Transcript

Welcome and Introductions

Stephanie Paul

[Slide 1] Welcome everyone and thank you so much for joining us today. **[Slide 2]** My name is Stephanie Paul, and I am the Vice President of Development and Marketing for the American Parkinson Disease Association or APDA for short. 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. APDA is pleased to bring you this program today.

APDA is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than 1 million Americans with Parkinson's disease live the best life in the face of this chronic neurological disorder. Founded in 1961, APDA has raised and invested more than $170 million to provide outstanding patient services and educational programs, elevate public awareness about the disease, and support research designed to unlock the mysteries of Parkinson's that will ultimately put an end to this disease.

To join us in 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.

APDA is so proud to support those living with Parkinson's by helping them live life to the fullest every day. We do this each year by providing more than 1,700 support groups that serve more than 75,000 people with Parkinson's and their family members and through running 770+ exercise groups attended by more than 21,000 participants. These exercise programs help improve symptoms of Parkinson's and lessen the impact of the disease.

We also offer educational symposia across the country on living well with the disease. These programs have been attended annually by more than 5,500 people impacted by Parkinson's. It's programs like these that distinguish APDA as the national organization working one on one with the Parkinson's community to make each day better.

And now to our program. **[Slide 3]** Our presenter today is Dr. Joel S. Perlmutter, who is the Elliot Stein Family Professor of Neurology, Section Head of Movement Disorders and Professor of Radiology, Neuroscience, Physical Therapy, and Occupational Therapy at Washington University School of Medicine in St. Louis, Missouri.

Today we are delighted to have Dr. Perlmutter share an overview with us about treatment and management options for persons with young onset 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.

You may view the materials for today's program and today's slides by clicking on the Resources tab on your screen. And now it is my pleasure to introduce Dr. Joel Perlmutter.

Presentation

Joel S. Perlmutter, MD

Well, Stephanie, thank you very much. I'm delighted to be here, and I thank you to the APDA, which has done a great job in supporting of Parkinson's disease research, education, and support for a number of people around the country and really around the world. Let us go ahead and begin. **[Slide 4]** And on the first slide, I want to first give my financial disclosures, and these are the sources of salary and grant support I've had in the last couple of years. Honoraria from various societies have asked me to give talks, and my relationship with industry is evidenced by speaker's bureaus and equity and consultant agreements, which the latter two are none, so that I am not influenced by any company in what I tell you.

So, let's start off. Young onset Parkinson's disease, I was asked to talk about that. The first real question is what is young onset Parkinson's disease? How do we define it? **[Slide 5]** And as you can see from this slide, there are multiple ways, and the literature includes multiple studies that define it differently, depending upon the age of onset. So, the average age of Parkinson's, as we'll come to later, is closer to 60 and even 60s and the 70s. But young onset can be defined as less than 49 or so, 45, 40; and juvenile is usually a separate category, starting less than 20 years of age.

So, we're going to talk a little bit about, I'm going to talk about the manifestations of Parkinson's and how some of these things might be different and are different in people with younger onset. And, really, the difference between onset less than 49 or 40 is not a huge difference. It's really a spectrum, and so I'll kind of emphasize that as we go along.

[Slide 6] Stepping right into it, the cardinal features of Parkinson's include the most classic as tremor at rest; and what resting tremor means is that people who have this kind of shaking, the shaking is more apparent with the limb really relaxed, rather than using it. In fact, the shaking typically goes away. It usually starts in one limb, most commonly a hand, but could be in the jaw, the head, or even a foot and, with time, frequently spreads to the other side.

Now I've said that we call it resting tremor because the tremor's usually present with the limbs at rest, but not everybody reads the book who has Parkinson's; and so sometimes with the arms outstretched in front of an individual, the resting tremor, even with the limbs outstretched in a posture-holding position, occasionally can recur. And so, we call that a re-emergent tremor. So, some people with Parkinson's have resting tremors. Sometimes that tremor persists with action.

Second cardinal feature, major feature, is bradykinesia and akinesia; and that's just really two different things, actually. Bradykinesia refers to slowness of movement. Again, that's more typical to be asymmetric or more prominent on one side. It's usually a side, if there's tremor, to be on that side. And this can be a functionally disabling problem because it can lead to difficulties, for example, buttoning or writing. And, in fact, a characteristic of this kind of bradykinesia is that as one continues emotion, the amplitude of those movements gets smaller and smaller. So as one initiates writing, the letters may initially be normal size. But as writing continues, the letters become smaller and smaller—the so-called micrographia of Parkinson's. And so, bradykinesia can be a real difficult problem because it interferes with a lot of fine motor activity.

Akinesia, on the other hand, which would seem to be the extreme or total lack of movement is really something different. Akinesia is a lack of spontaneous movement, and so that's an individual may have less associated movements that occur spontaneously. For example, sitting in a chair, the eyes may blink less frequently. There may be less spontaneous expression on the face. The little bit of normal fidgety movements of the hands may be diminished, and so that's more statute-like appearance.

The severity of that akinesia does not even correspond to the severity of the bradykinesia. They really are two separate things, even though we group them together as this second cardinal feature. It's really 2A and 2B.

