it. That's the substantia nigra, and you can actually see this. It doesn't take any special staining or methods. You can hold it in your hand and see these black cells, the area where these cells are, and the dopamine neurons have this black substance in them.

In someone who has died after Parkinson's disease, many of them are gone. You can see this on the right. In fact, more than 95% of those dopamine cells are gone. And this is the characteristic brain change of Parkinson's disease.

Below that is this pink figure, which shows some neurons. This shows two individual dopamine neurons at very high magnification under a microscope, and one of them has that round ball in it. That ball is a Lewy body. That kind of ball is abnormal. You shouldn't see that in the brain, and it's one of the things that lead us to diagnose Parkinson's disease.

And the bottom four figures are a newer test where we can actually scan the brain and look at dopamine function in someone who's alive. This is often done with something called DaTscan (dopamine transporter scan). These figures are actually a somewhat different technique, but the result is the same, that you can see the dopamine function. And this is one of my patients who was scanned every year for four years, and you can see the dopamine function fading away. So this is a way that we can study that in living patients and very valuable in many situations.

[Slide 8 – Parkinson's Disease: Non-motor Features] So this is how we've taught Parkinson's disease for many years. But one of the big developments is that we've realized that Parkinson's disease is much more than just slowness, stiffness, and shakiness. There are a whole set of features that are now called non-motor features. These include a group of early features. Among these I would list hyposmia, the loss of the sense of smell. Many Parkinson's patients lose the ability to smell. Most are unaware of this, but if you actually test them with a scratch and sniff test or something like this, you'll find that more than three-quarters of patients with Parkinson's disease aren't able to distinguish smells normally. And, in fact, if we go out in the population and look for people with a loss of sense of smell, that turns out to be a predictor of later Parkinson's. Now there are many causes for loss of smell, and most people, loss of smell, will not get Parkinson's. But if you turn it around, most people that have Parkinson's have loss of sense of smell. So this is one feature.

Another is the so-called REM behavior disorder. This is acting out your dreams at night. People who in their sleep will thrash around, sleepwalk, maybe cry out in their sleep, this release of normal dream behavior into physical movements is called REM behavior disorder; and it turns out to be another symptom that predicts later development of Parkinson's disease.

Lastly, autonomic function, the autonomic part of your brain is what controls your blood pressure, your GI system, so symptoms like low blood pressure, also constipation can emerge many years before the Parkinson's becomes apparent.

Then late in the game there are some features that emerge that are non-motor that are a part of the later part of the condition. These are things like excessive sleepiness, depression and anxiety, and in a good fraction of patients, ultimately, dementia.

To go with this idea that there are non-motor features, we've learned a lot more about the changes of Parkinson's in the brain; and that's what this little diagram at the top is. This is the so-called Braak

hypothesis, and really this comes out of study of many postmortem brains and tries to make the point that the changes in the brain begin in the brainstem and maybe the olfactory bulb, the figure on the left. The mid-stage of the disease is where the dopamine neurons are affected, and we see the tremor and the rest of this. And then later in the game you'll see changes in the rest of the brain, in the cortex, and that corresponds with the changes in depression, anxiety, and even dementia. So it's a progressive process that begins before the tremor and slowness and proceeds beyond it. And that's really a sea change in the way we think about Parkinson's disease.

[Slide 9 – Advances in Motor Treatments] So what about advances? So we are going to talk about motor and non-motor treatments. Let me talk a little bit about advances in motor treatment, so these are things that treat tremor, slowness, stiffness, and these sorts of symptoms. And I want to give you a little bit of a sense of the current state of the art very briefly and then talk about new treatments for motor symptoms, what's on the horizon. And these come down into two big categories; one is better ways of delivering the drug levodopa, and the second is deep brain stimulation. Really, there's a next generation of deep brain stimulation on the way or already arriving.

[Slide 10 – Discovery of Levodopa] Levodopa is, of course, still the most effective drug available for the treatment of Parkinson disease. It was discovered really through this work by Arvid Carlsson. So the picture on the left is a famous picture from Dr. Carlsson's work in the 1950s. These are rabbits, and the rabbits on the top, which look sort of floppy and as if they're not moving very much, were treated with a drug which depleted their dopamine. And then in the bottom figure, they were given levodopa. And as you can see, they look a lot better on the levodopa than they did before. The levodopa really restores their energy, just as levodopa can restore function in human Parkinson's disease. And this is one of the key experiments done now more than 60 years ago that really clued us into the importance of dopamine and levodopa.

It took a number of years after that to turn this into a true practical human therapy. The person who did that was Dr. George Cotzias, who's pictured on the right. He was a physician who went from these kind of rabbit experiments to figuring out how to dose this, how to treat patients with Parkinson's disease. And as you can see, this was published in the *New England Journal of Medicine* in 1967, describing the use of levodopa as a treatment for Parkinson's. And that's really where all our modern therapy begins.

