Transcript

Welcome and Introductions

Stephanie Paul

[Slide 1] Greetings everyone, and thank you so much for joining us today. **[Slide 2]** This is Stephanie Paul, and I am the Vice President of Development & Marketing at the American Parkinson Disease Association or APDA for short.

I'm so pleased to welcome you to this 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 thank AbbVie for generously funding this important program and to thank them for their continued appreciation for the need to provide education programs like this one to people impacted by Parkinson's disease. I'd also like to thank the Parkinson Association of Alabama for their collaboration.

The APDA was founded in 1961 with the dual purpose to ease the burden, find the cure for Parkinson's disease. Since then APDA has raised and invested more than $87 million to fund research, patient services, and education and elevate public awareness. As the country's largest Parkinson's grassroots organization, APDA aims to ease the burden for the more than 1 million Americans with Parkinson's disease and their families through a nationwide network of chapters, information and referral centers, and support groups. APDA pursues its effort to find the cure by funding Centers for Advanced Research and awarding grants to fund the most promising research towards discovering the causes and finding the cure for Parkinson's disease.

We also provide a number of educational programs and resources to the entire community, both healthcare providers and persons with Parkinson's disease and care partners live, online, and in print. We invite you to visit our website at www.apdaparkinson.org to find the latest information on Parkinson's disease and its treatments as well as information on upcoming educational programs.

[Slide 3] Our presenter today is Dr. David G. Standaert from the University of Alabama Birmingham School of Medicine in Birmingham, Alabama. Dr. Standaert is also the chair of the APDA Scientific Advisory Board. Dr. Standaert will provide an overview of the current Parkinson's disease treatment options, newly released products, and a brief overview of potential promising therapies in the pipeline.

After the presentation, we will open the program up 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 G. Standaert.

Presentation

David G. Standaert, MD

Thank you, Stephanie, and good morning. Thank you for joining our program this morning. I'm really excited to have an opportunity to talk with you today about treatments for Parkinson's disease. As Stephanie said, I'm a physician and a scientist. I treat a lot of patients with Parkinson's; I have for more than 20 years, and my research laboratory has studied Parkinson's for many years. I've had the privilege of being the chair of the APDA Scientific Advisory Board for several years now and have been affiliated with this organization for a long time. And it has done a great deal of good for the field, and I'm really pleased to be part of the organization and to have the chance to speak to you today.

What I'm going to talk about is Parkinson's disease and really focus on treatment. The idea here is to bring you up to date a little bit on the kinds of treatment that we have today, to talk about treatments that might become available in the near future, and then to look further down the road and ask really what are the treatments of the future and where is the cure for Parkinson's disease coming from? So, I will try to take it in that kind of sequential way.

But before I talk about treatment, I want to talk a little bit about Parkinson's disease itself, to make sure everyone is beginning with the same kind of baseline of knowledge of the disease and our understanding of where treatment and research on treatment is moving in this field.

[Slide 4] So this slide shows, on the left, a panel from the face page of a book written by Dr. James Parkinson; and he published this in 1817. This is really the first description in the Western literature of what we call Parkinson’s disease now. This short book was published after he spent time in London. He saw a few patients in his office and observed others just sitting on a park bench in London, and he described it as the "shaking palsy." That was James Parkinson's name for what we now call Parkinson’s disease.

He had a nice description there. It's called the involuntary tremulous motion, 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. So flowery language, but still a good description and one that has held up for nearly 200 years.

Parkinson's touches many people, and the pictures on the right are just a small collection of the public figures who have been touched by Parkinson's disease over the years. But it affects millions, probably about a million and a half people in the United States are affected by Parkinson's right now. Many more worldwide. And with the aging of our population and the increase in the number of people who are over the age of 65 in the United States, we expect this to grow considerably. So Parkinson's will become more common in our society simply by the aging of the population. And if we don't find better treatments for it, we're going to have some serious problems down the road. So, there is an urgency to this question of finding better treatments for Parkinson's.

[Slide 5] So, let me talk a little bit about the features of Parkinson's disease and partly here just to give you some of the vocabulary that neurologists and neuroscientists use when they talk about Parkinson's disease.

So, we diagnose Parkinson's disease primarily based on its symptoms. There still really isn't a definitive test that one can do while someone's alive to diagnose Parkinson's, but we can be pretty accurate using these clinical features together with some of the newer technology related to scanning of the brain I'll talk about in a second.

So the four main features that we teach all of our young neurologists and medical students to look for when they try to diagnose Parkinson's disease are these four on the left. A resting tremor, this is kind of a rolling tremor, typically appears on one side of the body, usually when the hand is at rest. If you pay attention to it, you can often quiet it. You can make it go away for a while. But then when your mind is off on something else, it reappears. So often when I'm trying to get a history of this, I'll ask people, "Do you notice it when, for instance, you're watching TV or reading a newspaper, when your mind is focused elsewhere? Is that when the tremor comes out?" And that's what we really mean by a resting tremor, a tremor that emerges when the mind is on something else. The body part is tremoring on its own. And then if you really focus on it, you can often suppress it for a little while. Bradykinesia is a fancy word for slowness of movement. So there is slowness of movement in Parkinson's disease, one of the key features. Rigidity is stiffness, so that's a stiffness or a resistance to passive movement. And then postural imbalance is really a tendency towards falling. So these are the four things that we look for classically.

Now, does everyone with Parkinson's have all four of these? No. In fact, the tremor is the signature feature, but it's present in only about 70% of people; 30% of people will not have Tremor, so we look for a combination of these features in diagnosing Parkinson's disease. But these are really the classic core features.