The third one is rigidity, and rigidity refers to a stiffness of muscles; and so, we test that by just moving the arm back and forth or rotating the neck front to back or the legs or rotating the wrist around. And this is a sense of stiffness in the muscles, and a lot of times people complain of stiffness and soreness; and their doctors may think they have stiffness in the joints and misdiagnose this as arthritis. And, in fact, it's really muscular stiffness, and that's the rigidity of Parkinson's that can lead to low back pain, for example. Some people notice this. The rigidity, like the bradykinesia, like the tremor, tend to occur on one side more than the other. And, again, it's usually the same side. If the Parkinson's is more severe on the right, it's usually all the manifestations are more severe on that side. Although that's not entirely correct for everybody, but most people, and that's probably 95% or more.

A much more disabling manifestation of Parkinson's is postural instability, and this is difficulty maintaining balance. And people with Parkinson's have this in a particular type of fashion, and that is side-to-side stability is usually not so impaired. But front and backward stability is really the worst, so that in people with Parkinson's, if they tend to lean backwards, they may fall backwards. So, for example, a common admonition or warning for people with Parkinson's not to climb up ladders because as you climb up a ladder, you tend to shift the center of gravity backwards; and that's not the first place you want to identify postural instability, because that can be devastating. So postural instability can be a major problem with Parkinson's as well. Again, all of these features, every person doesn't have to have all of them. Usually they have at least two to make the diagnosis.

A fifth area that's not always called a cardinal feature, but it's really quite apparent, is the abnormal gait. And that starts with abnormal posture, and people tend to be flexed. In other words, the arm, the elbow may be more flexed, the wrist may be flexed, the shoulder forward, the knee bent, the hip

forward. And, again, the flexed posturing may be more apparent on the side with the more severe Parkinson's; and this also can lead to abnormal gait with slow shuffling steps. Sometimes the gait becomes running because it's hard to stop, and we call that a festinating gait.

And so, as people walk with Parkinson's, their steps may be slower, there may be shuffling, that foot on the side where the Parkinson's is more severe may drag a little bit. The arms tend to swing less; and, in fact, the arm may swing even less on the side that's more affected. And so, all of these things together are the most common cardinal features of Parkinson's disease.

[Slide 7] Another key feature of Parkinson's is freezing, and this is something that can develop and can be a major problem for a lot of people, and freezing is really a sudden cessation of movement. And it's most common when first trying to start walking, and that's gait initiation. So, if somebody gets up from a chair, instead of just being, to move right out, it may occur that their feet feel like they're stuck to the ground. The foot on the side that's more affected may feel even more stuck than the other foot, and the problem here is the internal cues or what's inside your head to tell you to get going is not working as well. And so, providing some external cues like step over a line or step over foot can help break that freeze.

And freezing can be a problem, especially people with postural instability because it can be a time from which people can fall. And so, gait initiation is one place freezing commonly occurs, going to turn is another place that freezing occurs, going through a narrow passage, doing more than one thing at a time like holding something or putting on a coat, and then stress. And if you take all those things together, a common story that I hear is somebody's late to go out with their significant other, they grab their coat, they're trying to put it on, they're walking, getting up to the doorway, they freeze, and their significant other yells at them, "Come on, we've got to get going." Boom, they freeze, and they fall because they've done everything. They've tried to go through a narrow passage; they're dual tasking because they're trying to put on a coat. They're stressed, and all of those things lead to a freeze.

And so, freezing can be a major issue that we have to address with therapeutic type strategies, including physical therapy and occupational therapy can help to address that. Medication sometimes helps as well, but freezing can be a problem.

It's most commonly seen with walking. It's not exclusively that. It can be much less commonly with hand movement. So, while doing some activity to a hand, the hand suddenly freezes and stops.

[Slide 8] So how do we improve walking and reduce freezing? So, there have been a number of studies over the last 10 or 15 years to address this, and one of the hot new areas was dance, specifically Tango. And Argentinian Tango, with its repertoire of various movements was thought to be particularly good and could help gait. There was good evidence of gait improvement. There was good evidence of quality of life improvement. Then it turned out Waltz could do it, Foxtrot, Tai Chi, and strategies just saying take big steps and ways of trying to do that or enhanced external cues. And by external cues I mean if one's walking, one could have music with a strong beat; and that beat can help be an external cue for taking an additional step to help break a freeze or make steps longer or even projecting a line on a walker in front of you as you're walking, and you constantly step over that

line. So, there can be visual external cues, there can be auditory that we hear external cues, lots of things.

The real bottom line is almost any exercise program can do a good job with this, and there's increasing data that a number of different approaches can be important for that, and I'm coming at that with my physical therapy perspective as well.

[Slide 9] In addition to those kinds of motor problems, another classic manifestation of Parkinson's is soft, what we call hypophonic, means soft speech. Now the soft speech, like the walking and like handwriting, can have the equivalent of bradykinesia with it; and that is speech may initially sound good, but then as one continues to talk, the speech gets even softer and softer. And so, if you could hear what I was saying, my lips and tongue were having less and less excursion as I was continuing to talk so the words became less clear because I wasn't pronouncing the words as clearly. So that was the dysarthria or lack of clarity. And sometimes, like walking for some people where they, what we call festinate, start to walk and they just keep going faster and faster with smaller and smaller steps till they fall.