[Slide 11 – Standard Dopaminergic Treatments for PD] So what are our standard treatments for Parkinson's disease? I don't want to spend too much time on this. These are treatments that have been around for quite a long time; but levodopa-carbidopa remains the cornerstone of it. We use so-called dopamine agonist drugs. These include pramipexole, ropinirole, and rotigotine. There's apomorphine which is an injectable dopamine drug. Then there are other drugs that modify dopamine indirectly. These are enzyme inhibitors like rasagiline, entacapone, and all of these are used in different combinations in Parkinson's disease. They all have a role and each patient, you have to think carefully about the approach; and maybe we can answer some questions about that towards the end. But these are all standard dopaminergic treatments for Parkinson's.

[Slide 12 – Motor Complications of Levodopa] So what's the problem with it? Why aren't those the answer? Why isn't that sufficient? I know we have six or eight treatments; why isn't it enough? And I think this slide really captures the main reason that those are not enough. This is something that was drawn by one of my patients. I didn't ask him to do it; he just brought this in one day. And what he's done here is he's described his day. As you can see, it says 7 AM over on the left, and it says 1 AM over on the right, and this is his day. And he's got “On” at the top and “Off” down below, and he's got a line that looks like a rollercoaster where he starts off in the middle, he takes some medications, he goes up. He's on. Then they wear off, and they go down, and he's off. Then he goes back up again, and he really rides this rollercoaster during the course of the day. And I'm sure there are some people out there, on the phone or on the computer, who experience this themselves or have certainly seen other people experience this. This is called motor complications of levodopa. It's the erratic pattern of response you get to medications like levodopa. Typically, this appears about five years after the beginning of levodopa therapy, although people are different. I have people who are 10 or 15 years in and don't have this. Some people a couple of years in do have this, but this is one of the major problems with levodopa. It's the reason that we don't simply use levodopa in every case and every circumstance is because you run into these kinds of so-called motor complications.

[Slide 13 – Duopa®: Carbidopa/Levodopa Gel] So what are some new strategies to try and deal with some of these problems? Well, the first one to mention is a treatment which is already FDA (Food and Drug Administration) approved. This is something called Duopa (levodopa- carbidopa intestinal gel). What this is really an innovation in the way that levodopa is delivered into the body. So if the problem is that it's up and down and irregular when you take pills, this system bypasses that. You put a tube in the stomach, as you can see in the diagram. You thread a long, thin extension out into the jejunum. This is the part of the intestine where the levodopa gets absorbed, and you have a pump that you carry with you on a belt or in a pack or they actually have some vests, different kinds of apparel to carry this in now. And this delivers the levodopa-carbidopa in a continuous manner and has been very helpful for people who have wearing off, variable response, and really can't be managed by standard pills and other oral medications.

So this is an FDA-approved treatment and is available in most places in the US. It's been widely used in Europe for many years, even before approval in the US. So this is certainly something for someone who has developed motor complications of levodopa to consider.

[Slide 14 – Rytary®] Another strategy is controlled-release carbidopa-levodopa, and the newest brand or form of this is a drug that's called Rytary (extended-release levodopa). This is a capsule which, if any of you remember the old TV commercials about tiny time pills, essentially, that's what this has. It has a set of tiny time beads in the capsule that release levodopa at different rates, and this is another FDA-approved treatment for wearing off for irregular response to carbidopa-levodopa and can reduce wearing off in advanced Parkinson's disease. So that's two strategies that are already FDA approved and are available.

Now the next two I'm going to talk about are still experimental, but they've moved far enough down the road that I think it's worth knowing about them and being aware of what's in the pipeline and what's coming soon in terms of levodopa delivery.

[Slide 15 – Inhaled Levodopa CVT-301] The first would be inhaled levodopa. So this goes by the name right now of CVT-301. I'm sure if it gets approval, it will get a better name than that. But this is an experimental treatment, which is for off periods in people with Parkinson's disease. So people who experience sudden wearing off could have this little inhaler with them and inhale levodopa powder into the lungs. This turns out to work very quickly. It turns people on very rapidly; and as you can see here, this is still experimental. Most of the information on this is not from published medical literature, but it's from press releases. But the company that's working on this has announced that their Phase III study did show an improvement in off periods. The main side effect they saw was cough, and they are planning to file an application with the FDA later this year. And I think many of us are interested to see how this goes. If this does get approved, it certainly might be a useful treatment for those people who find wearing off in the day, unpredictable wearing off in stores and in places where they get stuck; this could be really a valuable step forward. So we're waiting to see how this turns out.

