



**Live Well Today Webinar Series:
Dementia and Later-Onset Parkinson's**
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Davis Phinney Foundation

Melani Dizon (Director of Education and Research, Davis Phinney Foundation):
Today we're going to talk about dementia with people who are later diagnosed with Parkinson's or later onset. Thank you for joining us again Dr. Savica.

Rodolfo Savica, MD, PhD (Neurologist and Faculty, Rochester Mayo Clinic):
Hello thanks for having me it's a pleasure to be here.

Melani Dizon:
So when we get started, I'd love to just kind of set a little, set the context for who we're going to be talking about and specifically what we're going to be talking about. We've talked a lot about cognitive issues and dementia and people diagnosed young onset but today we're going to be talking about people that have been diagnosed with Parkinson's later in life and Dr. Savica correct me if I'm wrong would we say maybe that's around 60 and later maybe?

Rodolfo Savica:
Yes, absolutely that is always a very important question. When we talk about, when we say young versus late, I would say late onset or quote quote regular onset of Parkinson's disease is fair to say 65 to 70, that is what the data are pointing us for the most part around that age group between 65 and 70 in terms of motor symptoms, so, onset of tremor, onset of rigidity, onset of stiffness, onset of falls, around that I would say.

Melani Dizon:
Great and so if you have not had a chance to watch our other webinars maybe you were diagnosed earlier, one of the things that we've talked about with Dr. Savica is when you're diagnosed younger, let's say you know under 60, under 55, that disease actually is quite different, so it'd be great for you to go back and watch those webinars and we will put up the links so that you can check those out because we might be talking about things a little bit differently today. So, let's say that we're talking, for the purposes of discussion today, let's do it sort of as a case study. So we're talking about somebody around 70 years old, they've been diagnosed with Parkinson's, they did sort of notice it with onset of motor symptoms even if they might look back and say, I experienced some other things, right, but that's going to be the general person that we're talking about. So, one more question before we get going, would we be talking about dementia, cognition, any of those things differently if it was a male or a female or is it pretty much the same?

Rodolfo Savica:

So I would say same typical, so if you talk about academic and science, we can think, we should and we have to, and hopefully even in the clinic, we will think differently between men and women. As we know men and women have different characteristics and we are talking about really sexual chromosomes so X and X, and X and Y, because this is what we know yet about I cannot talk yet about gender identification, we don't have the data yet to support any difference there. So we talk men and women, we are talking about X and X, X and Y situation and it's true in our world there is a substantial difference between men and women in terms of frequency, in terms of occurrence, of, I would say more cortical, more higher brain function complications in Parkinson's disease and also in Alzheimer's disease.

In the recent past for example, we were thinking, and the data were supporting, that women were way more affected of Alzheimer's disease compared to men, but nowadays the current studies are making men and women more or less even in terms of distribution. Whereas in Parkinson's disease, we know that Parkinson's disease is greatly more affecting men compared to women to start with, but what we observe in memory disorder, we observe the same thing that we observe as we get older in Parkinson's disease, the two curves are diverging, so in other words, men and women are different at 65, 70, but as men and women are getting older the two curves are getting back together. This is valid also for dementia, memory loss, they diverge and then as people are getting older in their 80s and 90s there seem to be some sort of similarities between the frequency of this condition. Men and women are different scientifically, biologically, so clearly, we have to think about different ways that the disease develops scientifically. Clinically, we don't have yet this translation that can make us think in such a different way. Not yet, but the data are mounting, so I wouldn't be surprised if in the next two, three, four years, we will have more data to support you know one versus the other in terms of even treatment or in terms of prognosis per se.

Melani Dizon:

Okay that's great. So for the audience listening you can assume that we are we're sort of talking about how they present clinically in the office, we're talking about people that are 70 and older, and if you have a specific question please put it in the chat, let us know you know, hey I'm a woman and I was diagnosed in such and such a time. Maybe there will be something different, maybe Dr. Savica will point out something that would differentiate the the situation. But we'll kind of go along with that. So we hear a lot of terms in the world of Parkinson's symptoms such as cognitive decline, mild cognitive impairment, dementia, can you define those three terms for us and let us know how they're different?