Speech can do the same kind of thing. So, speech can get really fast (mumbling, increasing in speed) and sound just like that for some people. For some people, the speech can be a major issue. That's one manifestation of an oral pharyngeal or a mouth-type problem.

Another manifestation is chewing and swallowing problems. The most common thing that's a problem can be moving food from the front to the back of the mouth. That's the most common thing we see. And then, in addition, **[Slide 10]** if we look at this particular slide, it's showing you on the left side of the image a diagram of a person where their food comes into their mouth, it goes to the back of the throat, down that pharynx that it's showing you, and then normally travels down the esophagus to the stomach. Now I say "*eso-pha-gus"* because my anatomy professor almost 45 years ago was from South Africa, and that's what he called it, esophagus. And so, I maintain that affectation.

But in any event, what can happen in Parkinson's as we swallow, instead of going down the esophagus, it can go off into the windpipe, and that is aspiration, where food goes the wrong way. And that can occur with liquids or solids, and people may not even be aware of it. And the danger in that occurring is that can make an individual more susceptible to pneumonia.

On the right side of your image is, actually, a frame from a video fluoroscopy or a video x-ray image. And this particular person, which is less clear, is actually oriented exactly like the left side of the image. And so up above would be the head turned toward your left side of the image, and what they did is they swallowed a tablet coated with barium that we can see on an x-ray ten minutes before this picture was taken. And that tablet, pointed out by the arrow, is stuck right near the entrance to the airway; and so, this person is showing how they have trouble with swallowing pills. And their pills don't work for their Parkinson's until they get down in the stomach and then are passed from the stomach into the small intestine, so that could be another reason for delay of medication working. But swallowing problems and speech problems are common in Parkinson's disease.

[Slide 11] Now in addition to those other motor problems, there are what we call the autonomic nervous system, and these are the nerves that go out to various parts of the body that have to do with

a number of different kinds of problems, including excessive salivation, too much saliva made, which can lead to drooling. But drooling is not only because of too much saliva, but it's also because with Parkinson's sometimes there's difficulty just swallowing the normal drool or moving the mouth to move it to the back. So, then it may be tend to drool out, again, the side that's more involved with the Parkinson's.

Constipation is very common and may precede other Parkinsonian symptoms by many years. And, in fact, when I talk about the pathology in just a moment, you'll see that people with Parkinson's may have pathologic changes in the intestine; and these changes may, in some theories, maybe that's where the pathology of Parkinson's actually begins and then goes up nerves to get into the brain. That's one thought.

Bladder problems also may occur with difficulty emptying the bladder and dribbling. In men that can be confused with prostate problems, but women can have the same type of problem, as can men, from Parkinson's autonomic nervous system. The autonomic nerves actually help control bladder function.

Orthostasis refers to a sense of lightheadedness when going from either a lying or sitting position to a fully upright or standing position. And what happens is the blood pressure drops, and normally when we stand up, an individual stands up, you do a number of things to keep the blood flowing up to the brain against gravity; and a lot of those things are not working properly with the autonomic nervous system dysfunction that may occur in Parkinson's.

For some people, this is sufficiently severe that every time they stand up, they pass out; and that can be a major problem, and almost all the medications I'm going to talk to you for treating Parkinson's disease tend to make that worse. So, there are some ways of strategies of addressing that specifically.

Sexual dysfunction may occur in people with Parkinson's. In men, this is erectile dysfunction. In women, they can have difficulties with lubrication, as well as both men with ejaculation and women with having orgasm.

Heat intolerance. We're passing that phase of the time of year, but we see that a lot in Parkinson's. People have difficulty maintaining their temperature, controlling their sweat regulation.

And convergence problems really refers to what you do with your eyes. So, if you're looking in the distance, and then you try to look at something close by, there are a number of mechanisms that go on in the eye to permit you to focus nearby; and that's called convergence. And that can be dysfunctional or not working well in people with Parkinson's and make it difficult for people to read and actually follow along the line for reading. Again, these things don't have to occur in all people, but they may.

[Slide 12] Psychiatric problems also may occur, and one of the most common is apathy; and that is a lack of motivation. So, some people will be more than happy just to sit in their chair in their living room and not really do much until their significant other gives them a little kick in the backside, and that can occur. A lot of people interpret that, a lot of caregivers, a lot of physicians interpret that as depression.

Depression can manifest that way, and depression is more common in Parkinson's than not in Parkinson's; and that's showing the right side of this slide. This is now looking at 423 people with Parkinson's, newly diagnosed, compared to 96 age-matched people without Parkinson's and following them over time and looking at the percent of those who have depression, and it's really much higher in Parkinson's. In fact, it's higher than people matched who don't have Parkinson's but have arthritis to cause the same kind of movement problem that people with Parkinson's may have or similar disability, and depression is higher. It may be part of the Parkinson's, rather than just a reflection of the disability.

But apathy, again, has to be distinguished from depression alone by talking to somebody and asking them if they're sad and down in the dumps, and a lot of people are not and are just apathetic and lost motivation. So, it's really two different things.

Anxiety disorders may also occur, and that can be a big problem, and so can psychosis or seeing things that aren't there, in particular, thinking bad things are going on.

