Transcript

Welcome and Introductions

Rebecca Gilbert, MD, PhD

[Slide 1] Welcome everyone and thank you so much for joining us today. **[Slide 2]** My name is Rebecca Gilbert, and I am APDA's (American Parkinson Disease Association) Vice President and Chief Scientific Officer. I'm pleased to welcome you to this Web teleconference education program designed for people with Parkinson's disease, care partners, family members, and healthcare providers. I would like to thank Genentech and Lundbeck for funding this important program and acknowledge their appreciation for the critical need to provide educational programs like this one to people impacted by Parkinson's disease.

During this time of uncertainty, we know that you still have concerns regarding your Parkinson's treatment and identifying ways to continue to live your best life with PD (Parkinson's disease). American Parkinson Disease Association or APDA for short is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than 1 million Americans with Parkinson's disease. APDA distinguishes itself as a national organization working one on one with the Parkinson's community to make each day better.

And now to our program. **[Slide 3]** We welcome our distinguished presenter today, Dr. David Standaert, John N. Whitaker Professor and Chair of Neurology at the University of Alabama Birmingham (UAB) School of Medicine in Birmingham, Alabama. Dr. Standaert is also the Chair of APDA's Scientific Advisory Board. He is here to share his perspectives on promising therapies in development to address disease progression in Parkinson's disease.

After the presentation, we will open the program for questions from both telephone and Web participants. We encourage everyone to complete the evaluation after the program because your feedback is instrumental in helping us plan for future educational offerings, including teleconferences like this and other programs.

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

Presentation

David G. Standaert, MD, PhD

Well thank you, Rebecca, and thank you for inviting me to join you today for this presentation on this really important topic about preventing progression of the symptoms of Parkinson's disease. This has been the goal of research, I think, since the early days; and as we'll see, even Dr. James Parkinson himself thought about this idea; and it is really a critical idea in the field. And I think it's the goal that we're all searching for.

[Slide 4] Let me go to the next slide here and just remind you about some disclosures. I do work with a variety of companies that are interested in this space, including AbbVie and others. I wanted you to be aware of these, but I don't think we're going to talk about any products that are relevant to these today.

[Slide 5] So Parkinson's disease has many faces. It's originally described in 1817 by Dr. James Parkinson. This is the faceplate from his essay on the "shaking palsy" he called it, and that's still a term that's used in the medical literature sometimes; and he described 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, this is more than 200 years ago, and we still recognize Parkinson's disease by these same symptoms that Dr. James Parkinson described.

On the right here, you see some of the many faces of Parkinson's. I sometimes get the question from patients with Parkinson's of "Have you ever seen anyone exactly like me?" "No, patients with Parkinson's are like snowflakes. There are no two that are exactly the same, but there are some common features and common experiences that are part of the course of Parkinson's disease," and we'll talk about that a little bit. But many of you will recognize some of these public figures on the right who are really part of the public face of Parkinson's, and many of them have stepped up and made a difference in the supportive research and the search for the cure.

[Slide 6] One of the things to appreciate about Parkinson's disease is there are some common features. These are the so-called classical features of Parkinson's disease. Neurologists really recognize four of these: resting tremor, a very particular kind of tremor present when the hands are at rest. Usually it is reduced when they're in action, and this is a signature of Parkinson's disease. Bradykinesia or slowness of movement. There is rigidity or stiffness. This is what the doctor feels when they move your arm or your leg. They're looking for rigidity. And then postural imbalance, which is a tendency to lose balance and fall, often backwards, a very particular symptom in Parkinson's disease.

And then these pictures on the right show some of the structural features of Parkinson's. The panel on the top there with the two things that look like butterflies, those are slices from a human brain stem. The one on the left is normal. The one on the right, the black area is gone. This is the substantia nigra. It's the region that degenerates in Parkinson's, and it contains neurons that make dopamine. The pink picture in the middle shows a single dopamine neuron, and there's a round ball in

the middle of that. That's a Lewy body. These are the particular bodies that are found in Parkinson's disease and are a signature of the disease.

And the bottom are some images taken of dopamine function from one of my patients over a period of about four years, so each scan was done at a different year. This is much like what's now called a DaTscan. It's a little bit different technology. It's an older technique, but this shows the kind of progressive loss of dopamine function that we can see in patients with technique like DaTscan. So, these are ways that we recognize and diagnose Parkinson's disease.

[Slide 7] Another critical factor to understand when you talk about Parkinson's disease and finding a way to prevent progression is that Parkinson's is very much an age-related disorder, and the good news is most Americans are living longer. Pretty much everyone who's alive today can expect to live to be at least 80, in many cases longer. But the truth is that as we get older, we're more likely to get Parkinson's disease, and that's shown in this graph here. Over on the left, people who are under 29 years old, very unlikely to develop Parkinson's. Quite rare. As your age increases to 40 to 49 or 50 to 59, it becomes more common. The average age for developing Parkinson's in the US is about 65. And as you get older than that, the odds go up even further, so it's an age-related disease. And as our population ages, as the baby boomers age, it becomes even more important to find ways to slow or prevent the development of Parkinson's.

[Slide 8] So if we're going to talk about the progression of Parkinson's, what is the progression of Parkinson's? How do experts in the field think about the stages of Parkinson's and the movement of Parkinson's from beginning to end? And this may be a little different formulation, but this fits a little better with the way I think scientists and researchers are thinking about this. We think about a stage where people are at risk for Parkinson's but have no symptoms. So, this is relatively young people. They really don't have any symptoms. They don't have any complaints. They don't know that they are going to get Parkinson's someday, but they may have genetic risk factors. There are genetic risk factors which have been identified, and these may be an important feature in the progression of Parkinson's. So, there is an at-risk stage here where the patients are really asymptomatic.

And then beyond that, there is a so-called prodromal state. This is what we might call pre-Parkinson's disease, and this is characterized by some symptoms that are not really Parkinson's but symptoms we now recognize as a state that comes on before the Parkinson's appear. Some symptoms you might have in this state are hyposmia, the loss of sense of smell; REM(rapid eye movement) behavior disorder, this is a sleep disorder, rapid eye movement sleep disorder where people are acting out their dreams. I often hear that people have become violent in their sleep, they're throwing the pillows around, they're punching imaginary dragons, they're talking in their sleep, and this is actually an early symptom of Parkinson's disease. Also, constipation turns out to be one of the very early symptoms of Parkinson's disease. This constipation, this can appear decades before the characteristic typical symptoms of PD appears. So really telling you that something's going on in the body here long before the characteristic motor symptoms of Parkinson's appear.

Then following this, there is a stage of early Parkinson's, and this is where we see the typical features – tremor, bradykinesia or slowness of movement, rigidity which is stiffness, and fatigue is another symptom of early Parkinson's disease.