Rodolfo Savica:

Absolutely, that is, so terminology getting the right terms of a condition and we know it's crucial to identify exactly what we're talking about. So, let's start from the latter, the last one you say. So mild cognitive impairment and dementia, what are they? Those are clinical symptoms, you know clinical syndrome, so syndrome is a combination of signs and symptoms

that define a disease. Mild cognitive impairment is a memory loss that the patient perceives, family around the patients are perceiving as well, that is not significantly interfering their daily life activities, means in other words the patient is struggling with some memory loss that he's able, he or she is able to overcome in the long run. In other words, let's say problems with finding direction, but ultimately, you're making your way, problems with cooking, well maybe rather than taking 10 minutes to do whatever dish you do in 10 minutes, I don't know, you make 25 minutes and maybe you make some mistakes along the line, but you correct yourself. These are good examples of mild cognitive impairment.

Dementia on the other hand is a group or set of symptoms but in this case is a memory problem that may or may not be perceived by the patient, is perceived by the family, for sure, and by the caregivers, that is significantly interfering with daily life activities in other words the patient doesn't have a clear insight of the problem but the patient is not able to cook, he's not able to drive, he's not able to function without assistance throughout the day.

Clearly this is a spectrum, so in other words usually when somebody is having mild cognitive impairment that for now on, I will call MCI, so mild cognitive impairment, MCI, there's a spectrum. So sometimes I tend to call things moderate cognitive impairment just because it's not quite into the dementia diagnosis but is not quite in the MCI so it's a spectrum condition that depends on how the memory disease, the memory problem is interfering with their daily life activities, and this has to do with our society. What I mean is that if our society wouldn't require us, I give an example, a very silly example, driving cars, and there was a self-driving car mechanism as we would have maybe in the future maybe many people would not feel that they have MCI because they say, I need to go to the grocery, press button, the car brings you there, that would be a way to reduce the number of people with a clinical symptom of MCI because you don't have the task that you need to be doing and that society is requiring you to be doing.

The other term we use is cognitive decline, cognitive loss, in the past we talk about brain fog... all these are synonyms basically of some difficulties and in the case of Parkinson's disease most of the time especially in young onset but also later onset we're talking about people that are talkingm I feel I am slow. I feel I'm slow mentally, not only physically, I feel I have trouble going point A to point B even mentally, not physically only. I feel I have trouble multitasking, so rather than doing three things at the same time I had to do one because if I do two then I get lost. Those are examples of memory loss, those are what we call cognitive decline, but we know we have to try to assimilate, put together the concept of cognitive decline with the concept of aging.

As we get older, we lose brain. After the age of 25, unfortunately, the brain shrinks down. So as we get older, we lose brain. We are losing brain and as we get older and older together, and it is an important concept for our conversation today, together with the brain that is lost naturally, we naturally accumulate plaques and tangles that are the same plaques and tangles that we will see in people that have Alzheimer's disease. So as we get older, people that are in

the late 80s, early 80s, early 90s, if I look at the brain I may see some plaques and tangles whether or not they do have a clinical diagnosis of dementia, whether or not patient has a clinical diagnosis of MCI as part of the aging process that our brain is undergoing.

Okay, so this is an important concept that differentiate young onset versus late onset because a young onset we do not have, we shouldn't have this accumulation of additional protein that can damage the brain whereas when we are getting older the age is something that we cannot control, and we will lose memory sooner or later. Somebody can argue, hey, Dr. Savica, myself or my grandfather lived until 97 and he lived great. Great, it's fantastic, and it's good, but many of the memory problems depends on the societal demand that we need, the tasks that we need to be doing, it also depends on some people are genetically and are able to sustain a longer longevity without having massive damage to the brain I would say.

Melani Dizon:

Okay great so that brings up several questions, first one is, do we have any data or that we can say with certainty the percentage of people later onset diagnosis of Parkinson's that they get dementia?

Rodolfo Savica:

Sure, that has been one of the, if you look at the literature and you put down dementia, memory loss, Parkinson's disease, you will find everything. I can quote your literature that says five percent of people are getting dementia in Parkinson's disease late onset or 95 percent, so it goes the entire spectrum and has to do a lot with a couple of things. It has to do on when things are seen, how long after diagnosis has been seen, age has to be in consideration, has to be always adjusted. I tell you I will report the data that we generated here in Rochester using our epidemiological data that I think are in line with other data, so we are not giving anything out of the ordinary. In about 10 years from the diagnosis of late onset Parkinson disease, so 70 to 80, about 39% of patients may have some memory problem. I didn't say dementia. I say some memory problem.