The pictures on the right show some of the iconic kind of images that physicians and scientists think about when they think about Parkinson's disease. The top is two pieces of a human brain actually obtained at autopsy. The one on the left is normal, has a black stripe in it you can see; and on the right, that black stripe is gone. That's where the dopamine neurons were which make dopamine, and they are destroyed in Parkinson's disease. Nearly 95% of them are gone by the time you get to an autopsy like this.

There's one of those neurons, the pink figure below with a big round sphere in it. That sphere is the famous Lewy body, which is one of the signature features of Parkinson's, and we'll come back to that later. And at the bottom, these are some brain scans from one of my patients that were taken over a number of years; and they show the dopamine function of the brain. This is similar to what we currently do with a technique called DaTscan. This is an older technology, but it produces a very similar picture. And you can see as you go from left to right the dopamine function in this patient gradually faded out over time. So these are really the core classic features of Parkinson's disease.

[Slide 6] Now I want to bring to your attention that there's some new understanding of Parkinson's, and there are now recognition of what we call non-motor features. These have been there all along. In fact, James Parkinson himself discussed some of these non-motor features. But they really were not the focus of most physicians and doctors until just the last five or seven years. We've kind of woken up to this idea that there's more to Parkinson's than stiffness, slowness, tremor, and falling.

And I've broken these out into two groups. One is a group of things that you can see early in the disease. One is so-called hyposmia, loss of the sense of smell. This is something that may precede the Parkinson's itself by five or ten years, but many patients with Parkinson's lose the ability to smell. They can't smell their food. They can't smell the environment. And this turns out to be a part of the disease process.

There's something called REM (rapid eye movement) behavior disorder. This is a sleep disorder where you act out your dreams. People often get violent behaviors at night. They'll thrash around, fight dragons in their sleep. Sometimes the sleeping partner gets injured by this, and this turns out to be an early warning sign of Parkinson's as well. People who have this tendency to act out their dreams at night, many of them go on to develop Parkinson's disease; and it's an early part of the process.

The next one, the autonomic disturbances, low blood pressure. Another common feature, constipation. These are all early features of it.

Late features, things like excessive sleepiness, depression and anxiety, and also even dementia develops. So there's a whole world of features here that are part of the Parkinson process that are beyond just the tremor and slowness and stiffness that are classically considered part of the disease.

[Slide 7] All right, so let's talk a little bit about treatments for Parkinson's disease and what the nature of the treatments for Parkinson's disease are, what these might look like, and what the goal of treatment is. What are we trying to treat? And I think that certainly those of us who work in the field break this into two big categories. One are treatments for the symptoms. So, these are treatments that try to suppress the problems that you have. They try to suppress the tremor, they try to suppress the stiffness, they try to suppress the slowness.

And we're actually fortunate in this field that we have some treatments that can actually succeed at this. I would say most people who come to my office for the first time with Parkinson's disease, we can find a treatment that does help them to some extent. You may be familiar with some of these. Some examples are things like levodopa, which we'll talk about more; ropinirole; pramipexole; and others. So, in terms of treating the symptoms of the disease, we actually have some reasonable success. There's certainly room for improvement, some symptoms we don't treat very well, but we do have a reasonable record of success in symptomatic treatments.

[Slide 8] Where we would like to go is neuroprotective treatments. What does that mean? These would be treatments that slow or prevent the progression of Parkinson's disease. This is really the goal I would say of 90% of the research that's going on certainly in the academic laboratories is to try and slow the progress of the disease. And this comes out of our knowledge of Parkinson's. It is a very slow process. And, as I said, I talk to many people with Parkinson's, and many of them may be concerned with the symptoms they have today, but their real fears are about their future. They want to know what's going to happen to me down the road. Do we have a treatment which can prevent this from getting worse? And I have to say at the outset here, there is no therapy which is proven to slow the progress of Parkinson's disease today. There are a lot of things in the pipeline, there are things under study, but if you asked is there medical proof of any treatment actually slowly the progress of Parkinson's disease, we don't have that yet; and that's what we really need in this field.

The need is increasing. As I said, about 1.5 million Americans have Parkinson's right now. If we get out to 2050, which isn't as far away as it used to be, we may have 4 million people in this country and many more worldwide with Parkinson's, and we really need better therapies to slow this down.

[Slide 9] All right, so let's talk a little bit about symptomatic therapies, therapies for the symptoms of Parkinson's disease. And what you see on the screen here, we're going to talk about levodopa. This is really the primary therapy, the oldest really effective therapy, and probably still the most effective therapy for Parkinson's.

This picture is a picture of some rabbits, and these are very famous rabbits. These rabbits are rabbits that were studied by Dr. Arvid Carlsson in the 1950s, who's really the scientist who discovered dopamine, the transmitter in the brain, that is the key to Parkinson's disease. And so what he did is he treated the two rabbits you see on the top, that are lying sort of flat and motionless, with a drug that really removed all the dopamine from their brain. And once you did that, they were Parkinson rabbits. They were stiff, they were slow, they can't move. And then he gave them levodopa, and as you can see, they perked up quite a lot in that panel down below. And so this was the first demonstration that you could take away dopamine, and you would get an animal that was stiff and slow and can't move; and you could give the dopamine back in the form of levodopa, and it would have a magical effect like this where they returned to normal function.

So, this was really the beginning, this is work done in the 1950s that discovered the effects of dopamine and its role in producing Parkinson symptoms. **[Slide 10]** And then the later part, this gentleman on the right, this picture I just put up there, is a doctor named Dr. George Cotzias. He worked at Brookhaven National Lab and in 1969 published a paper in the *New England Journal of Medicine* showing that you could use this levodopa as a treatment for people with Parkinson's disease. So it took almost 20 years from the discovery of dopamine to actually turn this into a real treatment. But Dr. Cotzias is the one who set out and did the work, published this, and the APDA in recognition of this, one of our most important research awards is the Cotzias fellowship, which is named after George Cotzias, in honor of this really seminal discovery which has been so valuable to so many people.