People with young onset Parkinson's tend to have a higher rate of depression than older onset Parkinson's, and so that's one of the first things I'm telling you now about the distinction. The other thing I forgot to tell you when we were talking about tremor, tremor is actually a little less common in young onset Parkinson's than older onset Parkinson's.

[Slide 13] Now, there also are three other areas that may occur long before the motor manifestations of Parkinson's, and one is called REM behavior disorder; and this is acting out dreams. So, REM means rapid eye movement sleep. Normally when we fall asleep, we go through various stages of sleep; and when we get to the REM phase, that's when we dream. And when we dream, our muscles are cut off and they don't engage, except for breathing and heartbeat. But with REM behavior disorder, the muscles don't disengage. In fact, they remain engaged, so the activities that we dream about we do, which can be dangerous for bed partners because they can get kicked or hit; and there can be screaming, acting out the dreams, and even falling out of bed. And this can precede Parkinson's manifestations by many, many years. Restless legs, a creepy crawly feeling in the legs that occurs at night, immediately goes away on standing, also may occur ahead, as can reduced sense of smell or olfaction. And since smell is a large component of taste, people with Parkinson's may complain about reduced taste as well.

[Slide 14] Now the progression of Parkinson's, it always progresses; and for people with Parkinson's that starts over age 70, in that range, their lifespan is shorter than what it would otherwise be and is, on average, about 9 years. Not a lot different from life expectation at that age without Parkinson's. Young onset, however, has a much longer survival, and so with young onset, the survival, on average, is in the range of 32 years. There's a lot of variability in this, but the point is people with Parkinson's that have younger onset tend to live a lot longer.

The other thing that this slide is showing was a nice study done by Carly Tanner in Northern California is that people who have predominant tremor initially, and not everybody with Parkinson's, so a third of people with Parkinson's have no tremor, but sometimes people get divided up into tremor-predominant so early tremor or lack of tremor and just trouble with walking and stability. And the people with tremor tend to live a lot longer, and that's what's showing in this survival curve. That

upper curve is showing the lifespan of people with tremor versus the lifespan and the lowest curve of those three, people without tremor at all.

[Slide 15] Now what about the age of onset? What is average we've talked here? So, in a community study that was done, an average age of onset, and this was done by the Wickremaratchi group. They did a community-based study, went door to door and evaluated people; and they found the average age of onset was in the late 60s to early 70. And of that group, a small percentage had Parkinson's beginning before 45 years of age; and that group was about 3.6%. You can contrast that with my center which is different because it's a tertiary care center, so we tend to get the more unusual things sent to us, so it's not a good epidemiologic study. But in our center, 8% of our people have onset before age 40, so we see this a lot. And the average age of onset overall in our center is 61.

[Slide 16] Now we know the risk of Parkinson's increases with age, and this is work that Brad Racette and Allison Willis, Wright-Willis at that time, did based upon Medicare data; and they found that the prevalence or the point prevalence of Parkinson's increased with age so that by the time people were in their 80s, 3% of the population had Parkinson's. Now that means the risk increases with age, but since there are a lot more younger people, still the average age of onset can be around 60.

The other thing we found from that study is men have it substantially more commonly than women, **[Slide 17]** and the ethnicity involvement is different, so if we look at, and this is, again, their study. Asians and Blacks in this country tend to have a much lower risk of Parkinson's disease than Whites and Hispanics.

[Slide 18] Now what's the underlying cause of Parkinson's in the brain? We know that there's deposition, deposits in the brain of abnormal alpha-synuclein, and that's deposited inside nerve cells; and on the left side, in the lower part of the picture, that's a cross-section through the upper part of the brain stem, in the back of brain, we call the midbrain. And on the person without Parkinson's, in that cross-section you see those two brown streaks? That's melanin in an area of the brain called the substantia nigra, and on the right side in a person who had died who had Parkinson's disease, the melanin is lost; and the nerve cells in that area are degenerating and there are many fewer. And in the remaining ones, if you look to the arrow to the right, there's what we call Lewy bodies, and these are stuck in the remaining nerve cells. And these are areas of a whole bunch of protein stuck in there, and one of the main proteins in that area is called alpha-synuclein. And these nerve cells, if you look to the image right above now on the right side of the image, the right side of your slide at the top, that's a cross-section of the brain looking towards the face. And two arrows are pointing, one on the right's pointing to what we call the caudate; the one on the left is the putamen. Together we call them the striatum, and that's where those nerve cells from the substantia nigra send processes up; and they use dopamine as their chemical messenger. So, there's a deficiency of dopamine in the brain in that area.

[Slide 19] And, furthermore, that alpha-synuclein can spread; and it normally starts, if you look at that side view of the brain, in the middle of the image here, that black part is, that lower part of the brain, that alpha-synuclein starts there and then spreads up higher and then may, in fact, affect higher parts of the brain that can lead to cognitive or thinking problems. And people with Parkinson's are at higher risk of developing dementia or troubles with their thinking.

In fact, people with young onset Parkinson's are less likely to be affected by dementia than older onset people with Parkinson's, and we know now that the dementia of Parkinson's is associated with the spread of alpha-synuclein out into the outer parts of the brain, the cortex we call it. And there also may be another abnormal protein, Abeta amyloid, which is associated with Alzheimer's disease; but Alzheimer's disease also has something, another protein called tau. Alzheimer's has Abeta amyloid and tau whereas Parkinson's is just alpha-synuclein. But alpha-synuclein plus Abeta. Having tau with Parkinson's or full-blown Alzheimer's disease seems to be much, much less common in people with Parkinson's disease.