So, I have patients that, I have some that will have MCI, mild cognitive impairment and some would have dementia some of them would report this slowness that sometimes happened in Parkinson's disease but I have to tell you something that is very important, very very important, other things need to be considered whenever somebody gets a clinical diagnosis of dementia or mild cognitive impairment, later onset or younger onset, but we're talking about later onset today. Remember, the diagnosis of dementia is clinical, so in other words it's based upon the report of the patient of the caregiver, caretaker of a substantial, significant memory loss that is affecting and I told this last time but I want to one more time, four domains of memory, this is what neuropsychologically we consider, working memory, that is short term memory loss, a phone number I'm not able to recall, a name, I'm not able to recall... short term memory, so what is called the working memory. Visual spatial memory, my ability to see myself in space, my ability to see tri-dimensional images. Language... some memory disorder is just language,

people are having problems with speaking, producing words, pronouncing words, understanding the words. And the fourth one is called executive function, the ability to plan things in a very precise way. If somebody's having a massive decline in one of these, just one of these, this can be a dementia symptom. It depends... depends... on how this is interfering with their life activities. If somebody is mute completely because is not able to pronounce, to enunciate, they can have intact memory, intact working memory, intact executive function, but they may be considered, what, demented, just because one of the domains is down.

So once we have this down, I have one of the four domains down, I potentially have dementia, I have to make sure that there's nothing else that can contribute to that, especially as we get older, even younger, but older there are other things that we need to be considered and I need to tell you this because this has to do with our well-being. Number one, easy, sleep disorder. If we don't sleep well at night, if we snore... snoring is something that is so much overlooked, but people that have even mild sleep apnea in their 70s and 80s, they may not have sleep apnea where they stop the breathing right and they gasp for air, but the oxygen level may be slow enough for many years enough that can worsen the memory, it can be maybe one of the things that we need to treat immediately whenever somebody reports memory problem.

So what I do in the office, I have my patient in front of me, I ask the spouse, does your husband, does your wife snore? If the answer is yes, I usually say, okay, let's do a screen, let's make sure your oxygen level is too low, because if it's too low we have to fix it and it doesn't need to be fixed with a CPAP, sometimes other things can be done for that. Another thing, since we're talking about sleep disorder, living out the dreams... dream enactment behavior disorder is incredibly common in later onset Parkinson's disease, in other words the thrashing at night, this is disrupting the quality of the night's sleep. So it's very important to fix it and to improve this and this can be improved with medications, I would say in the vast majority of the patients, not in all the patients but that is another part of sleep disruption that needs to be fixed.

Another overlooked thing that I want everybody here listening to hear, that can contribute to memory is late onset anxiety and depression. These need to be fixed. Clearly, we are dealing with somebody that has Parkinson's disease maybe a newly diagnosed, maybe a few years have passed, maybe my patient in front of me just retired so there's not only a major life adjustment which is retirement, already a diagnosis that still carries a lot of social stigma, everybody will be a little bit down and if depression and anxiety and/or anxiety are not treated sometimes they do not make patients crying or being hopeless or having somatic symptoms of the depression that can be just quote quote a memory issue. When people are fatiguing, are you know taking longer to think, so this has to be fixed.

So sleep disorder, mood disorder needs to be immediately fixed and any other concomitant condition. I'll give an example. Fibromyalgia, that is something that if it's concomitant can worsen memory, at any age, but if you have Parkinson's disease and you may be having a mild cognitive impairment then your symptoms can be looking worse just because you haven't

treated that particular core part. So those are things that seem to be silly seem to be clear to anyone but in reality, they're very often overlooked by that. Okay, so those are things that I would consider when I see, when I have a patient in front of me.