So, this is the beginning of therapy in Parkinson's, and 1969 really marks the turning point. It was the first year that we had a treatment that was really effective against the symptoms of Parkinson's, and that was levodopa.

[Slide 11] So, where have we come since then? We have a lot of other treatments that are based around the same idea. The idea is that Parkinson's disease is causing a loss of dopamine function in the brain. Those cells in the substantia nigra are degenerating. Their job is to make dopamine. The brain is not making enough dopamine any longer, and that by replacing that dopamine, you can improve people's symptoms. So the form that we use now, the levodopa is combined with a drug called carbidopa. So many of you have seen this as levodopa-carbidopa, sometimes carbidopa-levodopa. It goes by the brand name Sinemet®, and this is very much the mainstay of treatment in Parkinson's disease; and it works by getting into the brain and being converted into dopamine, replacing that missing neurotransmitter.

There's some others listed here that work in a similar kind of way. Pramipexole (Mirapex®), ropinirole (Requip®), rotigotine (Neupro®) – these are drugs that Parkinson's specialists call dopamine agonists. Agonist means they activate the dopamine receptor. So they're not dopamine themselves, but they look like dopamine. The brain thinks they're dopamine and responds as if they were dopamine. And so these are other strategies for increasing the dopamine signaling in the brain which is what's so critical.

This drug called apomorphine you may know as Apokyn®, which is another drug that activates dopamine receptors. This one currently is available as an injectable drug only. And then there's some others that work on the dopamine system indirectly, rasagiline, goes by the name of Azilect®; entacapone, goes by Comtan®. It's also in Stalevo® (carbidopa-levodopa-entacapone).

So, this is a list of different ways to augment the dopamine production or dopamine signaling in the brain. And I would say most patients with Parkinson's wind up on one or more of these drugs during the course of their disease. Many people do get benefit out of these, but like all drugs, they have side effects. They have different side effects, but there are none that don't have any side effects. And so often we do get benefit from these, but many times we find ourselves in the tradeoff here between getting a benefit, improving the symptoms of Parkinson's, and trying to cope with the side effects that these dopamine drugs produce.

So, certainly very beneficial. Many, many patients have gained greatly by being on them, but they're not the cure for Parkinson's. They bring with them other side effects, and they don't really change the underlying nature of the disease. The change in the brain, the degeneration of the substantia nigra goes on, whether you take these drugs or not.

It doesn't seem to effect the degeneration. People have tried to look at this and asked, "Well, does the levodopa-carbidopa make it slower, faster? I think the bottom line is there's no convincing evidence that it changes the rate. The condition seems to progress pretty much the same, whether you're on these drugs or not. Your symptoms are better, but the disease is carrying on.

[Slide 12] So, that's really a thumbnail sketch of the current state of drug therapy for Parkinson's. Another current therapy I wanted to mention before we start talking about new treatments for Parkinson's disease is deep brain stimulation (DBS). So this is a completely different approach to treating Parkinson's disease. This came out of work done here by these two physicians, primarily Dr. Mahlon DeLong and Dr. Benabid in France. They were recently awarded the Lasker Foundation Award last year, which is a very prestigious scientific award for their discovery and work to make deep brain stimulation possible.

And what deep brain stimulation does is it tries to normalize the circuitry abnormality in the brain, so the lack of dopamine leads to an imbalance in the circuits. You can try and fix that by putting dopamine back. But another way to do that is to go directly into the brain, put an electrode in the brain in the critical spot in the circuit, and then activate that with an electrical current. So, as you can see in the picture on the left here, there is a device that's very much like a pacemaker and then a wire that runs under the skin. All of this is internal. It goes up into the head, through a hole drilled in the skull, and down into the critical nucleus or one of the critical nuclei involved in Parkinson's and delivers a continuous stimulation there.

And this can have a very dramatic effect on Parkinson's disease. Can really help all the symptoms. It's often particularly good with tremor. Now, of course, not everyone needs deep brain stimulation; and we can have some discussion later of when this is most helpful. I think what we and others have found is that in patients who are experiencing some benefit from levodopa on the conventional drugs, but finding that the timing is too complicated, the drugs are wearing off at too short intervals, those are people who get really a big boost out of deep brain stimulation because of its continuous nature.

Unfortunately, people who find that the drugs don't do anything for them often don't get anything out of the DBS either, and that's a frustration to many of us. A lot of research going on and better ways of doing DBS, new kinds of devices. But this particular device and approach is the one that's widely used now, it's FDA (Food and Drug Administration) approved, and this is the standard therapy. It's not a research technique. This is something that's been approved by the FDA for quite a few years now.

So, drug treatment for Parkinson's disease, deep brain stimulation, these are approved and accepted kinds of therapies. **[Slide 13]** What's new, what's coming? And so, we're going to start first with the things that were approved within the last year. So, really, we have three new kinds of medications that were approved in the last year by the FDA for Parkinson's disease. So, these are all now currently available. We're going to talk a little bit about Duopa™, which is the levodopa-carbidopa intestinal gel, the gel pump. We'll talk a little bit about Rytary™, which is an extended release form of levodopa, and then I'll mention also Northera™ (droxidopa), which is not for the motor aspects. It's really for blood pressure problems in Parkinson's.

And we'll touch on these briefly. We can come back later if there are questions. But Duopa is something that was developed over a period of more than 15 years. This is a way of delivering carbidopa-levodopa. So the drug involved here is exactly the same drug that's in Sinemet, that's in the carbidopa-levodopa pills that you may be familiar with, but it's a different way of giving it. And, really, this treatment is intended for people who've been on levodopa for a number of years and have developed what we call "wearing off," meaning that they take their pills, they get an effect, but it doesn't last very long. After an hour or two, they may find it runs down. They have to take another dose, and they end up riding a roller coaster during the day where their pills work for a while, then don't work, and then work and don't work; and it's very unpredictable and annoying.