Beyond that, there's, of course, a state of more advanced Parkinson's disease. This is where you see impaired balance and falling. You start to see variable response to medications with wearing OFF and dyskinesia. You can see memory problems, and you can see things like hallucinations. So this is really a progression, and this progression, when you think about how much time is involved, this may involve 30 or 40 years here where people go from being at risk to having very early prodromal symptoms and then early PD and advanced PD. Obviously, that could take people into their 70s and 80s. So, you know, maybe 70 years altogether to go from the at-risk state to the more advanced PD. It's a very slow process; no question about that.

All right, so the good news about Parkinson's is we're not going to talk very much today about treatment, but I think everybody listening should be aware that we are fortunate to have treatments which are effective across the spectrum. We have treatments today that are effective in helping the symptoms of early Parkinson's. We have treatments that are effective in helping the symptoms of advanced PD. We can do a lot for people with Parkinson's. But what everyone wants to do is to stop the progression, to halt the process in the earliest possible stage, and prevent the progression to later stages. So, we're not going to talk about current treatments, even though they are very good, and I think it's remarkable that we have them. We're going to talk more about the idea of how could one slow the progression and prevent the later stages of disease.

[Slide 9] So, searching for ideas to stop disease progression, where do ideas for disease progression come from? So, one of the places that they come from is genetic discoveries. So, we've learned a lot about the genetics of Parkinson's disease. This is an area where there's been a tremendous amount of discovery in recent years. There are a number of different genes that are linked to it, and we'll talk about the genetics of Parkinson's. But then the final analysis, really three things emerge from what we know about the genetics of Parkinson's that are potential targets or ways to slow the progression of Parkinson's disease.

One is a protein called alpha-synuclein. The second is a protein called LRRK2, leucine-rich repeat kinase 2; and the third is a protein which goes by the name GBA. It's called glucocerebrosidase, but even I struggle to pronounce that correctly, so we just call it GBA. So, those are three genetic discoveries that we'll talk about specifically.

Another area that's become very powerful in Parkinson's is immunology. What's the role of the immune system in the progression of Parkinson's, and is this a way to modify the progression of the disease over the time?

A third topic to think about is exercise. Exercise is really important in Parkinson's, and we actually have increasing evidence that it may modify the progression of the disease over time. So, I think this is another really important area to talk about.

And then lastly, to take this together, I want to come to thinking about what is the future of Parkinson's therapy? What will this look like? How will we put these things together when we have these various treatments in Parkinson's disease and different ways of managing it? So, that's my goal for the next 20 minutes or so is to talk about these topics.

[Slide 10] All right, what about genetics of Parkinson's disease? So, the first thing I want to say about Parkinson's disease is in most families, this is not a strongly genetic disease. It does not run strongly in most families, and I often get the question of, "Well, I have Parkinson's. What are the odds my children will get Parkinson's?" The odds your children will get Parkinson's in most cases are no different than the odds of anyone else's children. It's not a strongly genetic disease.

But there are some rare families where it does run strongly in your family. How would you know if you're in a family like that? If you have six or seven people in your family with Parkinson's, there's a good chance that there's a gene that's responsible for that. And then also there are genes that have subtle effects. These are genes that each individually have a small effect but add up together. And what this diagram here shows is the 90 or so genes that are known to each contribute a small effect to the incidence of Parkinson's disease. This is not too different than other conditions. For example, if you have diabetes in your family, you probably have a number of different genes that contribute to that. Parkinson's is the same.

But from all of these studies of 90 or more genes, really these three proteins emerge; and we'll talk specifically about these. **[Slide 11]** All right, so what about alpha-synuclein? This was originally discovered in a large family, a family located in Southern Italy and Greece which had autosomal dominant Parkinson's, meaning every generation was affected. In this wheel in the middle, you can see is 11 generations of this family; and you can see these black dots; each one of them was an individual affected with Parkinson's, so that's a lot of Parkinson's in one family. Turns out they had a very specific mutation in this protein alpha-synuclein. And I remember when this came out, and we got very excited about this. We thought we discovered the cause of all Parkinson's, and we went to our clinic and started testing people for this gene; and we couldn't find any. We couldn't find any mutations at all.

It turns out this mutation is very rare. There's a few families in the world and that's about it. But on the other hand, the protein turns out to be a key component of the Lewy body, and those are found in pretty much all people with Parkinson's. So, if you have a mutation of this protein, causes Parkinson's, but mutations are very rare. However, all of us have the normal protein in our brain, and this protein seems to play a role in Parkinson's in almost everyone who's affected by the condition.

[Slide 12] So that was a very important insight. It led to another important insight, which is that there is a progression of this Lewy pathology over time in the brain. So, in the very early, the pre-Parkinson stages, you can find the synuclein in these pink areas on the left, in the brain stem and the olfactory bulb which is responsible for the sense of smell. In the middle stages, it spreads to the middle of the brain where it often causes the tremor and slowness; and then in late stages it seems to spread even further. So, this synuclein is building up across the brain over time and is contributing to the progression of the symptoms.

[Slide 13] So that obviously gets you to, "Well, how can we stop that? What can we do about that? How can you target alpha-synuclein?" This is a nice picture of the structure of alpha-synuclein on the right. What could you do to get the alpha-synuclein out of the brain or prevent it from building up? That might sound kind of space-aged, but we are in the space age. And we actually are developing treatments that can do this. One set would be a way of how can we have the brain make less

synuclein? So, there are ways to do this by inhibiting the gene that makes synuclein, so-called innocence strategy. Also, there are drugs that seem to turn down the expression of synuclein, and these are potential treatments.

Another is you could try to remove the synuclein from the brain. You could try to strip it out of the brain. There are different ways to do this. You could turn on the brain's autophagy, the normal sort of garbage removal system of the brain, or you could have an antibody that you infused into the blood, and it would pull the synuclein out of the brain.

A third way to go at it would be to say, "Well, the problem isn't synuclein. We all have synuclein in our brain, but it's when it aggregates and clumps up and forms as Lewy bodies that it's a big problem, and how can we prevent that? Can we have some kind of strategy of a drug that prevents that from happening? And all of these ideas are being studied. I'm just going to show you a couple that have made it to the level of publication and clinical trial in humans.

[Slide 14] This is a paper published by a group from a company called Roche. They've developed a humanized mouse monoclonal. So, this is an antibody that started in the mouse, was adapted to look like a human antibody, and was given to patients to remove the alpha-synuclein from their brain. And remarkably enough, it seems safe, and it seems tolerable. They've published that information.

They are now testing this in a Phase II trial. The trial's ongoing, but they've recently expanded the size of this trial which I take as a good sign; and they are pursuing with this with the idea that this would be a monthly infusion therapy. It would be an antibody. You'd go in say once a month, get an infusion of this drug into your vein; and it would actually pull the synuclein out of the brain. I think this is a really remarkable treatment.

It's actually very similar to what's being done in Alzheimer's disease as well whereas different infusions to a different kind of protein are being used as a treatment for Alzheimer's, and that work is very promising. There was an important paper on that just this weekend in *The New England Journal of Medicine*. So, I think a promising strategy and they are pressing ahead with this.