Another one is medications. Concomitant medication used for different purposes. I give an example. Many of our older gentlemen, or gentleladies are suffering over of overactive bladder. And sometimes, some of the medication used for the overactive bladder, they can worsen memory, especially if somebody's having already Parkinson's disease, so usually I generally speaking use just two medications, just to make sure that I don't have anything that is affecting the brain and that is very important to do because that can be another thing that can contribute and worsen the memory. Assuming that all these four aspects, medication, sleep, concomitant conditions such as pain, and mood disorders have been fixed, how? With medications, with lifestyle changes, with acceptance, with many different changes, then you say, okay, you still have memory problems. Okay, what can we do? What kind of memory problems we are dealing with? Is it Parkinson's that is getting worse? Is the protein of Parkinson's, the so-called alpha synuclein Lewy bodies accumulating spreading through the cortex causing the memory problems or there's a concomitant, a concurrent presence of aging a beta amyloid, the protein of Alzheimer, that combined together causing the memory problems.

Can I know that? Yes, I can find a way to know that. I, in front of my patient, in my office, I would say you know what, let's order some tests. Let's order some scans of the brain, why? Because if you do have degeneration similar to Alzheimer's disease, I'm expecting to see some areas specific errors of the brain shrinking down. If there was only Parkinson's disease, only quote quote, Parkinson's disease, I wouldn't see this massive shrinkage, maybe I would order then a pet scan on the brain. The pet scan would provide me more information, so remember MRI is a structural scan, shows you the bricks of the house, pet scan is showing the plumbing of the house. If you want to buy a house, you want to know both, so it's the same brain, but it gives you other information, but pet scan can tell me okay we are dealing not only with Parkinson's, so maybe the pattern or the change can be seen in Alzheimer's, so maybe this gentleman or gentlelady now is 75, 78, has maybe both.

What is important mostly for prognostic factors and mostly to be more or less aggressive regarding medication and what we can do. Somebody posted which is a very good question was what about Lewy body disease, what's the difference? Well the difference is nomenclature it's just a matter of finding the name. So we know that Lewy bodies are the hallmark of Parkinson's disease and the hallmark of Lewy body disease. If I look at the brain when people are dead they have the same appearance, the Lewy bodies accumulates. The problem is that Lewy body disease, the memory problem occurs within one year from the onset of Parkinson's disease and vice versa, so if somebody has memory problems within one year, they do have motor problems like Parkinson's disease, this is the definition, so, the memory disorder occurs early in the course of the disease whereas when we talk about Parkinson's disease dementia usually it's

above one maybe two years I would say stretching the concept, so it's something that is happening later on in life, okay, in the course of the disease. This is the main difference, but the treatment is more or less similar.

It's a matter of knowing the prognosis. So I have in front of me a patient, can I order spinal fluid analysis? I can. I can order a spinal tap and get a little bit more detailed information regarding the protein accumulation of Alzheimer's. Can I order beta amyloid scan? I can. It's very expensive, sometimes adds something, sometimes it doesn't add something, but clearly depends on this individual patient and what we are searching for and how much things are clear and after that we need to make sure that we are taking care of the symptoms, so memory disorders, see what we can do. Again, I'm assuming depression, the disorder, no medications, other conditions are under control.

Clearly, we need to optimize, first of all, optimize the Parkinson's treatment. So carbidopa/levodopa, let's say, the gold standard need to be at the optimal level because a sub-optimal level of carbidopa/levodopa can cause also slowing of the brain so not slowing of the motor part but also slowing of thinking. So first things first, let's make sure that we are taking the right amount of medication the maximum tolerated one the one that we can optimize. If it's not enough then we can add a medication to try to boost up the memory. Usually, unfortunately, we do not have a lot of them, most of them are called anti-cholinesterase inhibitors. So the typical ones are donepezil, rivastigmine, and memantine later on in a second phase. So we will use that to try to boost up the memory and in some cases it works. Sometimes whether with that I have to add an antidepressant not because of depression because I'm trying to sustain the chemical in a different way. So not only antidepressants are used for depression but also sometimes to sustain the biochemical reduction of some of the neurotransmitters that are present in Parkinson's disease with memory disorder.

And then I would say to the patient let's see how you're doing, let's observe you, because one point in time is not good, we have to have at least another point in time a few months or up to a year later. It's a big deal, it's a big deal, because that can define the progression of the disease. That can tell me when we are heading. There are other symptoms, and some are just posting, hallucinations, what about hallucinations? Are they a signal of dementing illness? It depends. Are they a signal of dementia lewy bodies? Can be, unless there's an explanation. Most of the time hallucinations are because people are taking medications. So we have to assume that there's nothing that's causing this problem then yes hallucinations can be one of the clinical characteristics for dementia lewy bodies but we have to make sure there's nothing else causing this problem. So hallucinations is a good sign to look, to make diagnosis, but it's incomplete we have to make sure there's some that is the only symptom without something else.