[Slide 20] Now how come people get this? So, one cause is a genetic reason, and that bottom line for that is that genetic factors, in total, probably contribute 20 to 25% of the risk of people with Parkinson's. But having risk means we can identify factors that put people at higher risk but doesn't mean they're necessarily going to get Parkinson's. A specific genetic mutation or genetic defect that causes Parkinson's does occur. The first one was found in a defect in the gene that codes for alpha-synuclein, that protein. But these known specific genetic defects are quite rare; and so, in general, if we looked at all the people in my center, of those, the most common one is this one called LRRK2 or "*lurk2*." And that's the most common genetic defect that causes Parkinson's that we know about. And having said that, in my center with a person who doesn't have a family history of Parkinson's, the chance of them having this genetic defect is less than 1%. If they have a family history of Parkinson's, a first-degree relative, a mother, father, brother, sister, child, then their risk, in our center, is a little less than 3%, so it's still very low.

There are a couple exceptions, however, that we know about. If there's a family history of Parkinson's in somebody who's an Arab from North Africa, then the risk of having that LRRK2 gene is 30 to 40%. And Jews from Eastern Europe, so-called Ashkenazi Jews, if they have a family history of Parkinson's, the risk of having LRRK2 is about 19%. So, there are some genetic factors that are of greater risk, but there're also clearly environmental factors.

[Slide 21] But what is Parkinson's? I've kind of talked about Parkinson's disease and Parkinsonism; what's the difference? Parkinsonism refers to those symptoms—the slowness, the stiffness, all the symptoms. Parkinson's disease is that group of illnesses that have the abnormal alpha-synuclein deposition, have these genetic defects that specifically cause it. But anything that interferes with the transmission of dopamine in the brain can cause that, and there are a number of other disorders in the brain that affect these neurons but affect other parts of the brain too and can cause Parkinsonism but that are not Parkinson's disease.

And so particularly in somebody with young onset Parkinson's, what are the other kinds of things that we need to be thinking about if somebody develops the symptoms of Parkinson's? **[Slide 22]** And the other kinds of things we need to think about specifically, is it one of the rare genetic ones, because some of the genetic things are more common in younger onset people. Has that person taken a medication or a drug that can produce Parkinsonism that, in fact, may be totally reversible. I see that all the time. And so, drugs, for example, for nerves like aripiprazole or Abilify® that you hear about or drugs given for schizophrenia, some drugs given for stomach problems like Reglan or metoclopramide, these are drugs that actually block dopamine's action in the brain and can

absolutely cause the same manifestations of Parkinson's disease; but they're not Parkinson's disease. They can just be Parkinsonism; and, in fact, it may be totally reversible.

As I mentioned, there are other neurodegenerative diseases that also can cause similar symptoms; and another one that's very rare is a disease we call Wilson's disease. It's a problem with maintaining or metabolizing and dealing with copper in the body. This can also produce very typical parkinsonian features in a young person, so it should be checked in somebody who has very young onset because it's a disorder that can be absolutely treated and fixed.

[Slide 23] How do we treat Parkinson's; the mainstay is to replace the missing dopamine. If we gave people dopamine, they would just throw up. So, instead, and it won't work because it doesn't get into the brain, instead we give the immediate precursor of dopamine called levodopa or L-dopa; and that gets converted by an enzyme to dopamine. And if we give it to people, they also will throw up because they'll convert their L-dopa into dopamine in the rest of their body instead of the brain. So, if we add to that what we call carbidopa, and that's on the next slide, **[Slide 24]** carbidopa blocks the conversion of L-dopa to dopamine; and that's blocking on the left side of the image, the AADC of the aromatic, the decarboxylase; and then that permits the L-dopa to get into the brain. And there the L-dopa can be converted to dopamine because the carbidopa doesn't get into the brain, and so that's been a great step forward, and this helps a lot of people.

[Slide 25] And then you can see this is the typical response early on; and it's a very complex slide, I can tell you that. But it does get more complex in a bit. And that is initially you can take the L-dopa, almost just sniff the bottle, and then with time, that's hours across the lower scale there, people do better. On means doing well. Off means they have Parkinson symptoms. And this is very gratifying early on, **[Slide 26]** but as the disease progresses, individual doses of the medicine may last a shorter period of time; and we call that wearing off. And the figure on the right is now showing you in the filled triangles, those are the curves of a single individual from top to bottom over the course of four years that their blood level, that's the closed triangles or the dark triangles, stayed the same. The blood levels after a single dose doesn't change, whereas the other curve, the one that goes out, is the clinical response, which initially at the top figure is long-lasting. But as we go down, it gets narrower and narrower so that there is more and more wearing off as disease progresses.

[Slide 27] Now there are other approaches to treatment. We can give drugs, and one approach was to give dopa. It gets converted to dopamine, and what you're seeing here is a picture of a nerve coming up from the substantia nigra, that's the arrow, and it releases the dopamine and hits this receiving nerve, the so-called postsynaptic neuron. And when dopamine's released, it has to hit a dopamine receptor that receives it and to, essentially, communicate its message to the next nerve cell.