Another company called AFFiRiS, which partnered with the Michael J. Fox Foundation, actually made a vaccine using a peptide. So, one of the things about the experience we've all had with the coronaviruses, we're all immunologists now. We're used to these terms of vaccines and antibodies. We hear these every day. This is a vaccine that was made against synuclein to create an antibody to take the synuclein out of the brain. And this publication shows the safety and that it does generate an antibody. Does it work? Is it effective? We don't know yet. This is a Phase I trial, but they are pressing on to a later phase trial, and I think it's another promising strategy.

There are others in this category. Some of these drugs are just listed here. There's three other companies that are all pursuing this same idea of how can we remove synuclein from the brain. So, this is really undoing the disease process, and I think this is really exciting. So, it's being done in humans. It's being tested, and I hope in the next year or two we'll have some results that'll help us to move forward with this.

[Slide 15] Second, I wanted to talk about this protein, the leucine-rich repeat kinase 2 or LRRK2. So, I said Parkinson's usually wasn't genetic, but if it is, this is one of the more common ones. It might cause up to 4% of cases in North America, so 1 in 25. If you go to certain populations, like people of Ashkenazi Jewish descent, it's much more common.

The interesting thing about the mutation in this protein is it turns this protein on. It's an enzyme, and the mutations make it more active. And if you're a drug developer, that's a good thing because maybe we can discover a drug to turn that protein back off again. There's a lot of work going on around this. **[Slide 16]** These are three drugs that have been developed for LRRK2, and these are being tested in Phase I or Phase II in humans. So that means we're actually testing these in people. Two of them are from a company called Denali Therapeutics, and the third is from a company called Biogen. They haven't published their studies yet, and there are still some lingering concerns about safety. We haven't seen all of the data, but I think this is another very exciting development. And the idea that we're actually testing this in people means it's not that long a distance from where we are today to answering the question of whether this is a useful treatment to slow Parkinson's disease.

[Slide 17] What about glucocerebrosidase? And as I said, that's too long a name for me to say, so we just call it GBA in Parkinson's. This is, in itself, a very interesting story. This enzyme, GBA1, has been known for many years because if you have mutations or abnormalities of this, that block its activity completely, you get a disease called Gaucher disease. This is a disease often presenting in children. They build up lipids in their brain, and they have severe neurologic symptoms. So, we might say what does that have to do with Parkinson's?

Well, it turned out that in 1996 it was observed that some of these patients also have parkinsonism, and that was a clue. And then went on with later work and discovered that mild mutations in GBA1 can be found in about 4 to 7% of Parkinson's disease. So, the defects in this enzyme do seem to increase the risk of Parkinson's quite a lot. And in fact, if you go measuring this enzyme in people with Parkinson's, whether you have a mutation or not, the enzyme seems to be down. And this is an enzyme that's involved in clearing abnormal proteins. So maybe there's a connection here that this enzyme's important. It might clear synuclein and other proteins when its activity is reduced because of mutation or other causes. You build up synuclein, and maybe if we turned up this protein and increased it, we would clear some of the proteins that are problematic in Parkinson's. So, can we turn it on? Can we activate this in PD?

[Slide 18] So, here's a couple of trials. One is doing something fairly simple. They're using a drug called ambroxol, which is actually used for treatment of cough. So, it's a common medication. It's mostly used in Europe, not commonly in the US. But this seems to improve the function of GBA, and this is in a Phase II trial for treatment of Parkinson's disease. So this is a drug that's been around for a while, so it's an example of repurposing, taking a drug we already know and feel pretty good about, feel pretty good about the safety of it, and testing it out as a treatment for Parkinson's disease.

On the other end of the spectrum, there's a trial called PROPEL by a company called Prevail Therapeutics. This is gene therapy. They're injecting a virus into the brain that makes GBA. So, the nice thing about this is it's just one treatment. They put the virus in there. It turns on. It makes GBA, and it can potentially clear out some of these misfolded proteins. Now obviously, this is a more radical

kind of approach. It's a more drastic approach. But on the other hand, if it's successful, this could be a one-shot treatment for Parkinson's disease. So, I think it's something that's more in the category of high risk, high reward; and we're really looking forward to seeing what's happening with that.

[Slide 19] All right, what about the immune system? I talked about the immune system and the role of the immune system in Parkinson's. This is an area that has really blossomed in the last few years, and it's come through a number of different avenues. In fact, we've known for a long time that there's immune activation in the brain, and this is a little panel showing some of the immune cells that are in the brain. The brain has its own immune system, and in the middle there you can see some cells that are, look fat and enlarged, and those are reacting in the brain. They're active cells, immune cells that are found in human Parkinson's disease. You can see IgG, which is antibodies that are deposited onto the dopaminergic neurons, and that's what's shown in this picture on the bottom left. And then there are cells that are coming out of the blood and going into the brain. They're called CD4 and CD8 T-cells. These are entering the brain, and they're part of the immune system. They're not found in normal brain, but they're found in Parkinson's disease. So, all of this is pointing to the idea that the immune system becomes activated in Parkinson's and might be part of the process by which the dopamine neurons get damaged.

[Slide 20] Another really important discovery was this work by a group in New York and San Diego which looked at blood from patients with Parkinson's disease. And what they found is that in the blood there are cells that recognize synuclein. So, you think of Parkinson's as disease in the brain, but this is telling you that it's actually a disease of the whole body. The body is responding to the Parkinson's. There are T cells there that are active, and they may be actually damaging the dopaminergic neurons.

[Slide 21] So, what can you do about that? Could you shut this off? Can immune modulation change the course of Parkinson's disease? How would you do that? What are the targets for immune modulating therapy? And when in the course of the disease is the immune modulation effective?

And this is a really important area, I think, because we treat a lot of immune diseases. We treat things like rheumatoid arthritis, we treat inflammatory bowel disease, we treat diseases like lupus, we treat diseases like MS (multiple sclerosis), and we have all of these conditions that we can treat effectively with immune therapy. So, what about taking some of those treatments and applying them to Parkinson's? Would that be successful?

[Slide 22] And just to give you a clue that it might, this is a very important study from a couple of years ago which looked at people with inflammatory bowel disease; so these are people with Crohn's disease and other similar diseases. They were able to use a Medicare database covering 16 years, and they found 144,000 people in this database with inflammatory bowel disease; and they matched those to 700,000 controls. Among those, about 1,700 of them had Parkinson's disease. So, you're able to ask is Parkinson's related to inflammatory bowel disease, and does the treatment of inflammatory bowel disease change the Parkinson's disease?