Melani Dizon:

Okay so that it brings up several different things and we have to get to some of these questions.

Rodolfo Savica:

Absolutely, that's great, some of them are fantastic.

Melani Dizon:

Yeah, they are, they're really great. What it really brought up for me you're explaining everything and you're talking about all the different things that could impact cognition is that, and this is something that we see on our side, as you know, people will start to feel it or their care partner will start to notice it and they get very scared, right? And they think okay, this happens they're gonna be, they're gonna have full-blown dementia and so I think that if you're out there listening and you're wondering this is great news and this is a good sign to kind of take a breath and say okay let's hold on here, let's not assume that because I forgot where the grocery store was that I'm gonna be completely, you know, have dementia I'm not gonna be able to do my life, but the key is to find somebody who can treat you and is as skilled as Dr. Savica at being able to look at all of those different things, look at your sleep, look at your depression, look at your mood, all of those different things before you you know take on that big thing like, oh this is all over, so I think that's a critical critical piece to notice and if you, like for example, if right now, if you're seeing a primary care doctor and this person doesn't have all of that information, this is a great time to see, do they have anybody they can refer you to? Is there anybody within driving distance? Is there anybody you can see via telemedicine? Somebody who actually has the very specific skill to be able to address all of these different issues is super important, so I want to make sure that we get that. Somebody, I want to address this question because it was, you were just talking about it, but somebody said, okay, so if I have no memory issues in year one after diagnosis this means no LBD in my future? What can we say about that?

Rodolfo Savica:

So, let's talk about something that is important. So, remember if I open up the brain, I see Lewy bodies, whether somebody is having Parkinson's or dementia lewy bodies because this is the hallmark. The answer is that the more time, I would say, that the more time you spend into the disease, the more years passed from the original onset of symptoms is less likely that memory can become an impact but you're getting older, so we have two offending problems here, Parkinson's disease that will progress, but also time and aging, and the problem is that I cannot anticipate how much your brain would age and how much that can be a problem. So it's possible that you're Parkinson's process that would develop dementia would not be very aggressive but your aging process would be more aggressive, so that is the point, I don't want to say, oh one year has passed, so if five years have passed, I'm out of the woods, but five years have passed, you're at now 85, the onset of dementia starts to be more common because you're getting older, so that would be something to consider that aging is something that unfortunately we cannot anticipate very much. Aging of the brain, we cannot know exactly who is developing what and when, you know, that is an important point. So there are two powerful

paths, one Parkinson's and one aging, plus all the others that I talk about but these two are the ones that are going parallel that is tough to anticipate which is going to be what.

Melani Dizon:

Okay. In terms of people getting assessed and people going through testing, you mentioned lots of different tests that you could order, what role does neuropsychological testing play?

Rodolfo Savica:

Excellent point. So that is good. If we can get a baseline, a neuropsychological assessment, the moment that memory disorders seem to be surfacing is good because this can serve us to understanding what I was talking about before. What are the four domains that are involved? And sometimes, you know, it's good to have repeated neuropsychological assessment through time. I have some problems with that in the sense that logistically it's not easy every time to do this test. There's a lot of demand, so sometimes you can be months out, so it's not always possible to be doing. So that's why I, not that I don't advocate, I do it all the time, but sometimes it's not easy if you're maybe not having easy access to a neuropsychologist to get this recurrent test but if you can absolutely. It's good to have the four domains and this can tell us because the symptoms, so we have four domains, right? Alzheimer's disease for example, the domain down is working memory, it's really down more than the others, dementia lewy bodies or Parkinson's disease is mostly visual spatial, okay, and executive function, so you will see a different pattern that can tell you what is what, which is important to know. I would say a baseline test whether it is a neuropsychological assessment if you have access to or your primary physician, your primary neurologist doing a memory test can already tell us what we are talking about, where we are going with that. So, it's good to do it, I strongly support it, but sometimes it's very difficult to have access to that.