[Slide 14] So, this is a pump system where you actually put a tube in the stomach, you run a thin extension all the way out into the intestines, and then you have this mechanical pump that you wear on your belt or carry in a fanny pack that pumps the gel in continuously over 16 hours. So the medication is the same. It's the carbidopa-levodopa, so the side effects of the medication are similar to what you would get from Sinemet or other forms of carbidopa-levodopa.

This can produce a very steady response, and many patients are happy with that. The downside, of course, is it does require this procedure to put a tube in the stomach; and there could be problems with the tubes. They do get clogged. They need to be repositioned. They need to be replaced, and so there is some ongoing management and maintenance of this. But it is an FDA-approved treatment, and many people who have tried all the other options do find that this is very helpful to them when they've been through other treatments and just haven't been able to control their symptoms that way. So, it's certainly a valuable new way of delivering carbidopa-levodopa.

But what's interesting is this is the same drug as described by Dr. George Cotzias in 1969. So we're using the same medicine, but we're just giving it in a smarter way. So that's one new therapy.

[Slide 15] Another is this new drug called Rytary, which is another twist on how to give carbidopa-levodopa in a different way. Carbidopa-levodopa is very successful, and so this is a way of delivering that in a time capsule. Probably many of you remember the old TV commercials about tiny time pills. This is tiny time pills of carbidopa-levodopa. So it's a capsule. It has these little granules in it, and they release the levodopa over time. So rather than coming out all at once, it spreads it out over time. Again, it's something that's valuable to people who are experiencing wearing off, who find that their pills don't last very long. You can stretch it out here. And in terms of side effects, it's similar to what you expect with carbidopa-levodopa because the drug itself is the same. It's just a way of releasing it more slowly and over a more extended period of time.

[Slide 16] The third new therapy that's been approved really in the last year is this drug Northera™, also known as droxidopa. This is not really intended for the movement aspects. This is for blood pressure problems. And low blood pressure is a big problem in Parkinson's disease. I'm sure many have experienced this. A lot of people get dizziness, lightheadedness on standing. We see quite a bit of fainting, passing out, particularly in hot weather. I live down in the South, and we get a lot of hot weather here. And in the summer, patients with Parkinson's really have to be careful.

Now, we do suggest some sort of common sense things first. If you're having problems with dizziness and lightheadedness, certainly should have your doctor take a look at your medications. Often we find people are on medicines for high blood pressure. One of the things that happens in Parkinson's is your blood pressure will go down over time. It's an effect of both, the disease itself, as well as the carbidopa and levodopa; other drugs can drive your blood pressure down. So, people who used to have high blood pressure now have low blood pressure, and sometimes they're still taking medicines for high blood pressure. And so, a first step is often looking at that, making sure you're drinking plenty of water, getting enough fluids, particularly in hot weather, compression stockings on the legs. These kinds of simple things can often go a long way. But once you work your way through that and you've checked the medicines and you've made sure you're drinking enough water and you've gone to compression stockings and you're still having dizziness and lightheadedness and blood pressure problems, then medications like droxidopa and others that can be used to increase blood pressure can be really helpful. Certainly, anybody who's passing out, losing consciousness from low blood pressure, this issue needs to be looked at carefully. You can get injured doing that, and we really do want to try and look at it carefully and try and find an answer to that.

So, those are three new drugs that have been approved by the FDA and are already in the pharmacy or available to you through your doctor right now. **[Slide 17]** What's coming soon? Well, you might ask how do I know what's coming soon? What's my crystal ball? And one tool I use is this very valuable website called clinicaltrials.gov. This is run by the US Government, and it's a site where people doing research in human patients need to register their studies when they start. So you can actually go and see what studies are being done in Parkinson's disease or any other condition. It's a really very helpful thing.

Now it produces a long list, so what I did is I went in and pulled out a few highlights for you, just to give you some sense. These are trials that are in so-called Phase III, so meaning they're fairly late stage. These are things where if the trial is successful, we might see them available within the next year to two years. So these are the near horizon.

[Slide 18] So what's coming in that short a time frame? Well, I think you're going to find there are more ways to deliver dopamine, even more than what we currently have. And that's because replacing dopamine works so well. There is a form of levodopa which is inhaled. It's actually like an inhaler you might have seen for asthma or allergies. And the virtue of this is it gets in your system very quickly, so if you're someone who finds that your medicines wear off and you're stuck and you can't move, an inhaled levodopa might be a very quick way to get you back on track and moving again. And this is in fairly late stages of study, and we may see that come out fairly soon.

There's something called the Accordion Pill for levodopa. This is sort of a fold-up pill, and, again, another slow release, sustained release means for delivering levodopa over time. So you can take one pill and get a continuous level over quite a long time.

And then apomorphine, which currently is available in the US only as an injection for relief of short-term freezing, is probably going to appear in other forms. There is a way to deliver this by continuous infusion under the skin. This is widely done in Europe but has not been approved in the US yet. There is a nasal form where you would inhale it as a nasal spray, and then there's these thin strips which are almost like the breath strips they sell in the drug store, which are mint strips or others. You can just put it under your tongue, and it dissolves quickly. So these are all ways of getting apomorphine in, which is a very fast-acting, effective treatment for stiffness and slowness. So in a matter of a minute or two, you can turn around your condition. And so those are all probably valuable ways.

Now which of these will actually make it through to approval? I don't know. But they are all in Phase III trials, so they're all fairly late in the game and may emerge fairly soon.