[Slide 28] We can give drugs that go directly to dopamine receptors and bypass dopamine altogether, and the list of those drugs are things like, in this country: pramipexole; bromocriptine; ropinirole; rotigitine, which can be given by patch; apomorphine, which has a rapid onset of action given by a subcutaneous injection. All of these medicines are a little less potent than L-dopa. Some of them can last much longer than individual doses, particularly the patch. They all have greater risk of side effects, compared to L-dopa, from each individual dose; and that is they can make the

orthostasis, the drop in blood pressure, cause people to see things, cause compulsive behaviors, a whole host of these things that you're seeing right there. But they're one of the other choices that we have for people with Parkinson's.

[Slide 29] Now as the disease progresses, an individual dose may last shorter, as I mentioned to you, and then also individual responses can include abnormal movements just from the medicine. So as the medicine's kicking in or wearing off, people can get twisting of different parts of the body, so-called dystonia. And that can manifest as cramps, like in the legs; and you see the picture of that person who has dystonia as his medicine's kicking in with twisting of his legs and his feet and ankles and arms up in that last five or ten minutes for him and then wears off. Other people get writhing-type movements we call dyskinesias. We know people with young onset Parkinson's are more likely to get dyskinesias than older onset Parkinson's.

[Slide 30] Another approach is to treat and try to smooth out the responses, to treat Parkinson's with continuous administration of the L-dopa. L-dopa is not very soluble, so you can't really just infuse it directly under the skin; but you can get a form that's called the L-dopa gel and give it through a tube that goes directly through the belly wall, into the stomach, and down in the small intestine. And this gel can be infused continuously to give us good blood levels, and what you're seeing in this first lower slide below the guy's belly is in the beginning there's some side effects associated with putting in this tube; and after a couple of weeks, it pretty much levels off.

And then on the figure on the right, you're showing, in the lower part of the figure, they have more off-time; so, there is less time when the medicine's not working and more on-time when the medicine is working, so it really can help some people. But the dose of dopa that they end up getting is, if anything, more than what they had before. So, if they had problems with drop in blood pressure, things like that, this is not a good choice.

[Slide 31] Another option is deep brain stimulation, and this is such an electrode that we can put into the brain. This wire contains four little tiny contacts that can be put into the brain, and this pulse generator you see between that person's fingers that are holding gets implanted under the chest wall.

And how do we do that? **[Slide 32]** We do that a couple of different ways, but one approach is to put a frame screwed into the skull, that we numb up those areas, and then we can take an MRI and identify exactly the spot we want to hit, which is deep down into the brain down here, which is, on the image on the right, is an MRI scan; and the dots are the dots from the frame. And the target we're actually aiming for is kind of in that dark spot near the middle on either side; and that's called, in this case, the subthalamic nucleus. And another place in the brain we hit is the internal segment of the globus pallidus. These are two parts of the brain in the area of the basal ganglia that we target.

But they're kind of deep in the brain, so how do we know where we are? **[Slide 33]** With this frame and the MRI, we can target it pretty well. But pretty well is not good enough, and so looking at how the surgery actually is, and this is done with the person awake, we have that frame on, and we can get near that area. But then you see in that skull x-ray above, we're showing you at the upper left of the skull x-ray the kind of trajectory of how this electrode goes down into the brain. And as it goes into the brain, in that raster, the diagram below the skull x-ray there, you're seeing nerve cell firing; and

so, we can record the electrical activity of the nerve cells and identify the precise location to implant this electrode. And it can be very dramatic and help a lot of people.

So, there's a number of medication treatments, there are different ways of giving medicine, lots of different approaches, which I can't go through in this quick time, and there's deep brain stimulation which is being done.

[Slide 34] What is another important factor is who's treating you, and this is another study by Allison Willis, and this is looking at lifespan or survival, based upon Medicare records. Again, about 455,000 people in the Medicare records with Parkinson's; and people lived longer if they were treated by a neurologist compared to their primary care doctor. And that's what you're seeing in green is their survival, and this is predominantly older onset. But younger onset, it's probably even more important.

[Slide 35] So in summary, tremor is a little less common in young onset. Family history of Parkinson's is more common in people with young onset. There tends to be more depression in people with young onset. People with young onset tend to have more dyskinesia. They're less likely to have dementia or thinking problems, and they certainly survive a whale of a lot longer than older onset people with Parkinson's.

I think at that point I'm open to questions.

Stephanie Paul

Thank you, Dr. Perlmutter, for this very comprehensive and informative presentation.

Question & Answer

Stephanie Paul

[Slide 36] It's now time for the Question & Answer session. I would like to remind all of you that we have hundreds of people on the phone and on the Web. For everyone to benefit, please keep your questions general in nature; and Dr. Perlmutter will provide an answer that is general in nature.

Okay, Dr. Perlmutter, we'll take our first question from the Web; and this comes from Kimberly in Maine; and her question is, "Is there a correlation between young onset and a faster progression of symptoms?"