[Slide 16 – Subcutaneous Levodopa Infusion] The next one I wanted to mention is another experimental treatment, but it's a variation on the idea of giving levodopa continuously. This is another pump but a different kind of pump. So the Duopa pump pumps directly into the stomach and does require a tube in the stomach. This is a new formulation which pumps only into the skin, so it's more like if you have seen insulin pumps or other treatment like this which uses a small needle just under the surface of the skin. And there are two little circles here. The top one shows a pump which might be worn on a belt. It has two little infusion devices going into the skin of the abdomen there. The lower one is another at least potential way of doing this where they've miniaturized the pump and the needle, and it's just really a patch you can apply.

But it's carbidopa-levodopa. It's a continuous infusion, and this has also had a very successful trial recently as well. In this trial, they started with people who had about 5.5 hours of off time at baseline, and that certainly is something I would consider who has a major problem with wearing off. If you have five hours a day when you're medicines aren't working, that's a significant problem. And they reduce that by about 2.8 hours with this therapy, which is pretty impressive. It's actually comparable to what you would see with Duopa. And about 42% of the patients in this study had a complete reduction in off time.

So, again, a very intriguing kind of study, it's still experimental, not FDA approved yet. But with this kind of information, we all expect that they will go to the FDA to seek approval fairly soon. And this may become available to us in the near future.

So I think the overall theme here is that levodopa is still our most powerful drug. Its problems have been related to the irregular response that you get, the wearing off, and the dyskinesia. And so a lot of different companies and investigators are thinking about ways to smooth this out. How do we level this out? You can do it through Duopa, you can use things like Rytary, you can think about inhaled

strategies, you can think about subcutaneous strategies. And there are several other variations on this theme working their way through the discovery pipeline, and I think you'll see these becoming available to patients, probably in the next year or so.

[Slide 17 – Deep Brain Stimulation] All right, let's talk a little bit about deep brain stimulation (DBS). So this is a technology that is now nearly 20 years old. It is a technique where you place an electrode in the brain; and as you can see in the picture here on the left, there's a pacemaker-like device in the chest, an electrode in the brain, and you treat the symptoms of Parkinson's with electricity, really a remarkable idea. Two of the main physicians involved in discovering this, Dr. Mahlon DeLong is pictured there together with Louis Benabid. Many people are involved, but these two really had a central role in discovering how effective this is in Parkinson's disease. They were awarded the Lasker Foundation Award in 2014, which is a very prestigious medical award for discovery of important new findings and new techniques in medical treatment. So, a very valuable technique.

And DBS has been used very widely, it's FDA approved. Many centers do practice this, but the technique has not changed very much. So in the 20 years that we've been doing this, really we're doing it exactly the same way that we were doing it when we first started—the devices, the wires, the approach really hasn't changed very much.

[Slide 18 – Next Generation DBS] And one thing I wanted to talk a little bit about today is that we're coming to a next generation of DBS, and there are two aspects to this next generation that will move us forward into the future. One is that there are new device technologies, and the other is there are better ways to program the DBS devices.

[Slide 19 – St. Jude DBS Device] So in the new device category, there is a new device that was approved for deep brain stimulation. This is manufactured by a company called St. Jude. It was approved in October of 2016. In some ways this has similarity to the current device, which is made by Medtronic; but there are some significant changes in this. One is over on the left. You can see there's a device that looks almost like a pocket watch or something there, which is the device that gets implanted in the chest. There is an electrode that goes into the brain. But to program this, it actually has Bluetooth, and it can be programmed with an iPhone or an iPad or a similar device; so it really opens up the ability to program this device in a much more sophisticated way than the current devices. It also means patients can be empowered to monitor their device, to see what it's doing, and with the approval of their physician, to even make some adjustments in the way that their device is set using an iPhone or an iPad or other similar device at home. So that's really a kind of revolutionary idea to open up the access and open up the ability to really think about these devices and program them. So that's one major advance.

The other is the electrodes that go in the brain are getting much more sophisticated, and there's some diagrammed over here on the right. The conventional one, the one that has been used for 20 years, is an electrode that has four different contacts in the brain. So the surgeon places this in the brain, and then when you come to the office to have it programmed, the physician or the nurse practitioner is

working with those four different contacts and adjusting different settings to try and find the best setting for that person.

But four contacts are not very much. The brain is much more complicated than that, so these newer devices have more and more contacts. You can see on the extreme right there, there's the one that looks like a honeycomb. Actually, you can get up to where you have 64 different contacts on that one electrode in the brain; and each one of those contacts can be set to different voltages and different currents, so you can really shape the area of the brain that's activated and change the way that you're influencing brain behavior in a much more sophisticated way.

This is a really, I think, major step forward. We're going from, kind of, a four-channel system here. It's like going from black and white television to high-definition color. It's really going to be transformational in the sense of what we can do with these DBS devices, how we can program them, and what kind of effects we can achieve by using this neuromodulation technique. So new devices, a big step forward. The St. Jude is the only new one approved, but there are several others in the pipeline; and I think within the next year you'll see some additional companies receiving FDA approval for their devices, and it will really become a competitive marketplace that will really benefit patients by driving innovation and driving change in a very positive way. So I'm enthusiastic about that.