[Slide 19] Another group, drugs for treating wearing off and dyskinesia. So, we talked a lot about wearing off, the tendency for levodopa to lose its effect at the end of a dose. The other side of that is dyskinesia, the excessive movement, thrashing around that you can see when the levodopa's high in your system. There are different ways of dealing with that, and there are some important studies going on with new ways to try and control that. One is, there's a drug called amantadine that we currently use; but there are improved versions of this – slow release, long-acting versions, versions that may be more effective than what we have. Several of those are in trial. And there's a group of drugs called A2A antagonists. These have been in study for a number of years that are finally reaching maybe the end of the pipeline. These are drugs that would be used to control dyskinesia and reduce the side effects of levodopa. So that's kind of the near term that you might see in a year or so coming out of the clinicaltrials.gov pipeline.

[Slide 20] But let's look a little further down the road and ask, well, one more thing before I leave that is exercise. Exercise is another treatment for Parkinson's; and I would say that most of my patients are familiar. If there are any of them on the line, they have heard my discussion of exercise and the importance of this. I feel it's equally as important as all the medications that we have. Exercise is a critical ingredient in treating Parkinson's.

But one of the big questions is what's the right exercise? What's the best exercise? What's the prescription for exercise as a medicine? And that we don't really know the answer to. We don't really understand exactly what the best exercise for Parkinson's is, how much, how often, what kind. And there are trials going on right now that hopefully will give us some of those answers so we'll be able to be more specific about what is the best exercise as medicine for Parkinson's disease. So that's another, I think, near-term benefit.

[Slide 21] All right, now let's look further down the road and talk a little bit about neuroprotective therapies because this is where everybody wants to go. We want a treatment that slows the disease or even cures it. And this graph tries to convey that idea. You have a line on the top which is labeled normal aging, suggesting that over time we lose some function. But most of us stay above the horizon there. We stay in the yellow and don't get into the purple and don't develop symptoms of Parkinson's disease.

[Slide 22] But in Parkinson's, something happens. We turn the corner. You go downhill faster, the dopamine cells are lost, and you cross into that zone of neurodegeneration where you have slowness, stiffness, and the other symptoms of Parkinson's. What we'd like to do is come up with a treatment that would bend that curve, that would slow it perhaps before the Parkinson's appears, certainly shortly after the Parkinson's appears, and stretch that out. And as many of my patients have said, if I could delay the Parkinson's till after they're 100, they'd be very satisfied with that result. So we don't necessarily even need to completely cure it; but if we can delay it by 10 or 20 years, that is essentially a cure for most people. So that would be a tremendous thing.

So, this idea of a neuroprotective therapy that would really modify that disease is a very powerful one, and this is where I think we'd all like to go. If we're going to get one of those, where's it going to come from? It's going to come from discoveries about the fundamental nature of Parkinson's disease. I could give you a long lecture on the science of Parkinson's, but I wanted to just talk about one or two features that are really critical to the whole field in thinking about the ideas behind it.

[Slide 23] One is this protein called α-synuclein, not a very poetic name, but this is one of the genes that can cause Parkinson's. Generally speaking, Parkinson's is not a genetic disease or not a strongly genetic disease in most people; but there are families where there is a mutation in their gene, and it causes a lot of Parkinson's. That's what's here on the left. This is a little pedigree that shows 13 generations of a family, a very large family. All those little black dots are people who had Parkinson's. That's a lot of Parkinson's in one family, and it turns out that they had a mutation in this protein called α-synuclein.

There's this paper which was published in 1996 that's really a cornerstone of this. It was an important discovery of this protein, linking it to Parkinson's. Turns out the Lewy body is pretty much made out of this α-synuclein protein. So, this is at the core of the disease, and we could talk for a long time about the different ways in which this protein builds up, becomes too abundant, gets stuck to itself, forms these kind of insoluble fibers you see on the bottom right there. But that seems to be a critical part of the process.

[Slide 24] Another key part, and one we've worked on quite a lot, is the response to that. When α-synuclein is overabundant, there seems to be inflammation in the brain. Too much synuclein seems to activate immune signaling, immune cells, and this is part of the process by which the brain is damaged. So, these are two kind of key ideas. One is can we do something about the α-synuclein? The other is if we can't change the α-synuclein, what about the brain's response to this? Can we reduce the inflammation and the response to that? So, those are two broad kinds of ideas. How do we take that to neuroprotection? How do we take that to treating or preventing Parkinson's?

[Slide 25] Well there are a couple of efforts already underway. There may be some people on the phone who are already participating in this. One is studies of a drug called isradipine, which is a calcium channel blocker. It's a drug used for hypertension, but it seems to reduce damage to dopamine cells. It protects them from some of the damaging process that α-synuclein and these other kinds of injuries may produce.

There's also interest in urate. So urate is a normal substance found in your blood. It seems that people with higher urate are more resistant to Parkinson's. So the question has come up of, well, can we make urate go higher in the blood? Is there a way to do that? In fact, there is. And would that reduce the risk of Parkinson disease? So, that is actually being studied. One of the tricky things about that is if the urate gets too high, you get gout, and gout is no fun. It makes your feet sore and gives you a swollen joint. So you have to be very careful about how much you raise the urate, but there is a NIH-funded study which is going to take a closer look at this.

[Slide 26] So that's two things that are under study, but what's the next wave? Where are the really important changes in this game going to come from? And I've got three kinds of examples here. One is what about reducing α-synuclein in the brain? Could you find a way to prevent all that α-synuclein from building up or if it's built up, could you get rid of it? And this is where some of the really more novel and unusual ideas come from.