Joel S. Perlmutter, MD

Well, absolutely, and so that is one of the slides that I showed and that people with young onset survive, actually, substantially longer. As I said, on average, about 32 years, compared to 9 years in people who have older age of onset, so the disorder tends to progress much more slowly. However, dyskinesias, or the involuntary movements associated with treatment, are more common in the younger onset; but thinking problems tend to be much more delayed and much less common than in the older onset people, so there is that relationship.

Stephanie Paul

Okay, thank you, Dr. Perlmutter. We have another question from the Web. This comes from William in Florida, and the question is, "Has Gocovri™ (amantadine) been studied in young onset Parkinson's disease population?" That's the new drug that's come out for levodopa-induced dyskinesia.

Joel S. Perlmutter, MD

This is, actually, that drug is a very old drug, amantadine. So, amantadine's been used for many, many years for Parkinson's, and so Gocovri, a major advance here is instead of taking it two or three times a day, you take it once a day. So, otherwise, no difference. So, it has been used in young onset. In fact, it's almost exclusively used in younger people with Parkinson's, not older people, because it's not tolerated well in older people. So, most of the information we have about using amantadine in younger onset is, in fact, from younger people because they tolerate it much better. Older people have trouble with thinking problems from this, drops in blood pressure, difficulty with bowel and bladder function.

Stephanie Paul

Okay, terrific, that's great clarification. Thank you for that. We have another question from the Web. This comes from Bob in Iowa, and he would like to know more about how exercise affects Parkinson's disease. How often should one exercise, and how intense does the exercise need to be?

Joel S. Perlmutter, MD

Right, so this is an increasingly active area of investigation; and what's increasingly clear is that exercise is critically important. It looks like more exercise might not only improve quality of life, but it may, in fact, slow the progression of disease, although we need more data one way or the other about that. How each individual exercise program carries over, in other words, if you do exercise today, does it help you next week or do you have to repeat it in three days or repeat it every week? And how much do you have to do each time, this is intensely being researched right now, and there are different kinds of exercise programs. It's very clear that a regular exercise program is important. The specifics on that remain to be determined for what's optimal.

Stephanie Paul

Okay, terrific. We're going to go in a little bit of a different direction now. We have a question from Drake in Michigan, and his question is, "When is deep brain stimulation not an option?"

Joel S. Perlmutter, MD

Deep brain stimulation is not an option if the person does not have regular Parkinson's disease. It will not work, and it may cause substantial side effects.

Another stopper for deep brain stimulation is dementia. If people have substantial cognitive impairment, putting in stimulators, if anything, may make that worse. So that's a major no-no. As far

as age, there is no age limitation on either end; and so that has worked. I usually have the approach if pills work, don't make two holes in your head. But that approach is varied from place to place. Other people tend to do it earlier. I'm not sure the data warrants that.

Stephanie Paul

Okay, thank you. We have a question from Georgia from North Dakota, and the question is, "How effective do you think DaTscans are? I'm 42 years old, diagnosed at 38. I recently underwent a DaTscan which showed decreased uptake bilaterally, but I currently only have right-sided symptoms."

Joel S. Perlmutter, MD

Well, Georgia, you're asking the right person because my area of research is neuroimaging, but let me be very direct and very clear about this. I think it has very limited to almost no role. That's different from what a lot of people will tell you, and that's because I do neuroimaging research, and I understand it quite well. So, I think there is no relationship. In fact, the data that we've been publishing in the last several years shows that that imaging, which is incredibly useful for research, can show in the very early stage it can relate to the amount of change that we see in the brain. But once the very earliest stages of that brain change occur, DaT imaging becomes totally noise because it no longer reflects severity of disease, so I don't think it's useful for predicting anything.

Stephanie Paul

Okay, thank you. I believe we have a phone caller, so let's go to the phones at this time.

Operator

Thank you. Our first phone question comes from the line of Mark from Connecticut. Please go ahead.

Mark from Connecticut

Yes, my question was already answered. I was interested in what type of exercises were helpful in relieving the Parkinson's symptoms.

Joel S. Perlmutter, MD

Yes, and so, again, it depends on your specific symptoms; and so there may be different exercise programs that are pertinent for each individual and what you like to do. But those exercises that you will, in fact, do and stick with are going to be the most important and that don't cause repetitive strain injury.

Stephanie Paul

Okay, thank you. We have another question on the Web, and this comes from Marlena in Texas, and her question is, "Are there dietary restrictions with regard to limiting protein that may be helpful in preventing off periods?

Joel S. Perlmutter, MD

Okay, so this is a very interesting issue and is one that's been studied for more than 30 years now, and the answer is, theoretically, absolutely yes. And let me tell you what the basis of that is.

When L-dopa gets into the brain, actually, it has to be absorbed to the gut and then get into the brain, there's an area that separates the bloodstream from actually penetrating the brain. It's called the blood-brain barrier. L-dopa crosses the blood-brain barrier by a very specific carrier system, and it's the same carrier system that takes across large neutral amino acids. Amino acids are the building blocks of protein, and there's 20 different amino acids, but there's a group of them that are large neutral amino acids. It's just a certain kind.

L-dopa looks just like those. So, for some people, a large protein meal that contains a lot of large neutral amino acids may interfere with the L-dopa getting in and can cause them to turn off. And so, the classic is somebody does great all day, they go home and have a steak dinner, and then they're a slug and their spouse yells at them, "You're not helping around the house." Well, that's because they ate the steak dinner.