And what they found is that actually having inflammatory bowel disease does increase your risk of PD somewhat, but the treatment, which is used for inflammatory bowel disease, these are antibodies to TNF (tumor necrosis factor), these are infusions these patients get for their inflammatory bowel

disease, results in a ten-fold reduction in the risk of Parkinson's. This is a tremendous effect. Now I wouldn't recommend anyone run out and have this treatment right now because these anti-TNF treatments have significant side effects. But it shows you how powerful an immune treatment might be in Parkinson's. And if we could refine this and fine-tune this a little so that it's safer, this might be a way forward in terms of both preventing and perhaps reducing the progression of Parkinson's. So again, an example of here we have a treatment. We're using it for something else. Could we adapt this for Parkinson's disease? And that one could be done in a fairly short space of time.

[Slide 23] I did want to mention the work we're doing locally. We have an NIH (National Institutes of Health) federal grant, something called the Alabama Morris K Udall Center of Excellence in Parkinson's Disease Research. This is one of the six federally funded Udall Centers around the country. These are the big federal centers for Parkinson's research, and ours is focused on the immune system in Parkinson's. That's really the work we're doing locally, funded by the NIH.

And our idea is that immune cells are active early in PD and inhibiting their activity will protect from neurodegeneration. We're doing this study of inflammation in early PD patients using PET (positron emission tomography) imaging, blood, and CSF (cerebrospinal fluid) studies. We also have animal model studies in parallel. This is underway and hopefully in the next couple of years we'll have more data about the immune system and inflammation emerging from this important federal funded study.

[Slide 24] All right, what about exercise and Parkinson's disease? Well, exercise, I recommend exercise for all of my patients. This has established ability to improve PD symptoms. I think we've all seen this in our daily practice, and there's actually very good clinical trial data. These are two trials that have looked at this one called Park-in-Shape, which is a stationary trainer approach, three times a week for six months, and it showed that the UPDRS (Unified Parkinson Disease Rating Scale), which is a standard rating scale of Parkinson's, improved quite a bit, 4.2 points. And then there's another called SPARX (study in Parkinson disease of exercise), high intensity treadmill training for six months. And again, the Parkinson's got better, which is the opposite of what you'd expect. We expect it to get somewhat worse over time, and here these people are improving with exercise.

Another aspect that improves with exercise is actually sleep. Some very nice work from Dr. Amara here showing that if you do vigorous exercise, you actually can improve outcomes of sleep, which is a major problem in Parkinson's. This work was recognized by the 2020 Research Article of the Year from *Movement Disorders*, the major journal in the field. So, exercise clearly has beneficial effects.

Now the real question is does it modify the long-term outcome in Parkinson's? What's it doing in the brain? Is it changing the nature of the disease? Does it produce a long-term improvement? We don't know those answers. As I said, I recommend exercise for all of my patients. But how much exercise? What's the exercise prescription? These are very important areas where we need further research.

[Slide 25] Taking all this together, what will the future of Parkinson's disease therapy look like? I think that we'll have different therapies for different stages of the disease. And we talked earlier about how there are at-risk stages, there's a prodromal Parkinson's disease stage, there's an early PD stage, and there's a more advanced stage. I think that we're going to probably have gene-specific therapy. So, for people we can identify that are at risk that perhaps have a gene which gives them high risk, most people don't really have this; but this might be 5 or 10% of the population. If we can find a gene

early on, we might have gene-specific therapies, a drug like a LRRK2 inhibitor. I think for people who have either prodromal Parkinson's, where they have symptoms like REM behavior disorder, anosmia, or early Parkinson's, there might be therapies against synuclein. These might be these infusion therapies we talked about or even there are other kinds of drugs to reduce alpha-synuclein.

I think as you get out a little further, certainly beginning with prodromal PD, certainly in early PD, and well into advanced PD, exercise is beneficial; and I think we're going to see more and more evidence for that coming in the future.

Beyond that, inflammation strategies to shut down the inflammation in Parkinson's. This will probably be applicable from very early symptoms of Parkinson's through late in the disease. And another advantage of the anti-inflammatory therapies is we have a lot of these drugs on the market already. We're already using these in other diseases and bringing these to bear in Parkinson's will be very important.

Levodopa and other medications are very effective. They do people a lot of good. A lot of people are able to really regain a lot of function, and I think we'll continue to see those used.

And lastly, there's a class of things like deep brain stimulation and other surgical therapies that can be quite effective in advanced PD. But of course, the goal would be to slow the progress before we get there and avoid the state of advanced PD entirely.

So, this is a little bit of my personal view of what the future of Parkinson's therapy will look like. **[Slide 26]** But I did want to return to Dr. Parkinson because in this essay on the shaking palsy, he actually made a very specific prediction about this. He wrote that, "There appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped." He wrote this in 1817, and then some 200 years later, I think we're getting awfully close to having what Dr. Parkinson promised; and I really hope we see that in the next couple of years.

So, with all of that, I will conclude my section here and turn it back to Dr. Gilbert and see if we can take some questions.

Question & Answer

Rebecca Gilbert, MD, PhD

[Slide 27] Thank you so much, Dr. Standaert for that very, very detailed and informative presentation; and it has generated a large number of questions as you can imagine.

So, it's now time for our Question & Answer session. We'll take our first question from the Web audience. This is from Art. "Would you comment on the efficacy of terazosin or more generally repurposed medications for use in Parkinson's and potentially to prevent progression in Parkinson's."

David G. Standaert, MD, PhD

Yeah, so let me start with the repurposed medication. So, what that means is taking a medicine that's already approved for another use and adapting it for use in Parkinson's disease. And I think that's a very valuable strategy because medications that are already approved, we know a lot about their safety. You can shave years off the development process, and it can be a much faster pathway to getting medications to patients.

So, terazosin has been studied in the context of really model systems, animals, and cells, in terms of reducing synuclein aggregation. There's not been a good trial in humans yet. Now it is a widely used medication. It is used to reduce blood pressure and also for prostate hypertrophy, and so I think the safety of terazosin is pretty well-established. In terms of does it work in people, we don't know yet. Haven't done that trial yet, so I wouldn't recommend anyone start it for prevention of Parkinson's unless they're part of such a trial. But it is perhaps time to do a trial like that.

Rebecca Gilbert, MD, PhD

Excellent, thank you. The question from Susan, actually a number of people have asked variations on this question, "What is the role of diet in PD progression?"

David G. Standaert, MD, PhD

Yeah. So, I don't think we've really identified specific dietary features that affect PD progression. Now diet is important in Parkinson's. Constipation is a huge problem. I recommend everyone, you know, have a healthy diet, colorful fruits and vegetables. You want fiber in the diet because constipation is such an enormous problem in Parkinson's.

But in terms of specific dietary supplements, we've studied a few. We've studied vitamin E and found that that didn't really seem to make much difference one way or another. Same with creatine we've studied in a large study; didn't really seem to change the progression of Parkinson's. So, we really have yet to identify a dietary supplement that changes the course of Parkinson's, but on the other hand, a healthy diet and fiber is really important just to management of the condition itself.