One idea that's been used is vaccines. Could you, for example, create a vaccine and get the body to create an antibody to attack that synuclein and remove it? This has actually been tested in Alzheimer's disease to some extent. There are vaccines that have been used there to reduce amyloid, which is the protein that builds up in Alzheimer's. And to learn from the Alzheimer's lesson, the initial studies were somewhat difficult because the very first vaccines actually produced some bad side effects. They produced inflammation in the brain and caused problems. Then a second generation was developed where rather than actually giving a vaccine, they produced an antibody, gave it as an infusion, and that does seem to reduce the protein that builds up in Alzheimer's. Whether it really helps the dementia or not is something that's still under active study. But a lot of technology and a lot was learned in that experience of making antibodies and vaccines to amyloid in Alzheimer's which we're now hoping moves over to Parkinson's disease. So vaccines, antibodies to synuclein, ways of clearing synuclein out of the brain, and would that prevent the damage? So that's one approach to it.

Another approach is can you get the body to activate the clearance? And this is where I know there will be questions later about this drug which has been very much in the news, nilotinib. This is a drug that is a cancer chemotherapy drug but seems to have some effect on enhancing clearing of

misfolded proteins. And there was a small study done at Georgetown which was announced earlier last fall. It's only about 12 people. There were no controls. It was unblinded, but they saw some results which they thought were promising. There hasn't been a follow-up of that yet; and, in fact, that study is still not published in the medical literature. So there really isn't much more detail available than what was in the media last fall. So, we're all waiting to hear more about that.

I'm sure someone will ask if I recommend this as a treatment. No, not now. I recommend studying this, and I think we should investigate this and other strategies to clear synuclein. These are very important approaches, but I wouldn't treat any of my patients with this right now. We just don't have enough information, and we don't know what the side effects long term are going to be. But this is a really important approach in the field.

[Slide 27] Another strategy, what about blocking inflammation? If you can't block the synuclein, maybe you can block the reaction to it. There is, in fact, some evidence out there that simple drugs like ibuprofen can reduce the risk of Parkinson's disease. Now do I recommend that for treatment? No, not really. Long term, taking ibuprofen for years can damage your stomach, can damage your kidneys, so it's probably not worth it as a Parkinson's prevention. But that's a clue that if we made a better drug that didn't cause those side effects, maybe that's a way that you could actually slow the progress or the development of the disease.

[Slide 28] And the last is what about restoration? There has been work with a growth factor called GDNF, which has been delivered in different ways – infusing directly in the brain, or with viruses that make it grow in the brain, and there is active work now looking at these growth factors and asking can they prevent the dopamine cells from dying or can they bring them back?

And then, of course, there's always the question of stem cells and transplants. Can you make a stem cell that would be a treatment for Parkinson's disease? Really, what you're talking about there is taking some kind of stem cell, either embryonic stem cell or the newer ones which are just derived from skin, from pieces of skin, and reprogrammed it to stem cells, turning them into a dopamine neuron and putting them back in the brain to replace the missing ones. This has been something we've been talking about for a long time, but I think we're actually getting close to where there may be some stem cells that would be something to consider.

The risk with any kind of cell transplant, of course, is you want it to do what you want, which is to be a dopamine cell; and you don't want it to turn into something like a brain tumor. That would be the problem, and that's been the challenge in this field for a long time. But we may be getting closer to the day where we'll see some ability to do these kinds of things. So I think that this is really the next wave of where we're going, synuclein-based treatments, anti-inflammatory-based treatments, and then neurorestorative kinds of approaches.

[Slide 29] So to summarize all of this, I think you have to recognize in Parkinson's we're very fortunate. We already have some treatments that can help with many of the symptoms of Parkinson's. These are mostly dopamine-based, but they do work; and many people get a lot of benefit out of them. They're not a cure, but they certainly help. Deep brain stimulation, also very valuable for people in that situation where that's the best treatment for them.

I think soon we're going to see a lot of better treatments for the symptoms. You're going to see better ways to give dopamine. You're going to see treatments for the non-motor symptoms, the blood pressure, maybe better treatments for depression. We'd like to see better treatments for memory problems. These are all really important to work on.

And then lastly, the last category to see is really the cutting edge of research. Where is the treatment of the future? The treatment of the future is the neuroprotection treatment. That might be antioxidants because this oxidative stress – we haven't talked a lot about this – plays into synuclein. Synuclein's one of the things that's damaged by oxidation and contributes to the process. Anti-inflammatory strategies, other kinds of strategies that would be neuroprotective or neurorestoratory; and so these are really the therapy of the future.

So, I think I will conclude there and turn it back over to Stephanie to see if we have some questions.

Question & Answer

Stephanie Paul

[Slide 30] Thank you so much, Dr. Standaert, for this very informative presentation today. It's now time for the Question & Answer Session.

Stephanie Paul

We will take our first question from the Web audience, and we'll start with Geraldine from Michigan. And the question is, "Is there validity to treatment with amino acids adjusted by urinalysis?"

David G. Standaert, MD

We really don't have much data on that at all. The amino acids and the question of diet and dietary balance hasn't been answered all that clearly in Parkinson's disease. Now one of the things to be aware of is that levodopa itself is an amino acid, and so it is involved in much of the amino acid metabolism. And when people start to take amino acid supplements, it can actually modify the way that levodopa works. So that's a little bit of a tricky aspect.

But in terms of changing the course of the disease, altering the progress of the disease, we really don't have any clear evidence that changing dietary intake has much of an effect one way or another. We recommend a normal healthy diet, lots of brightly colored fruits and vegetables. But beyond that, I don't think we really have any clear answer or clear evidence that that works.

Stephanie Paul

Okay, we'll take the next question from the telephone audience please.

Operator

Thank you, our question comes from Millie calling from California. Please state your question.

Millie from California

Yes, what is best medicine right now for mental problems?