Now the reality is for most people it doesn't make a measurable difference. Some people are very sensitive to the amount of protein, and for those people, we do not recommend a low protein diet, rather you just spread out the protein and adjust the amount of L-dopa to compensate for it. In the old days, we tried very low protein diets, but those things are probably not, that's passé. It's probably not the appropriate approach any more.

Stephanie Paul

Okay, thank you. Here's another question from Tom in Massachusetts, and the question is, "What is the status of stem cell therapy?"

Joel S. Perlmutter, MD

Yes, well, first of all, let's talk about what stem cells are. Stem cells are cells that have not yet decided which specific kind of cell they want to become, so they're kind of like little babies, sometimes teenagers, until they grow up and find a particular profession. Stem cells can come from fetal cells. One source of cells that has the most controversy. In addition, stem cells can be drawn from brown fat. Stem cells can be drawn from skin. And, in fact, that's the biggest push these days is to be able to go to skin biopsies because now, all of a sudden, we've eliminated a lot of the controversy and ethical concerns that some people have about using fetal tissue.

So, stem cells can be coaxed into making nerve cells that produce dopamine, so it can be a way of producing dopamine, making those, and injecting them in the brain. Taking the stem cells from your brown fat and injecting it into your veins or up your nose, as is commonly done in a number of operations across the country, is, I think, quackery, if I can be so direct, and a way of taking money from you.

Stem cells, on the other hand, the other way, can be coaxed to produce dopamine neurons, can be put in the brain, can be effective. The problem we have right now is we don't know how to control them. We don't know how to control the dose. So, in a study done a number of years ago, some stem cells that were taken from fetal tissue were put in the brain; and it produced so much dopamine it caused side effects, and people had to go in and destroy some of those cells. So, it's another way of delivering dopamine. It doesn't cure the disease, but it is a way of delivering dopamine but a little bit more work on how to control the dose still needs to be done.

Stephanie Paul

Thank you for that really candid answer, Dr. Perlmutter. We have another question from the Web. This is coming from Kathy, who is in Virginia, and her question is, "Is there a benefit in delaying medication?"

Joel S. Perlmutter, MD

Ah, what a hot topic that is. So, there are people who believe that giving L-dopa can also cause damage in the brain, and so they want to avoid it as much as possible. There are other people who believe that when you do that, it makes the risk of getting dyskinesias worse. I think there's now substantial evidence showing that those things are wrong. That's my opinion.

We've learned from studies that would give dopamine agonists, those other drugs like pramipexole, ropinirole instead of dopa when somebody's first diagnosed, in the hopes that they wouldn't develop dyskinesias down the road, what those studies demonstrated is people who tried to stick it out with these other medications that are not as potent as dopa, lost their jobs, had poorer quality of life. So really, I think the answer is take the amount of medicine that provides the benefit you need and not higher than that. Okay, so you would reduce your risk. But I think the data that dopa actually harms the brain cells is very limited, and I don't think it's actually very convincing.

Stephanie Paul

Great, thank you for that. I believe we have another person who is calling out on the phone who has a question.

Operator

Yes, our next phone question comes from the line of John from Delaware. Please go ahead.

John from Delaware

Doctor, thank you. I just had a question about medical marijuana. Has there been any proof that medical marijuana helps with slowness or stiffness?

Joel S. Perlmutter, MD

Easy answer, no. No proof, but we certainly do know that medical marijuana can impair balance more and make somebody probably at higher risk to fall. The real answer though is there are no good studies to show anything one way or the other. There's just not enough data.

And there are some theoretical reasons to think that cannabinoids, which is what medical marijuana, one of the key pharmacological ingredients, may interact with dopamine receptors; and whether that's good or bad or how that works is unclear still, but there is an area of potential for research in this area. So, I say we don't really know the answer on this one yet. I would be very cautious about taking anything that in any way could sedate you or impair balance more though.

Stephanie Paul

Okay, terrific, we have time for one more question. This will come from the Web, and this is coming from Stewart in Oregon, and the question is, "I'm a medical provider and would like to provide better support and resources for those young onset patients who are still working."

Joel S. Perlmutter, MD

Great idea. So, organizations like the APDA have a whole series of support groups and local information services throughout the country, and a lot of those places, I know the one in St. Louis, we have two or three support groups just focused on young onset Parkinson's. So, this is really important, and I wouldn't be surprised if there are now Web-based support groups, but I don't know specifically, but that would be another way. And so, there are different organizations that do this, and so I think this is a great source of information for young onset Parkinson's and especially to reach out and connect with other people who have a similar condition. That can be very helpful.

Closing Remarks

Stephanie Paul

[Slide 37] Terrific, thank you so much, Dr. Perlmutter. I want to thank everyone for participating in today's telephone and Web education program. I apologize that we couldn't get to all of the wonderful questions**. [Slide 38]** But if you have a question and would like to speak with someone in our Scientific and Medical Affairs Department, I encourage you to visit our website or call 1-800-223-2732 and you can ask your question there. Again, I do want to thank Dr. Perlmutter for his wonderful presentation. I also want to emphasize to everyone on the phone that we really do appreciate your feedback and comments and want to make sure that you complete the program evaluation form.

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

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