Melani Dizon:

Yeah, also, I could be completely wrong to suggest this, but I guess if I were diagnosed and I were living somewhere that I didn't have access to somebody that could do this with me but I had a care partner or had somebody in my life, you know, what is the downside of saying let's check it out ourselves, let me see, you know, can we create some sort of baseline together where you give me, you know, maybe you go for one assessment and you see what that person does and then six months later your care partner helps you. I just wonder if that's...

Rodolfo Savica:

Oh yeah no, there's nothing wrong with that and there's plenty of decent valid online tools that you can use to test memory and to have an idea, but I always would say that it would be always very good not to use just a single test. This, a single test whether it's a neuropsychological assessment, whether it's an MRI, cannot be the only test that tells you what's going on. It has to be a part of a bigger picture, it has to be a part of a much more comprehensive overview, it needs to be interpreted correctly. That's the difficult part. It has to be interpreted correctly. I say it's always good and to re-review for example all the MRIs that have been done, to re-

review all the pet scans, to re-review the neuropsychological assessment, because sometimes the person that reads, let's say the radiologist that reads one test, or the neuropsychologist that reads one test, they read that test but they don't have the rest of the information. So that can give them a skewed view so I think it's great to do self-assessment, but then the self-assessment should be interpreted maybe by a provider in a bigger picture considering everything else because unfortunately we do not have one single test so far that can tell us with certainty what is happening.

Melani Dizon:

Right. So some of these tests you indicated that you can see, you know, you would expect to see Lewy bodies, you'll see them. If somebody gets to that stage, is there anything that can be done or is this like, no, I mean this is the issue with Alzheimer's, right, like there's no coming back from that right? It's just, it's a progressive thing, it's gonna happen, versus somebody who's just experiencing sort of maybe mild to moderate cognitive decline, you know, what is the path there? Is it kind of like well there's nothing I can do but there's something I can do over here?

Rodolfo Savica:

So I tell you something. Clearly when the dementing illness, the dementing symptoms are very much advanced, those are difficult to be treated. Then we have to talk about quality of life we have to talk about goals of care and see what we can do, make sure people eat, because as somebody mentioned there's a change in appetite that can occur when as the progression of disease is occurring so it's very important to consider that. So being fed, being well-rested, and so forth, but you're right. I think we need to be proactive, and we need to be proactive with what we have, which is not very much, but it's something at least, okay? We need to make sure that, even before if possible let's say we have, I have in front of me the usual patient 70 year old man or woman with diagnosis of Parkinsonism, maybe 72, two years of diagnosis, few years of non-motor symptoms, and now she or he complains of a little bit of a memory problem, what would you do? I would do exactly what I would do in regular late onset Parkinson's disease.

We need to be proactive, exercise 30 minutes, 5 times per week, again 30 minutes, 5 times per week of vigorous exercise something that makes people sweat, perspire, any kind of exercise. If you tell me what is better than the other, doesn't matter, whatever people like, I have people that are in the pool, people that are running, people that are biking, doesn't matter, whatever people like. It's very boring, you're right at times so I always tell my patients, you're not allowed to watch tv or watch Netflix, unless you put a bike in front of the tv and every time you turn a tv, you move your legs, that would be a good way. So exercise. Somebody mentioned lifestyle changes, diet, clearly, we have to prevent the concomitant, the presence at the same time, of strokes or cardiovascular diseases. So, making sure the diet is, we don't eat too much quote quote junk food, not too much food with a lot of fats, and make sure in other words that my

cardiovascular health, cholesterol, diabetes, hypertension, is all under good control because this can accelerate the process quite a lot.

So diet, do we have any diet for memory? You heard supplements, you heard this, you heard that, I would say there are a number of good studies reporting Mediterranean diet, so a diet eaten in the Mediterranean area, Italy, Spain, Lebanon and so forth, Greece, that seem to be you know a little bit better in terms of preventing the condition. But if you go in these countries you have still dementia, you still have Parkinson's, it's not the only thing. But I always recommend to my patients, you know, eat more olive oil, eat more fish, you want to take omega-3 take it, but if you eat fish fresh fish, you're good. What about flavonoids, little chemicals that are present in what is purple and blue in nature? Yes, please. Eat more blueberries, eat more raspberries, eat more of these chemicals, natural chemicals that seem to be healthy. What about curcumin? What about vitamins? You know, I'm very strong about vitamin b12, folate, and b6 and I want all my patients to take that because there's a slight risk reduction of dementia in Parkinson's disease in patients that are taking vitamin b6, b12, and folate every day so those are important things that you can do proactively and one thing I want to tell you and to me that is very important, more important maybe than the others sometimes... pleasure.