Another aspect of this is the programming of these. So as you may know, if you've had DBS or been to see how it's programmed, it's done in the office. It's a lot of trial and error. We work through testing the different contacts, testing the different voltages, seeing what effect they have. Sometimes these days we'll set the stimulator up with two different settings. We'll call it A and B, and then we'll let people go home with a device that lets them switch between A and B; and they can come back and tell us, well, did you like A better or did you like B?

[Slide 20 – BRAIN Initiative DBS Projects: $20M in New Research Funding] But it's still, very much, a trial and error kind of process. There must be a smarter way to program this; and, in fact, there's some very important projects which have just been launched looking at the question of is there a smarter way to program and manage these devices. Much of this is being funded by something called the Brain Initiative. This is a federal government undertaking. It's through the National Institutes of Health, and, overall, it's a very large effort to understand the brain and to learn better ways of treating brain diseases.

Three new projects have just been launched through this Brain Initiative. They're listed here. One of them is at the University of Florida, another is here at UAB (University of Alabama Birmingham), and the third is at UCSF (University of California, San Francisco). All three of these are looking at smarter and better ways of programming the DBS device and managing the DBS device. And between these three, this is about $20 million in new research funding that is going towards this specific question of what is the best way to manage a DBS device, how can we best make this work, how can we make the device as sophisticated, perhaps not as sophisticated as the brain, but really making a smarter device to go with a smarter brain?

This is really, I think, in my mind a really critical step. We've been stimulating the brain in a fairly simple-minded way for a long time. We really need to start getting smarter about it. Things like closed-loop stimulation, which is what this first grant is about. If someone has a tremor, could we measure the tremor and tell the device about the tremor and use that to control the stimulator so there's really a feedback?

Work here with Dr. Walker is looking at biomarkers, meaning recording from the brain and trying to figure out smarter ways to program the device and to be more accurate in that. So these are really, I think, the key. A new device but you need smarter programming, a better way to use these, and so this kind of research funding's really critical to that.

[Slide 21 – New Treatments- Non-motor Therapies] All right, so let's talk a little bit about non-motor therapies. So non-motor therapies are not the movement; but they're the other symptoms. There are two recently approved therapies here that I would say fit into this category quite well. These are droxidopa and pimvanserin, which are two new treatments for non-motor symptoms.

[Slide 22 – Northera® (droxidopa)] Let's talk about these just a little bit. So droxidopa, which goes by the trade name Northera, is approved for the treatment of orthostatic hypotension in Parkinson's. So this is light-headedness, dizziness, low blood pressure, very common in Parkinson's disease. It can arise from several things. One, often patients with Parkinson's don't drink enough fluids. That's certainly something we try to encourage. You can see it as a consequence of some of the medicines like levodopa tends to lower blood pressure.

But it turns out that the disease itself is attacking the part of the nervous system that controls blood pressure. So the degeneration, although we focus on dopamine so much, affects other parts of the nervous system. And one of the parts that it attacks is a part involved in regulating blood pressure.

So the bottom line is patients with Parkinson's often develop low blood pressure, particularly when they stand up, particularly in hot weather. We go through a number of steps in working with that, encouraging people to drink fluids, encouraging people not to spend too much time out in the sun if they're prone to these kinds of problems. There are other medications that are used, compressive stockings. But Northera is a new tool in that arsenal to treat low blood pressure. So that's certainly an option for people who have that problem.

[Slide 23 – Nuplazid® (pimvanserin)] Another is pimvanserin, which goes by the trade name of Nuplazid, and this is an antipsychotic, so it's really a treatment for hallucinations. It works in a different way than most other antipsychotics. Many of the antipsychotics that doctors have used for years are drugs like haloperidol, and these are really a problem because they block dopamine. If you block dopamine, you might reduce hallucinations; but you'll make Parkinson's much worse because Parkinson's is already a dopamine deficiency state. So we can't use many of the drugs that are often used in other medical settings for hallucinations in Parkinson's. So this really opens up a new area, a new approach to treating hallucinations in Parkinson's disease.

The hallucinations can be very troubling in Parkinson's. Often they start in a fairly mild way, simply seeing small furry animals, things like this, shadows, people in the room that aren't really there. But they can become very destressing. People can get very upset about these. They can get very concerned, and sometimes they act on them. Patients will run away from hallucinations and may really injure themselves doing this. So it can be quite a disruptive symptom and something that we haven't had great treatments for in the past. So this is certainly a step forward to have a new treatment for this particular symptom.

[Slide 24 – What is coming soon? Some Highlights From Clinicaltrials.gov] Let's talk a little bit about what's coming soon in terms of motor and non-motor therapies. So we talked about several new ways to deliver dopamine. There are more of these in the pipeline. There's the so-called "accordion pill" levodopa, which is a pill that unfolds and produces slow release in the stomach. Apomorphine, which is a drug which has been around for years. Currently, it's available in the US as an injection for treatment of freezing, short-term wearing off; but there are other formulations of this coming—infusions, nasal sprays and strips of various kinds. So I think that will be interesting to see how that develops.