David G. Standaert, MD

The best medicine for the mental problems, so that's a difficult area. So, there are mental and cognitive problems that appear in Parkinson's disease. There's really two major kinds of these. One is memory loss, forgetfulness. The treatments that are used are similar to those that are used in Alzheimer's. They're the so-called cholinesterase inhibitors. You might know them by the name of Exelon® (rivastigmine tartrate) is one that has FDA approval for this. They're not really all that great. They don't work as well as we'd like them to do. They help, but they are not something that can completely turn the condition around; so it's a frustrating area.

Another area that you will see is hallucinations and confusion in Parkinson's, and this comes out of both the disease itself, as well as the effects of dopamine. One of the side effects of all these dopamine drugs is hallucinations and confusion. So sometimes that's adjusting the drug, sometimes that's using things to limit the side effects. This whole area though of mental problems and cognitive disorders is one where our treatments are not as good, and we really need better treatment in that area.

Stephanie Paul

Okay, let's take another question from the Web. We have Lynn in Florida asking what is your feeling about marijuana as a treatment option?

David G. Standaert, MD

Well, I think that we don't have much data one way or another about marijuana as a treatment option. It's a very uneven system right now. We have some states where it's legal to use it and other states where it's not. And really the upshot of that is that the organized, the carefully done medical research is really lacking on that. Marijuana has a bunch of different chemicals in it. Some of them have very powerful effects on the brain, and there has been laboratory work suggesting they may have different effects on movement.

I think there are things to be discovered there, but we're not going to probably really get to the answers when we have this kind of patchwork of different laws and regulations right now that really prevent scientists from engaging on this question clearly.

Stephanie Paul

Okay, thank you, Dr. Standaert. We have a question on the Web again from Illinois. Alan is asking the question, "What is the best time for someone to have DBS, and what makes someone a good candidate for DBS?"

David G. Standaert, MD

That is a really good question. And this is something that may be shifting a little bit. The usual practice in most centers that do DBS is that we offer it really once patients reach the point where their symptoms cannot be controlled by regular medications any longer. So, that has long been the practice, and probably still is the practice in most places.

The kinds of patients that do the best are the ones that get a response out of levodopa and these other drugs but find that they wear off too quickly. So, patients who maybe take levodopa find they have a really great hour, and then the medicine wears off, and that's really it for the rest of the day. They don't do very well. What I usually tell my patients is that DBS, what it can do for them is if you have one really good hour in the day, the DBS can stretch that out and make it last all day long. If you never have any time at all where medicines work, if you really can't get a result at all out of the medicines, then you're probably not going to get a result at all out of the DBS. So, it's really those people where it's the timing of the medicines that is the problem where DBS is most effective.

Now there is research going on to ask the question of well, what if we didn't wait so long? What if we did this earlier? I think that there's interesting questions there. I wouldn't recommend doing it. We don't do it routinely in people early in the disease. But in the context of a research study, and there are several research studies around the country, I think that's a valuable question to ask; and we would learn a lot from people participating in those kinds of studies. So, there's more to learn there.

Stephanie Paul

Okay, let's take another question from the Web. We have Donna in New Hampshire, and she's asking about dementia and taking any dementia medications prophylactically to ward off dementia.

David G. Standaert, MD

Yes, unfortunately, I don't think we have any ability to prevent dementia with medications. What we know from Alzheimer's is the ways to prevent dementia are to keep your mind and body active. This is really what's done in that field, and I suspect the same is true in Parkinson's. It's not been studied rigorously, but we do recommend being physically active is critical in Parkinson's and I think being mentally active is very important as well. And that's really the best prevention we have right now.

We do know that the dementia and the memory loss is part of this whole same process. So the synuclein buildup that we talk about takes place in the dopamine cells and produces the movement abnormalities. But this spreads beyond the dopamine system. It spreads to other areas of the brain, and the buildup and accumulation of excessive synuclein is what's driving a lot of these memory and cognitive problems. So, if we can get to a treatment that really changes synuclein buildup and its

consequences, that might really be a transformation that might really have a direct effect on it. We don't have that right now, so we're left with the "keep your mind and body active" is probably the best thing you can do.

Stephanie Paul

That's great advice. Let's go to the telephone audience for the next question.

Operator

Thank you. Our next question comes from Herb calling from New York. Please state your question.

Herb from New York

I've been falling. I've had several falls, and I want to know what is the cause of the fall and can we be alert to its coming on and is there a way to prevent it?

David G. Standaert, MD

Well that's a really great question. Falls are a major problem in Parkinson's disease, and they do, sometimes don't respond to the medicines as well as the other symptoms. So I have patients where we are able to treat their slowness, stiffness. We get the tremor under control, and they're still falling. It can come from several different causes. Sometimes when the medicines wear off, people fall. And you can deal with that by changing the timing of the medicines or using one of these strategies of longer duration treatment.

But sometimes the falling is there even when you've tried to correct all the other problems. It seems to come from changes in the brain that are outside the dopamine system and often are refractory to medicine. So, the medicines may not help the falling. Physical therapy could be very useful, teaching balance strategies, assistive devices are very useful, and there is some experimental work with doing DBS – not in the places that we usually do it, but deeper in the brain, going after some of the centers involved in balance.

But this is a big problem, falls are a major problem. People will injure themselves, break a hip. It can be a very serious event in Parkinson's disease. So I think the best we have right now is it's important to look carefully at the medicines, to look for wearing off, to think about low blood pressure issues. Is that part of the reason that you're falling? Certainly that can be addressed. Physical therapy measures, assistive devices, but you really have to try and do the best you can with this because falls cause so many injuries and lead to so much trouble in Parkinson's.