I keep saying, find something that is good for you, it doesn't need to be exotic, if you want it can be, but it doesn't need to be. Strolling with your spouse in the park with the dog, spending time every day reading your favorite book, favorite music, dancing to the sunrise, something that you do that you like and you enjoy has to be incorporated every day whether you have Parkinson's disease, whether you have young onset, whether you have late onset with memory loss, because people that are doing this, all this, are the ones that are doing better. I can guarantee that. People that are active mentally, physically, and socially, are the ones that in the long run are having less complications, whether it's memory, psychosis, problems with medication, problems with Sinemet, and so forth.

Melani Dizon:

Great. One of the initial questions that we got that I think is super interesting to talk about is, it has to do with deep brain stimulation, because they talked about, you know, does any cognitive decline get better with deep brain stimulation? So can you talk a little bit about, that's actually an issue that maybe you're not the best candidate for it, but can you talk about age of DBS and a little bit? And for those people who don't know what what deep brain stimulation is, can you just give a real quick?

Rodolfo Savica:

Absolutely. So this is a great point. So, deep brain stimulation is basically a technique that is developed in the late 90s, middle to late 90s, in France, and basically this particular technique allows to stimulate with a lead inside the brain in some structures of the brain the cells that are responsible, allegedly responsible, to generate some of the motor symptoms of Parkinson's

disease. So, tremor, rigidity, stiffness, and so forth. When is it used, classically, typically? It's used later on in the disease, so not right away, when people are having what we call fluctuations. In other words, when people are going taking the medication, they're good for two hours, but then a medication wears off immediately, so they are OFF then they're ON again after a medication in an hour and so forth so there's this huge fluctuation in response.

What this brain stimulation does is smoothen up this particular wave to a much more smooth wave with less ups and downs in the response. There are some targets in the brain that are the ones that are targeted whenever we use this technique, it depends on the symptoms of the patient. Some targets are better for tremors. Some targets are better for stiffness. Some targets are a combination of both and it's a technique that initially was not including in terms of clinical criteria people that had memory loss, because people that have a clear form of dementia in the beginning also clear from a mild cognitive impairment, they were not included because there was the idea that this could worsen the memory loss, it's a technique that can worsen memory loss. Likewise people that have severe depression usually are not good candidates for the same purpose because initially, and now a little bit less, but still initially there was some suicidal episodes that were making everybody a little bit more concerned.

Nowadays, with somebody that has mild cognitive impairment, we do not worry that much. In other words, it's somebody that can be still considered as a possible candidate. If there are no other reason why this is the disease if otherwise a good candidate but with some memory loss, it can be good. Usually dementia or usually hallucinations, those are not the best candidate to be going there. The question is very specific and it's very important, does the stimulation, can the stimulation improve memory? There have been some reports in people with Parkinson's disease that improving the overall motor well-being was translating in an improvement of the memory loss or the subjective memory loss people were having. So, we see that. I saw that and we have seen that some improvement of memory after the brain stimulation, but this is not what we had to search for. In other words if it's coming, great, I take it, but it's not something that I'm expecting. Can be... yes, but it depends. Now if you're talking about age... when to do the deep brain simulation. This is very variable. Deep brain simulation should not be seen as a last resort, it's a treatment that can be used at one stage of the disease, but some people are getting to this stage earlier, some people later. The stimulation can be removed, can be literally removed away, but it's not the last resort, it's one treatment, as many others. Somebody's talking about ultrasound, do you want me to address that?

Melani Dizon:

In just a second, I want to stay on this one real quickly, just because I'm curious... so a lot of, some people experience issues with language after deep brain stimulation and so I've certainly gotten questions before, is this a sign that I'm actually having cognitive decline or is it the symptom and so yeah can you talk a little bit about that?