Rebecca Gilbert, MD, PhD

Very good. Thank you. We have a number of questions related to genetic testing. You mentioned a few genes that increased the risk of Parkinson's, and they may help us look at ways to stop progression. Would there be any value of Parkinson's patients getting genetic testing to see if they have mutations in these genes?

David G. Standaert, MD, PhD

Well that's an interesting question, and I think the answer to that is changing over time. So right now, we don't have a treatment that's based on genetics which is available to people with Parkinson's. So even if you were willing to have genetic testing, it's a little difficult to act on it today. On the other hand, trials are coming. For example, LRRK2 is being tested in a small group of people with those mutations, so I think the interest and utility of those is growing. There are a number of different ways to get genetic testing done.

Another point to make too is that I said in most cases genetics is not a strong factor in people with Parkinson's of the typical kind that might begin in their 60s or 70s. In someone who has very young onset of Parkinson's, that's a different story. If your Parkinson's began before you were 40, the odds that it's genetic in origin go much higher, and there there's really a role to understand the nature of the Parkinson's. So, patients with very young onset I think it's valuable. Also, people with a strong family history. Not just one or two people in the family, but if you have six or seven people in your family, I think it's a value to understand that, and I would encourage genetic testing. But that answer is going to change pretty quickly. As soon as we have a treatment, which is based on the genetics, then I would advocate that everyone gets genetic testing, so that day is not that far away.

Rebecca Gilbert, MD, PhD

Great. We have a related question which Gary asks. "Can you talk a little bit about CRISPR (cluster regularly interspaced short palindromic repeats) technology? Is there going to be a solution to Parkinson's disease using CRISPR technology in the next few years?"

David G. Standaert, MD, PhD

CRISPR technology is a means for editing genes, so if there's a mutation, you can go in and cut out the mutation and replace it with something different. It's a very powerful technique that we use in the lab a lot as a way of manipulating genes. It's a fantastic tool for research. The question is in a person, would you use CRISPR technology in a person; and if you did that, what would you edit? You might possibly think about editing things such as the GBA gene in a cell, so there might be, for example, a way to take some cells from the body, say white blood cells, edit the GBA gene, and put them back. A way of kind of correcting genetic defects.

CRISPR in neurons though in the brain itself is difficult. There really isn't a good approach right now to using CRISPR in the brain itself. So, I think at least for the foreseeable future, it'll be restricted to cells like blood cells or experimental techniques.

Rebecca Gilbert, MD, PhD

We have a great question about exercise and how it interfaces with a decreasing progression. "Is there a relationship between consistency of performing exercise and minimizing progression?"

David G. Standaert, MD, PhD

That's a really great question. How much exercise is enough and how much should you do? And we don't really have that answer in a clear way. You would think we would, but we don't. I mean as just a practical matter, I usually recommend that patients with Parkinson's try to exercise four to five times a week for at least 20 minutes to start with and more as they build their endurance. But that's really based on just my experience in the clinic. In terms of real scientific proof how much exercise is enough, that's an area we need more research in. And, you know, would a short aerobic exercise be enough or is a longer period of less intense exercise just as good? I have to say we really don't have that answer yet.

Rebecca Gilbert, MD, PhD

Okay. What about, "Have you ever seen any proven remissions of Parkinson's disease in your clinical practice?" And a related question is someone asks, "I have noticed that my sense of smell has started to return. What do you make of that?"

David G. Standaert, MD, PhD

Well, have I ever seen a true remission? No, I've never seen a true remission where somebody who clearly had Parkinson's clearly all the symptoms went away, and they didn't need medicines any longer. Now, of course, the medicines can improve people dramatically. You could take someone who has quite a lot of symptoms and sometimes with the medicines, they could look completely normal on the next visit to the office. And that's great for them, but it does require the medicines to achieve that.

In terms of it just spontaneously going away with no treatment, I've never seen that. I don't know of a really convincing example of that. Some people do progress very slowly, and I have patients who've gone many years sometimes without much change, but in terms of going away entirely, haven't seen that yet.

And then sense of smell can fluctuate some over time. Generally, if you test the sense of smell, and we have a scratch and sniff kind of test that we do, most people with Parkinson's will test out

abnormal. So, it doesn't have to be completely gone, but in Parkinson's usually they don't smell as well as other people. And the only way to really measure that is with these kind of scratch and sniff tests.

Rebecca Gilbert, MD, PhD

Okay. You mentioned a number of clinical trials that are ongoing. If someone is listening and wants to participate in one of those trials, what are the steps they should take? And you mentioned your center is doing trials. How would a person participate in your trial?

David G. Standaert, MD, PhD

So, there are a lot of clinical trials going on. And I honestly think the best tool for finding them is probably the one run by the Michael J. Fox Foundation that's called Fox Trial Finder. It's an online website where you can look up the trials that are in your area. Now some trials do require you to be physically present, and so our particular trial, Alabama Udall Center, involves PET scans and other tests like this. So really, unless you're willing to visit Birmingham several times a year, which is a lovely city to visit, it would be hard to participate from far away, so that one's a little geographically limited. And some studies like that, drug studies, often are looking for people who can be local to a particular center.

There are other online studies though. There are internet studies of Parkinson's that are really important as well. So, I do think that Fox Trial Finder is a really good place to start. Also, if you're seeing a movement disorder expert, they'll often know what's in the local area.

Rebecca Gilbert, MD, PhD

Okay. Wendy asked a great question, which is, "Can some of the therapies you described help you if you've had Parkinson's for a long time? Do these trials require you to be very early in the disease or are some of these trials designed for further along in the disease?"

David G. Standaert, MD, PhD

Well that's an interesting question because a lot of the studies focus on the early part of the disease. Why is that? Well a lot of the studies that are asking if we can alter progression are done with people who are not on any medicines. And the reason for that is the medicines work so well that they can cover up the progression. So, when we try to study progression in people who are taking say levodopa, actually they have no progression for quite a few years because the medicines work really great. So, as a scientific matter, a lot of the studies are testing these therapies in the very early state when there are no other medicines involved to kind of muddy the waters.

But that doesn't mean they're not going to work later on. I suspect they're going to work just fine. For example, synuclein therapy the studies that are going on today are testing them in very early disease for the practical matter of that's where you can see their effectiveness clearly. But if they worked, I would think they'd work just as well in somebody with more advanced disease. So, there's a little bit of disconnect here between where we're testing them and where they may ultimately be used. They may be used much more widely if they're successful than in the sort of narrow audience we test them in.

Rebecca Gilbert, MD, PhD

Thank you. Now you talked a lot about genes and genetic contributors to the risk of Parkinson's disease and how those might be modified to change progression. What about environmental toxins is that something that we need to address as well?