Stephanie Paul

Okay, we have a Web question from California. "I am being seen by a general neurologist, not an MDS (movement disorder specialist). How should I approach my doctor about seeing if Rytary is right for me. He has not suggested switching off my levodopa."

David G. Standaert, MD

Well, I think you will have to talk with your general neurologist or maybe even think about a one-time visit to a movement disorder specialist. So, as many on the phone will know, movement disorder specialists are a subgroup of neurologists who've taken time out, usually several years, to study movement disorders in particular. And I do recommend that people try and visit one at least once a year, even if your regular doctor is a general neurologist because there are things you can learn.

In terms of the question of switching from one form of levodopa to another, which is really what you're asking when asking about switching from levodopa to Rytary or one of these others, the question is, is it necessary? Is it something that you need? And, really, Rytary, what it's approved for and the purpose of Rytary is to give you a longer duration of benefit out of each pill.

So, if you're taking carbidopa-levodopa and it's lasting all day and you really don't notice much up and down, there's unlikely to be any benefit by changing to a different form. On the other hand, if you're someone where the drug is wearing off, you're taking the carbidopa-levodopa, it's lasting an hour or two and then it's quitting and you're having to take another pill at that kind of short interval, that's a situation where something like Rytary might be helpful. As I said, it is the same medicine; but it's in those tiny time pills and will stretch it out. The downside, of course, is it's a new medicine. It's going to probably be more expensive. But if it works for you, that may be worth it.

So, really it's a drug intended for these wearing off symptoms, and that would be the critical question, do you have wearing off. If you have wearing off, what are the approaches? Rytary is one of them.

Stephanie Paul

Okay, we have a Web question from Washington. "Are there any treatments for someone who has lost their sense of taste and smell?"

David G. Standaert, MD

Unfortunately, not really, there aren't and that's a very frustrating symptom. It turns out that the loss of smell actually comes from that synuclein protein, damaging the areas of the brain that are involved in smell and the olfactory sense. It may happen a decade before the other symptoms of Parkinson's appear, and it's quite troublesome. People find that food doesn't taste right to them anymore, and often they lose weight, sometimes to a dangerous degree.

So, I think that, again, much like the mental cognitive syndrome, the answer to that is probably in finding a way to treat the synuclein disease. And as I said, there's a lot of research going on right now but not something that is ready for prime time yet. So, I hope to see that in the near future.

Stephanie Paul

Okay, we have only time for one more question, so I will take a question from the Web. It's Beth from Ohio, and she is asking, "My husband has friendly hallucinations. Is there anything that can be done to treat these?"

David G. Standaert, MD

Right, so hallucinations are a big problem in Parkinson's as well, and to some degree they're caused by the condition; but often they are brought out by these dopamine drugs. And so the first question is to ask whether you can alter the medications. So, drugs like the dopamine agonists – ropinirole, pramipexole – the drugs in that family particularly likely to produce hallucinations. We usually start by reducing those first. We ask whether patients are taking levodopa-carbidopa, and are they taking too much? Can you cut back on that? Are there other medical issues going on, problems with electrolytes and blood, this kind of thing?

And if that doesn't work, there are medicines that are sometimes used to control hallucinations. One of the drugs we use is this drug called quetiapine. This is also known as Seroquel®. It's approved for treating mental illness, but in low doses can be very helpful in hallucinations and Parkinson's. So, really it's a progressive exercise. First you ask whether you can reduce some of the medicines people are already on. Can we cut back on what they're currently taking? And, if you really can't, they really need them, then you think about adding drugs like quetiapine and others to see if you can control the hallucinations.

Stephanie Paul

Okay, great, and actually, one final question from Texas. Sarah is asking, "Who is the best candidate for Duopa?"

David G. Standaert, MD

Well, it's in many ways very similar to the best candidate for DBS. They are similar populations of people. Duopa and DBS are both very useful in people with wearing off. So, Duopa often the people we consider there who've been through all the other strategies still having a lot of wearing off, a lot of fluctuation in the course of their day, many hours of the day where they're off and their medicines are not working. Usually we look for more than two or three hours of off time in a day, would make you a candidate for Duopa. So, it's a similar profile to DBS, and they have similar efficacy actually. They both can produce a very dramatic improvement. If you look at the double-blind studies, the improvement was improvements of four and five hours a day of on time. So, this is pretty dramatic with both of those therapies.

Which is better, DBS versus Duopa? I think that there are a lot of individual considerations that come down to the difference between having a brain surgery and having a tube in the stomach, having an electrical device versus a pump. This is something to have an individual discussion with the person involved. Some people will prefer one, and some people will prefer the other. But they're used in a very similar setting, which is that when people reach the point of their medicines wearing off frequently and uncontrollably and they've tried other strategies, then it's time to think about either Duopa or DBS and have a discussion about which is the best in this situation.

Stephanie Paul

Wonderful, terrific information.

Closing Remarks

Stephanie Paul

[Slide 31] I want to thank everyone for participating in today's telephone and Web education program. I apologize that we weren't able to get to all of the wonderful questions. **[Slide 32]** If you have additional questions and would like to speak with someone in our Scientific & Medical Affairs Department, I encourage you to visit our website or call 1-800-223-2732 and you can ask your questions there.

I want to thank our speaker, 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 do complete the program evaluation form that was in the confirmation email you received.

We at the American Parkinson Disease Association are so proud to invest in patient services and education and to be funding partners in most of the major Parkinson's disease scientific breakthroughs to get one step closer towards discovering the causes and finding the cure. To do all of this, we rely on the support of the entire Parkinson's disease community. If you're interested in supporting us, you can find out more information on our website at www.apdaparkinson.org.

[Slide 33] So, again, thank you so much, 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.

David G. Standaert, MD

Thank you Stephanie.