There are some other ways to treat wearing off and dyskinesia. These include amantadine, which is an old standby drug many of us use. But taking that to a more controlled release form may be valuable. There are also drugs that work on the so-called A2a receptor that are under development for treatment of dyskinesia.

And the last thing I feel I really have to mention is exercise. In a way, exercise is not experimental. I think nearly all of us who work in this field think that exercise is beneficial for nearly all Parkinson's patients. I recommend it strongly, and I really tell my patients that the medications are half the treatment, and the exercise is the other half. It's really critical to well-being and success in Parkinson's disease.

But that brings you to the question of what's the right exercise? What's the prescription for exercise? What would be best for Parkinson's patients? We, honestly, don't know that. We know that lots of things are useful and popular. They range from simple physical therapy, if that's appropriate. Boxing is very popular these days, dancing has been studied, Tai Chi, a variety of other exercise forms. I think all of them are better than no exercise; but we don't really know the answer to what is the best exercise, what's the most effective way to do this in Parkinson's? And there is good research going on into this question, and I hope we'll have better answers to that soon.

[Slide 25 – Neuroprotective Therapies] All right, so let me come to the last question here because we talk about motor therapies and non-motor therapies; but I think most of us in the field really would like to have a therapy that changes the disease rather than just treating the symptoms. And what's the state of that and where is that going?

So this is really in the category of neuroprotective therapies, and this little diagram is supposed to show normal aging, which shows some decline in function over age. But in Parkinson's disease,

something happens. You turn the corner, function declines much more rapidly, and you cross into this purple zone of neurodegeneration where you have symptoms of Parkinson's.

If we could slow that down or interrupt that or delay that, as in this red line here labeled neuroprotection, you could either delay the onset of the disease, or I think if we delayed it to beyond 100 years, most people would be pretty satisfied with that result. And, in fact, most patients I speak to with Parkinson's tell me they can live with the symptoms they have today, but their concerns are about the future. How can we prevent Parkinson's from getting worse, even if we can't turn the clock back? Many people would be very grateful if we could just slow down the progress of it, and that's really where this kind of work is going.

[Slide 26 – Alpha-synuclein, a Gene for PD] So let me talk a little bit about some of the things that are in the pipeline here. Many of them are based on this particular protein called alpha-synuclein. This was discovered as a gene for Parkinson's disease. There's a little pedigree on the left here of a family from Southern Italy and Greece that was the basis for discovery. And what was found was a protein that turns out to make up the Lewy body. So the Lewy body, which had been described 100 years ago, before we knew what was in it, is made of synuclein. So this is a protein that clumps, aggregates, forms these abnormal structures in the brain, and is part of the process of damaging the brain and the dopaminergic system. So synuclein, too much of this clearly causes Parkinson's. Abnormal synucleins clearly cause Parkinson's. So much of the work now is thinking about, well, how do we get the synuclein out of the brain? How do we reduce this, and how do we prevent that?

[Slide 27 – Anti-Synuclein Therapies] So anti-synuclein therapies, can we cut back on the amount of alpha-synuclein in the brain? Would this slow the disease if we did it? And if it did, would it prevent motor and non-motor symptoms?

Another important question we'll come to is when would we use the therapy if we had it? Would you do it early in the disease? Would you do it later? Obviously, you want to do it as early as you can; but that's going to be an important question as we move forward.

[Slide 28 – Anti-synuclein: Immunotherapies] Let me just tell you a little bit about the state of discovery here. So probably the most immediate things you will see in terms of clinical research are immunotherapies. So these are antibodies or, in one case, a vaccine to synuclein that are administered. And the idea is to reduce it from the brain and the blood, really removing synuclein from the body and asking whether that will improve the condition in Parkinson's disease.

There have been a number of trials. There are two listed here which are from clinicaltrials.gov, sort of the authoritative source of active trials. One is an antibody study. The other is actually a vaccine against synuclein, both with similar approach though. And these two were early stage trials. They're now both going on into later stage trials. At this point, all we really know about these trials is that they seem to be safe; nothing really drastic in the way of side effects has been reported. Whether they are going to be effective or not is, I think, entirely unknown at this point. But certainly I think it's a very promising strategy, and I'm encouraged that they seem to be safe at this early stage. And so there

are studies going on around the country, and if you have an opportunity to participate and be one of the people to move this forward, I'd encourage you to give that consideration because it's this kind of study that's going to lead us to the next therapy for Parkinson's.