David G. Standaert, MD, PhD

Yeah. That's a very important area. So, genetics clearly does not explain all of the cause of Parkinson's disease. In other words, you know, the genes that we know of are not enough to explain why one person has Parkinson's and the other doesn't. So, the other obvious contributor is what's out in the environment? And there are some things that we clearly know are in the environment. So, for example, high level exposure to pesticides. Very nice work that's been done in California looking at people who live in areas where there's a lot of agricultural pesticide use and crop dusting, those neighborhoods and homes which get high levels of pesticide exposure clearly have an increased rate of Parkinson's disease. Other toxins. We actually have an investigator here, Dr. De Miranda, who's studying a chemical called trichloroethylene (TCE). This is a common dry-cleaning solvent, also was used in the military and aerospace industries for years and is a major contaminant of Superfund sites around the country and that seems to increase risk of Parkinson's. So, I do think there's an environment element.

One of the things that's a little frustrating, I think, for people is there's no way to test that. In other words, Parkinson's has such a long trajectory by the time I see somebody, and I diagnose them with Parkinson's, if they were exposed to something in the environment, it was 25 or 30 years ago. We don't have any good way- There's no blood test that would tell you what was going on 20 years ago, and we don't have really a good way in most cases to reach back and understand what the triggers might be. So, I do think environmental exposure is very important. Certainly, we need to try and reduce our exposure to these environmental toxins and understand more about them.

In the end, there's probably an interplay here between the genetics and the environment that genetics set you up for this and getting exposed to the right chemicals may be the trigger for it.

Rebecca Gilbert, MD, PhD

Okay, thank you so much for that. We have a couple questions about deep-brain stimulation. Any evidence that deep-brain stimulation may have a role in slowing disease progression?

David G. Standaert, MD, PhD

Well that's a really good question too, and that's something that's still being actively studied. So deep-brain stimulation is a very effective treatment for advanced Parkinson's disease. It works really well for wearing off and for dyskinesia. It's an FDA (Food & Drug Administration) approved therapy for those settings and more advanced parts of the disease. But there has been interest in whether doing the DBS early would actually have even more benefit, and how early should you go? There's some experimental work in animals that suggest it might actually slow the loss of dopamine cells. and there have been a couple of trials that have looked at using DBS very early in the condition with some promising early results.

Now, of course, the downside to early DBS is you have an electrical device in your body for much longer, and that gives it a longer time to need battery changes and to develop mechanical problems over the years. So, there is some increased burden to having DBS very early on. But I think this work is really important, and we'll learn more. There are trials going on now that are going to tell us more about how early should we be thinking about DBS. I think the conventional thinking right now is we use it mainly in advanced disease when wearing off and dyskinesia are a problem, but that may change in the next few years as we learn more.

Rebecca Gilbert, MD, PhD

Very good. Thank you. We have a great question about young onset PD. Can you talk about the difference in progression between young onset and later onset, and is there any relationship to controlling disease progression in the different ages of onset?

David G. Standaert, MD, PhD

Yeah. So early onset PD is different. As I suggested earlier, the cause of early onset PD may be somewhat different than later onset PD. So, if your Parkinson's begins before the age of 40, I would consider that an early onset Parkinson's disease. And if you look at the genetics of that, actually, almost half of the people who have Parkinson's before the age of 40 have it from one cause. They have a mutation in a gene called parkin, P-A-R-K-I-N. And these mutations you have to have a mutation in both copies, so you got it from both sides, one from each parent. It means it's autosomal recessive. You're probably not going to pass it on to your children, although maybe your brothers and sisters might have the same problem. Parkin related Parkinson's disease comes on early, often before the age of 40. These patients get a lot of tremor; they get a lot of slowness. They typically do respond really well to the medicine, so they get a big boost from the medicines, and they don't tend to develop the memory problems and cognitive problems that you see in more common later onset

Parkinson's. And, in fact, when you look in the brain, if it causes a parkin mutation, there's actually very little synuclein in the brain. It seems to be damaging the dopamine neurons in a different way so that it gives you a different course, and it may need different treatment. In other words, you may need to replace the missing parkin function in those patients.

So, I think young onset Parkinson's is different, and young onset Parkinson's is a reason to think about genetic testing because you may uncover these specific genetic causes, and that may alert us to different ways of treating the progression.

Rebecca Gilbert, MD, PhD

Thank you. We actually have a few questions from a phone line.

Operator

Our next call is from Dawn from Florida. Dawn, please state your question. Your line is now live.

Dawn from Florida

Yes. I'd like to know your thoughts on cannabis therapy for Parkinson's or the immune system.

David G. Standaert, MD, PhD

Yeah. So, cannabis is very much a hot topic these days, and I have to say we don't know as much about cannabis as we should. I'm very much in favor of more research on cannabis and its component parts. Now one thing to know about cannabis is it's a plant, and there're a lot of different ingredients in there. The two main ingredients that have been studied are CBD (cannabidiol) and THC or tetrahydrocannabinol. CBD has been studied extensively in epilepsy. We've done a lot of work with that. And it does seem to have a very powerful effect in treating seizures in people with epilepsy, and CBD has now been approved by the FDA as a treatment for seizures.

THC seems to be responsible for some of the hallucinations and the euphoric effects of cannabis. In Parkinson's disease, you know, there are very few what I would call scientifically sound studies. I've talked to a lot of patients who've used it. Some of them have found it helpful for tremor and some of the anxiety aspects of Parkinson's. On the other hand, I've found others who've found it's made some of the hallucinations and memory problems worse. It's a bit of a mixed bag, and our information on this is really not very clear.

The other problem with cannabis is it's hard to know exactly what the qualities of the particular batch you get are. In some states where it's legal, even there it's hard to know from day to day what's actually in the cannabis you're getting. And other states, like Alabama where I live, it's still not even legal to have cannabis, so it's very much a patchwork. And I really wish we could do more research

on this and have more scientific information for people because I do think there are potentially useful effects there, but it's very hard to get anywhere with the current state of government regulation of cannabis which makes it very hard for scientists to work on it.

Rebecca Gilbert, MD, PhD

We have a wonderful question from Kayla, which is, "Is there any hope of regeneration of dopaminergic neurons, not just slowing progression?" And tied to this is, "What are your thoughts on stem cell therapies?"

David G. Standaert, MD, PhD

Right. So, what about bringing back the dopamine neurons that are missing, and are there stem cell approaches to this? This is work that's actually going on as well that I think is very promising. We've been talking about stem cells for probably 20 years now, but they're finally reaching the point where that may be an accessible therapy. So, there's a group in New York, there's another one in Japan that have developed a kind of stem cell that makes dopamine. It could be transplanted back into the brain to replace the missing dopamine. The number of people who've been treated with this is probably less than ten in the world, so it's a very early-stage therapy, but I do think that they have done the work to understand the nature of the stem cells and how to control them and how to get them to survive in the brain and produce dopamine. I think we'll see interesting data coming out from that. So those are proceeding.