[Slide 29 – Anti-Synuclein Therapies: The Next Wave] All right, beyond immunotherapies, what else is there? There are a lot of other ways that people are thinking about reducing synuclein in the brain. There are things called antisense oligonucleotides. These block the production of synuclein. There are things that might enhance the clearance, that turn on the sort of trash removal systems in the brain, the autophagy system which clears out abnormal proteins. Nilotinib, which has been in the news quite a bit, is in this category. Still only some very limited data available on that, but it's an interesting idea. And there are others that work in a similar way that are being studied. Perhaps there are ways of reducing the aggregation of synuclein. Could we keep it from clumping up? There are antibody studies and small molecules being studied that might do that.

[Slide 30 – PD and Inflammation: Turning Down the Heat] The last point I wanted to make about neuroprotection is about inflammation. So, in addition to this idea that synuclein is aggregating the brain building up; one of the consequences of that is that it activates the immune system so that immune cells and antibodies attack dopaminergic neurons as a result of these abnormal forms of synuclein. And so there's a lot of interest now in asking whether that is a target for slowing down the progress of Parkinson's disease.

So I just wanted to give you a little bit of a sense of the excitement of the field, I think. Certainly there are some major steps being made in therapy, but there's also very important work going on towards neuroprotection and, ultimately, slowing the course or preventing this disease.

[Slide 31 – Summary] So just to try to summarize some of this, I would say we have some very important new treatments for both motor and non-motor symptoms that are already approved and that are available today. Some of these are based on new and better ways to deliver levodopa. There is a next generation of DBS, which is already here with new devices and new thoughts about how to program these devices. There are new treatments for blood pressure symptoms and hallucinations which are already approved. Very soon we're going to see other additional, better treatments for Parkinson's. There are going to be more effective ways to deliver dopaminergic drugs, and I think there are a number of different treatments we didn't touch on today for various non-motor symptoms for cognition, for blood pressure, for constipation, for some of these other aspects that are really troubling.

But I think in the end the cutting edge of research is the search for neuroprotection. The things which are really on the front burner today are these anti-synuclein strategies, and I think we'll see some very important tests of these coming in the next year or so. Anti-inflammatory approaches also are not far behind. So I think it's really an exciting time where we're starting to talk about this and starting to see actual human studies of things which are seeking to slow the progress of the disease.

So with that, I will conclude, and we can probably arrange to take some of your questions here.

Question & Answer

Stephanie Paul

[Slide 32 – Question & Answer] Thank you, so much, Dr. Standaert. This is really terrific information. And as Dr. Standaert said, we are now going to go to the Question & Answer session.

Stephanie Paul

We will take our first questions from the Web audience. So, Dr. Standaert, you talked a lot about many different treatments. We have a question from Michael in California, and his question is, "Is the newer time-released form of Sinemet® (levodopa-carbidopa) clinically superior to the conventional formulation?"

David G. Standaert, MD, PhD

Well that's a really good question, and so the question is about the newer forms of Sinemet and the controlled-release forms. The new forms are really intended to treat situations where the conventional forms are not working well. So for many people, certainly when they start on carbidopa-levodopa, they do just fine for a number of years on what's the so-called Sinemet, the yellow pills that we're all familiar with. And I don't see any reason to use the newer forms as an initial therapy in Parkinson's. What they're really intended for is when you reach the phase where the regular forms are wearing off too quickly and you need to find a way to sustain the effectiveness of that; that is where they've been shown to have a role. These controlled-release forms are, indeed, more effective when you've reached the point that you have wearing off with the conventional form.

Stephanie Paul

Thank you, Dr. Standaert. We do have several people on the telephone, so I would like to take the next question from the telephone audience please.

Operator

Thank you. Our first question comes from the line of Marianne from Florida. Please go ahead.

Marianne from Florida

Is there always a continual progression of mild cognitive deficiencies, such as executive functions to more serious and apparent deficiency? Non-motor question.

David G. Standaert, MD, PhD

Okay, so the question is about progression of cognitive dysfunction, and is there always a progression? The answer is no, there's not always a progression. Many people with Parkinson

disease have some degree of mild cognitive dysfunction, often difficulty with multitasking. That's a very common problem in Parkinson's disease. Sometimes just a little bit of hesitation getting words out. These are very mild kind of defects, and we can detect these by more sophisticated testing.

Not everyone who has those will go on to develop more serious problems. Some people do, but many, it just stays in that mild form for quite a long time. So the presence of very mild cognitive abnormalities in Parkinson's is extremely common, and it doesn't necessarily mean it's going to go on and be more serious.

Stephanie Paul

Okay, Dr. Standaert, we have several questions in relation to Duopa, so let me start with the first one that comes from Betty in New Jersey. And the question is, "I'm considering Duopa but nervous about the surgery to have the tube inserted. Is there anything I can do to improve my anesthesia recovery and not have my PD regress? This is happening to somebody in my support group."

David G. Standaert, MD, PhD

Right, so the question is about Duopa. So Duopa, the main risk with Duopa is, of course, you do have to have a tube put in the stomach. In most places, this is done as an outpatient procedure. It's an endoscopy, but it does require sedating medications. It's not usually full surgical anesthesia, but it is sedation; and there are risks to doing that procedure. And certainly you should talk with your doctors about the risk and benefit of doing that.

Is there anything to do to reduce the risk? I don't know that there's too much that you can do to change that. Obviously, speaking with the gastroenterologist and having a clear idea of what to expect is very important.

In the end, like any medical therapy, this comes down to risks and benefits. These procedures do have some risk. It's fairly low. On the other hand, Parkinson's has a lot of risks too; and a lot of my patients I talk to are trying to decide, but the truth is that without that therapy, they're having trouble, they're falling, and they're not doing well. And that has a risk in itself too, so I think this is something where you really need to talk with your doctor about the risk of not doing anything is often considerable as well. And these need to be weighed.

Stephanie Paul

Okay, another question about Duopa, Dr. Standaert. This comes from Andy in Colorado, and the question is, "Does avoiding taking Duopa around meals make it work better? What is the recommended time to wait before and after meals and any foods especially that should be avoided?"

David G. Standaert, MD, PhD

So if we're talking about Duopa, Duopa's a continuous therapy with a pump; and generally that's turned on in the morning and let run all day long and shut off in the evening. It's delivered right to the area where the Duopa's absorbed. So, generally, it's not much affected by food.

Now if we're talking about carbidopa-levodopa, just your standard pills, that is a little bit more complicated. So oftentimes people do take that after meals because they find they have less nausea. Most people don't have a big interaction with food, but some individuals find that protein in their diet can interfere with the standard oral carbidopa-levodopa tablets. And if that's the case, you probably need to talk to your doctor and may want to talk with a nutritionist about how to redistribute protein during the day. A good way to pick up on this is if you have eggs for breakfast or something like this and your pills don't work at all, it's possible you have an interaction between protein and the carbidopa-levodopa and something to explore with your doctor.

Stephanie Paul

Okay, great. So we would like to take another question from the telephone lines, please.

Operator

Our next question comes from the line of Steven from New York. Please go ahead.

Steven from New York

Well, I'm wondering if there's any research with the CBD (cannabidiol) component of the cannabis plant.

David G. Standaert, MD, PhD

Well that's a really interesting question. So he's asking about CBD, which is cannabidiol. It's one of the components that is found in cannabis or marijuana. It's a very interesting compound. There's a lot of work going on in various places. Actually, here at UAB, we have a large program looking at that in epilepsy.

In Parkinson's there's been very little research, I would say. It's actually quite hard for scientists to work with that compound. There are so many federal regulations that restrict the ability of scientists to use that, even to give it to a rat is quite a lot of difficulty and red tape and paperwork. So I think it's an area that needs more research, but at the moment I would have to say there's not that much in the way of scientific evidence one way or another as far as CBD and Parkinson's.

Stephanie Paul

Okay, we have another question related to Sinemet, and this comes from James. "Sinemet does not help with my speech dysphagia. Are there other remedies available now?"

David G. Standaert, MD, PhD

So speaking specifically about speech disorders and swallowing difficulties, Sinemet or carbidopa-levodopa can help some people. But, you're right, oftentimes is doesn't really make that big of a difference. The thing that's most effective with speech is actually speech therapy. There are different programs of this. There's one particular program called LSVT or Lee Silverman Voice Therapy that many people probably have heard of. Really, this is a vocal exercise approach; and it has been shown time and time again to be effective in Parkinson's. Swallowing dysfunction, often speech therapy is the most effective strategy there as well. So I certainly share your frustration that the medicines don't help that much, but I would certainly try to investigate the speech therapy approaches to this because they can be quite effective.

Stephanie Paul

Okay, thank you, Dr. Standaert. We have a question that moves over to DBS. This comes from Beverly in Illinois. The question is, “Is DBS possible for a patient who has epilepsy?”

David G. Standaert, MD, PhD

I think it's possible. That would be something that you would have to talk with your physician about. It's not an absolute contraindication. It would really depend on how well-controlled the epilepsy is and what kind of risks are involved.

Actually, interestingly, there are some devices very much like DBS that are used in epilepsy. There are some stimulators that are now being used specifically to suppress seizures in people with epilepsy. So I wouldn't say it rules it out, but it would take a discussion with a specialist in DBS to consider what is the nature of the epilepsy and what would the likely interaction of these two things be.

Stephanie Paul

Okay, and here's a question that is similar in terms of comorbidity. The question comes from Andy in New York, and the question is, "I'm dealing with a comorbidity of Crohn's disease. The diets for both diseases are very different. How can I accommodate?"

David G. Standaert, MD, PhD

Right, well that's a challenge. Crohn's disease is a difficult condition and can lead to problems. Now in Parkinson's, most people don't need a special diet in Parkinson's. The majority of people need just a

normal healthy diet with colorful fruits and vegetables and a reasonably well-balanced diet. The need to reduce protein is something that I find in only maybe 10% of patients or possibly less. It's talked about much more than actually seen.