Another really interesting idea that's emerged – it's been done in animals, not yet in humans – is now that we understand stem cells and some of the ideas about where neurons come from and how they're made in the brain, there are actually ways of taking some of the other cells in the brain. So, the brain has neurons, but it also has cells called glia, and you can actually convert glia back into neurons. So, this has been done in rodents now by several investigators. They inject particular pieces of DNA (deoxyribonucleic acid). They're taken up by the glia, and the glia change themselves from being kind of a supporting structural cell into a neuron that makes dopamine and actually improved the Parkinson's in the animals. So, you're reprogramming a cell that was doing one thing to do something else. It's almost like you took a piece of your liver and made it act like a kidney. This is what's going on in the brain. You're taking a glial cell, which is normally kind of a structural supporting cell, and you're telling it, "Nope, it's time to turn into a neuron and make dopamine." And it actually works. So, there's a way to reprogram the cells you already have in your brain to make more dopamine. This is a very cutting edge kind of work, but I do think there's promise to that too. So, neuro restoration is another thing to think about here, and there's good work going on in this area.

Rebecca Gilbert, MD, PhD

Great. We have a question from Linda. She's in a clinical trial sponsored by Neuraly to slow progression of PD. I think she's referring to a GLP (glucagon-like peptide)-1R activator. Can you talk about this group of medications and how they have some potential to slow progression of PD?

David G. Standaert, MD, PhD

Yeah. So, I guess I would consider them part of the spectrum of immune modifying therapies that are changing the immune function in the brain and perhaps slowing the injury to dopaminergic neurons. And that is one of them. There are several others going after this particular target that are, I think, probably best thought of as really immune modifiers. And this is a really exciting area because I think that if you think about what's going on in the brain of a person who has Parkinson's, if there is an environmental exposure, if they were exposed to a pesticide, that was years ago. If they have a mutation, can't really do anything about that. But what's happening that we could change? We could change the inflammation, and I think this is one of the strategies that people are pursuing to look at that. So, I'm excited to see what comes out of that trial.

Rebecca Gilbert, MD, PhD

Fantastic. This is a related question because that medication that you were discussing, some similar medications are already approved for diabetes. And we have a question, "My husband is in mid-to-late stages of PD and also has diabetes. Can you talk about the relationship between these two conditions?"

David G. Standaert, MD, PhD

Well, yeah. So, there are some medicines that have been approved for diabetes, like exenatide and others, that seem to have some protective properties, at least in animal model systems of Parkinson's. And these are the ones that are being tested in a research basis now. Of course, you have to be careful about this because diabetic medications change your blood sugar, and you can get into serious trouble if you overdo that or really modify the blood sugar can cause a lot of brain injury. So, I think that these things are interesting, but I think you have to be careful and do this really in a carefully controlled clinical trial setting where they're watching all the variables. So, although some of these medicines are available out there, I wouldn't recommend anyone rush out and try them unless you're in a clinical trial where they're really keeping a careful eye on you to watch for side effects.

Rebecca Gilbert, MD, PhD

Thank you. Very important information. We have some more questions from the phone. Operator, could we get another question from the phone line, please.

Operator

Our next call is from Patricia from Michigan. Patricia, please state your question. Your line is now live.

Patricia from Michigan

Thank you. I'd like to know the stats of infrared sauna or cryotherapy or hyperbaric chamber?

David G. Standaert, MD, PhD

Yeah. So that's a couple of different topics of cryotherapy and hyperbaric. Hyperbaric chambers, there's some conditions it's certainly valuable to treat with that. It's been used extensively for wounds, carbon monoxide poisoning; but in terms of the brain in Parkinson's disease, I've not really seen any convincing evidence that hyperbaric oxygen is helpful. In fact, you wonder because some of the mechanism of Parkinson's is related to excessive effects of oxygen and oxidative stress will oxygen therapy increase that or decrease that? I'm not really sure we know. So not really sure that there's a lot of good data on hyperbaric therapy at this point for Parkinson's, although certainly there are other accepted medical uses of that. Cryotherapy I think even less clear. Even in animal models we've not seen a lot from cryotherapy yet, so I think more study is always good, but I've not seen a lot that's very convincing so far.

Rebecca Gilbert, MD, PhD

Okay. We have a quick question from Joel, and this is a general question about clinical trials. Joel's been trying for years to get into a clinical trial and has always found he cannot be on a specific medication or taking specific medications and there's lots of limitations in joining a trial. "Any suggestions on finding trials that you can participate in if you are on medications and don't want to be changing them?"

David G. Standaert, MD, PhD

Right. Well they are very restrictive, and this goes back to the earlier point about when you test something new, you want to do it in a very narrow group of people where you don't have to worry about is this going to interact with some other medicine that this person is on. Of course, if it gets approved, we're going to use it much more widely in many other people. So, I think, again, Fox Trial Finder is useful as a tool because it will let you put some of those exclusion medications in there and working with your movement disorder physician is important too. But it is a problem, and I can understand your frustration at trying to work around that. On the other hand, they want to test the medicine in a small number of people and as simple a situation as possible, and that's why they wind up excluding various kinds of medications from those studies.

Rebecca Gilbert, MD, PhD

Okay. We have a great question from Jim. "Are there any risks of reducing alpha-synuclein too much in the brain?"

David G. Standaert, MD, PhD

That's a good question, actually. So, in a mouse, you can remove alpha-synuclein completely and the mouse is pretty much fine. There are some subtle abnormalities, but they're not drastic. And that's because there are three synucleins. There's alpha-synuclein, beta-synuclein and gamma synuclein; three different kinds of synuclein in the brain. And they seem to have similar functions. So, if you reduce alpha, the beta and the gamma seem to take over the functions that are needed but only the alpha clumps up and causes the damage in Parkinson's.

So, I think most people think that it's probably safe to reduce it somewhat. Now if you reduce it all the way to zero, I think that might not be great; but that's also hard to do, and I'm not sure that's really necessary to stop the progression of Parkinson's. I think that just reducing the amount somewhat may be enough.

Another aspect of this is that some of these treatments are not removing all synuclein from the brain. They're just removing the abnormal synuclein from the brain, so some of these antibodies that are being tested are just stripping the abnormal synuclein and leaving the normal synuclein behind. So, it's a good question.

Rebecca Gilbert, MD, PhD

We have another great question from William. "Can you talk about the microbiome and potential therapies involving manipulation of the microbiome to affect progression of PD?"

David G. Standaert, MD, PhD

Right. So, the microbiome is the billions of bacteria that live in your gut and are part of your daily life because they live with you every day and they go with you everywhere you are. And there is very clear evidence emerging that the microbiome in Parkinson's is different from people who don't have Parkinson's. We've done some of that work here and other people have done that elsewhere. And we actually found that in the gut of people with Parkinson's, there are some organisms that you would normally call pathogens – this is work from Dr. Payami here at UAB who's found some organisms in the gut that can cause infection and can be a problem in human disease.