In the end, you may, with that kind of combination, you may actually need to meet with a nutritionist and talk through some of these issues because it is a tricky balance; and I don't know that there's an answer I'm going to give you over the phone that's going to be completely satisfactory here.

Stephanie Paul

Okay, thank you. I think we still have more people on the phone, so I'd like to take another phone call please.

Operator

Our next question comes from the line of Gilbert from Arkansas. Please go ahead. Gilbert, your line is now live.

Gilbert from Arkansas

Yes, we had a question about the name of the drug that you said was an antipsychotic for hallucinations; and I didn't catch what you said.

David G. Standaert, MD, PhD

It's a drug called pimvanserin or Nuplazid is the trade name for that. Recently approved, approved last year for hallucinations in Parkinson's disease specifically.

Stephanie Paul

So let's take a question from Marie in Delaware, and her question is, "Is there such a thing as inner tremors where you feel tremors but they do not show outwardly?"

David G. Standaert, MD, PhD

Absolutely, I hear this all the time that people have an internal sense of tremor that is really quite disturbing, even though there's very little or nothing to see on the outside. So, absolutely, yes, you can have that in Parkinson's.

Stephanie Paul

So another question similar to that from Jeanette in California is, "What is the best way to treat tremors of the jaw, teeth, lips, and tongue?"

David G. Standaert, MD, PhD

Yes, tremor is a very difficult symptom because it doesn't necessarily respond all that well to the dopaminergic medications. Levodopa is a great drug, but what it does best is it works on the slowness, the stiffness, sometimes the balance problems. And oftentimes the tremors will persist. And I do tell my patients that sometimes we can't completely control the tremor, and we have to accept some tremor if all the other symptoms are well-controlled.

Now sometimes tremor is so troublesome that people simply can't live with it. The treatment, which is most effective against tremor, is DBS. Now whether DBS is appropriate for face and jaw tremor would depend on how severe it is. But DBS can be remarkably effective against tremor; and so when all other things are not working and the tremor is really the main problem or really troublesome, DBS is something to consider.

Stephanie Paul

Okay, I think we have another caller on the phone.

Operator

Our next question comes from the line of Caroline from Oregon. Please go ahead.

Caroline from Oregon

Yes. Prior to today, it was my understanding that dopamine was a chemical, and yet the statement was made that dopamine is actually a neuron. I was wondering if you could clarify that for me.

David G. Standaert, MD, PhD

No, no. I'm sorry if I misspoke there. So dopamine is a chemical. It's a small molecule. It's made by neurons that are called dopaminergic neurons because they have the enzymes and the capability to make dopamine.

Stephanie Paul

Okay, thank you, Dr. Standaert. I believe we have another caller on the phone.

Operator

Our next question comes from the line of Gail from Tennessee. Please go ahead.

Gail from Tennessee

Oh, thank you. Is it a good idea for somebody who already has DBS, if you wanted to have the new treatment? Can the old DBS be reversed?

David G. Standaert, MD, PhD

It's possible to remove a DBS device, but we try not to do that very much because, obviously, you can take the device out of the chest, the battery. If you actually want to take the wire out of the brain, there is some risk. It can trigger bleeding and other problems. So, generally, we try not to remove a DBS device unless it's infected or something else like this.

Now can you add other treatments in addition to DBS? Yes, you can do that. We've had some patients who had DBS years ago and now have problems with wearing off of medicines and have gone to using Duopa or a Duopa pump in addition to their DBS. So that is possible. You can do both. But removing a DBS can be problematic, and we try not to do that unless absolutely necessary.

Stephanie Paul

Okay, we have another caller on the phone please.

Operator

Our next question comes from the line of Judy from Wisconsin. Please go ahead.

Judy from Wisconsin

I'm taking furosemide and Eliquis® for atrial fibrillation, am I going to get in conflict with my medication for the Parkinson?

David G. Standaert, MD, PhD

No, generally not. Furosemide doesn't really interact with any of the other medicines. It is a water pill, and the biggest problem we see in Parkinson's is they make people dehydrated and dizzy and lightheaded, so you have to be a little careful how much fluid you remove with a furosemide. But it doesn't directly interact with any of the Parkinson's medications.

Closing Remarks

Stephanie Paul

[Slide 33 – Closing Remarks] Okay, I want to thank everyone for participating in today's telephone and Web education program. I do apologize that we weren't able to get to all of the wonderful questions. **[Slide 34 – Additional Information]** But if you have a question and would like to speak with someone in our Scientific and Medical Affairs Department, I encourage you to visit our website or call 1-800-223-2732 and you can ask your questions there.

I would like to thank Dr. Standaert for his presentation. 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 us or want to learn more, please visit our website at www.apdaparkinson.org. Our special thanks to Dr. Standaert 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.