Now the question, of course, is are they causing the Parkinson's or is it that in Parkinson's you have a lot of constipation and abnormal gut motility and that leaves these things to build up? So, it's kind of the chicken or the egg question; which came first, the Parkinson's or the microbiome? We actually have some work that's funded by the Department of Defense (DoD) where we're trying to look at that. We've taken mice, which overexpress synuclein, so they're a mouse model of Parkinson's. We've made them germ free, so we've put them in a housing unit where they have no bacteria at all, and we are putting back some of these Parkinson's-associated bacteria and asking about whether that influences the condition in the mice. And that's also been done in some other labs, and it does seem that the organisms you put in the gut affect the progression of the Parkinson's in the mice.

Now this mouse work is very early days and comes around to, all right, if this is true, what should we be doing with the human microbiome? Do we know enough to tell you what organisms we should increase and what we should decrease? I'm not sure we know quite enough yet, but we're learning pretty fast. And I think in a year or two, we may be in a better place to recommend what kind of a microbiome people should have. Not quite at that stage, but I do think there's a very important interplay here, and this is really exciting work for the near future.

Rebecca Gilbert, MD, PhD

Great. We have a wonderful question from Romaine. "What is your timeline? How long do you think it will be before a disease-modifying medication is on the market?"

David G. Standaert, MD, PhD

Well, you know, these things tend to happen gradually, right. You get a partial solution, and then you get larger solutions. I would expect given that five years ago we were testing all these things in mice. Now we're doing a lot of things in humans. That's big progress. When will one get actual FDA approval as a disease-modifying therapy? I think you're probably looking on the order of three years or so if these antibody infusions work, which probably are the ones furthest down the road at this point. And will they completely stop Parkinson's? No, but if they slow it down even 10 or 15%, that would be huge. So, I would look for the next three years or so if these trials come to some conclusion.

Rebecca Gilbert, MD, PhD

Fantastic. Now let's take one more question from the phone. Operator, could you open up one more phone line?

Operator

Our next call is from Ann from North Carolina. Ann, please state your question. Your line is now live.

Ann from North Carolina

My husband is currently taking carbidopa-levodopa 25/100. He's taking 11½ pills a day. Is there a max that isn't damaging?

David G. Standaert, MD, PhD
Okay. So, carbidopa-levodopa is, of course, the old standby for treating Parkinson's. It is, without a doubt, the most effective medicine for Parkinson's. Been around since 1969 and is the most widely used treatment. And, no, there's not really a single maximum number. Now as the dose gets higher

and higher, the side effects tend to go up. And that's really the limiting factor, but 11 is certainly not the upper limit. We have patients that take more, but I think it's one of those medicines where you want to just take the smallest amount that does the job. And over the years, you will find that the dose needs to increase and really what limits you is, not the dose itself, it's the development of side effects from the medicine if the dose gets really high.

Rebecca Gilbert, MD, PhD

All right. Thank you very much. We have a question from Franklin. "Is there any evidence that taking an over-the-counter dopamine supplement would be helpful in progression of PD or even in treating PD symptoms?"

David G. Standaert, MD, PhD

Not particularly and most over-the-counter drugstore dopamine supplements don't have a lot of dopamine in them, so it doesn't have a big impact. And if we just want to give dopamine, levodopa is extremely effective at replacing dopamine and is a generic drug of fairly low cost. So, I don't know that there's much advantage to using something else to replace the dopamine with. What we really want to get to is where we don't need to replace the dopamine as much rather than just finding other sources for it. I mean that's the miracle of Parkinson's. We have levodopa, and it's a very good source of dopamine. It does work. But as I mentioned before, it's the side effects of that that get you into trouble in the long run.

Rebecca Gilbert, MD, PhD

Okay. This is going to be our last question. Thank you so much everyone for your wonderful questions. This is a question from Art. "Can you talk a little bit about tea and potentially coffee as well as things that might impact PD progression?"

David G. Standaert, MD, PhD

Well these are things that have come out of epidemiologic studies. So, people have looked at caffeine consumption and both the occurrence and the progression of Parkinson's disease. It does seem to have a small effect. The right dose is somewhere between two and four cups a day. Now those cups are the old six-ounce cups, not a Starbucks Venti, which is a lot more caffeine than that. So, a small amount of caffeine, at least in large populations, seems to have some beneficial effect. I find it's also helpful for constipation, so a single cup of coffee a day is not a bad thing in Parkinson's in most cases. These are not big effects, but they're enough if you have thousands of people, you can see a small effect.

Same could be said for things like green tea, which is high in antioxidants, and that's been studied. And I don't think either one of these is the homerun we're looking for. I think that they're interesting. I

think it's a clue. But in terms of really halting the progression, we need something more powerful than that for our patients who have Parkinson's.

Rebecca Gilbert, MD, PhD

Okay. We actually have time for one last question, and we'll end on an exercise question. You talked a bit about exercise and how it can potentially help the progression of PD. Are there specific exercises, specific ways of exercising that are better than others?

David G. Standaert, MD, PhD

Well that's the million-dollar question. I wish we really knew the answer to that, and there's several things that have been studied. I mean high-intensity exercise has been studied, but also Tai Chi and boxing has been studied and a variety of other exercises. And to me, in the end, I think where we stand right now is that all of the forms of exercise are better than no exercise and really it comes down to what is it you're willing to do? What are you willing to do and do on a consistent basis? And that's probably the best answer for most people. So, what are you willing to do four or five times a week for 20 minutes plus? If that's walking, that's fine. If it's swimming, if it's cycling, if it's Tai Chi, boxing, tango, ballroom dancing, all of those things are better than a sedentary lifestyle and really that's where to start. Now I think research on this question is really important can we find a better answer than that? And I think more study of that is needed.

Rebecca Gilbert, MD, PhD

Fantastic. Thank you so much, Dr. Standaert, for joining us today.

Closing Remarks

Rebecca Gilbert, MD, PhD

[Slide 28] And, again, I want to thank everyone for participating in today's telephone and web education program and for all your wonderful questions. I apologize we couldn't get to all of them. If you have a question and would like to speak with someone from our Scientific and Medical Affairs Department, I encourage you to visit our website at apdaparkinson.org or call 1-800-223-2732, and you can ask your questions there.

[Slide 29] If you enjoyed today's webinar, we hope you will consider supporting APDA with a donation. With your help, APDA can deliver more programs and services like this one which are needed now more than ever during these challenging times.

[Slide 30] And remember to check out the APDA Symptom Tracker, an app that helps you or your loved one track their PD symptoms. The Symptom Tracker is now available in English and Spanish and can be downloaded from the Apple Store or Google Play.

[Slide 31] I also want to emphasize to everyone on the phone and watching that we really do appreciate your feedback and comments and want to make sure that you complete the program evaluation form.

To join us in this fight against Parkinson's and to learn more about the support APDA provides across the country through our network of chapters and Information and Referral Centers, as well as our national research grant program and centers for advanced research, please visit us at apdaparkinson.org. 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.