Rodolfo Savica:

Not necessarily. So not necessarily. It's not necessarily to do with the, actually it's not, I'm going to say it's not, it's not not necessarily at all, why? Well this stimulation is in, the stimulator is in an area that has a lot of pathways including all the motor pathways, so sometimes once I stimulate, I am catching some of the fibers that are responsible for my speech, responsible for my articulation on the mouth, so most of the time changing the parameters, changing the voltage, changing the place where the stimulator is going will improve the speech. So it's not necessarily meaning, oh I have a speech disorder, I for sure will have memory loss. There's not this correlation. The speech disorder coming from a stimulation usually has to do with the placement of the stimulator and the stimulation the electric current going through that and where it is located, I would say. So, I wouldn't be particularly worried that that would cause a memory disorder.

Melani Dizon:

Right. So a couple of people have talked to us about like that tip of the tongue situation and I would assume that's sort of the language piece of the four pieces and some people that's the only thing that they experience, that's just sort of hey, there's just something blocking that feeling.

Rodolfo Savica:

And that's to do because the tongue for example has a huge representation in the brain. Think about it how much we use the tongue every day all day long. So the muscle representation of the tongue in the brain in the fibers is very big, so if the stimulator can catch some fibers that are involved to that causing sometimes numbness right on the tip, sometimes lips not feeling that you can articulate that well, but it's stimulator dependent.

Melani Dizon:

Great, okay yes, let's talk about the deep brain stimulation that is done by an ultrasound or focused ultrasound, focused ultrasound.

Rodolfo Savica:

Focused ultrasound, it's not exactly stimulation, it's ultrasound. So, that is a technique that is relatively old in terms of the theory underlying that but now it's been adopted and it's used in the US not just in Israel. It's used in the US and all over the world, especially in persons that have tremor for the most part. So what is that? It's a technique that allows to create a heat, so it's an ultrasound, it's not the same ultrasound we do for the heart or for the pregnancy, no. It's an ultrasound that creates almost a laser, a heat current inside the brain through the skull and cause a damage to the cells. So it's a lesion that is causing the cells.

The idea is to target the cell that can cause the tremor because we know more or less where they are, and this can improve the tremor per se. It's not that you go, because I had a patient myself, that they came to me and say, "oh I want to do focused ultrasound, let's do it right now." And I say no, it's not working this way. We have to do the same tasks that are done for

the selection in deep brain stimulation, so the same one. It's a process that requires some preparation, head needs to be shaved, you need to be, for a few hours, still, you have to get basically an inverted plate like this full of water to reduce the heat to the head and there's a little problem that we have to consider. Some people are not possible to be doing that because their skull is too thick.

So the thickness of the skull can prevent you to be a candidate and I'm not kidding about that. It depends on the level of the amount of bone that you have because you remember we have to pass through, despite there's not any scars, because you don't do damage outside, you can go straight into the area. You can cause a lesion into the brain. It's used, in this moment FDA is still using for one side only, so not two sides at the same time, so one side only. And it's an alternative sometimes to deep brain stimulation but I would say only, for the most part, not only, in patients that have tremor so far, because it works better for this group of patients at this point. Clearly things move in this moment, so we don't know where we're going.

Melani Dizon:

Okay. So somebody asked, said that his wife speaks incoherently and inappropriately like as she's falling asleep, is this related to cognitive issues, dementia?

Rodolfo Savica:

No. So, the question is that as she's falling asleep, she's talking a little bit incoherently, not necessarily, this is more of a parasomnia, so more of a sleep disorder. It's similar, not to the extent of, but can be similar to the RBD, it can be similar to dream enactment behavior disorder, so similar to the thrashing out loud, but it, sometimes we see at the beginning of the sleep, if you're having a, if you're a very fast REM sleeper, there are people that are getting into REM within minutes and I think that is what it is, I don't think it has to do too much with cognition especially because it happened only in that window during sleep.

Melani Dizon:

All right, we're almost to the top of the hour. If you have any last questions, we've gotten to every one of them I think, so if you have any last burning questions that you want Dr. Savica is right here. Is there anything that I should have asked that I didn't that you think is important for our community to know?

Rodolfo Savica:

No, I think the questions were great as usual and I always enjoy that. My final remark is that clearly, we do not have a cure for Parkinson's, we don't have a cure for dementia in Parkinson's, but this doesn't mean that we have to be still. We have to be proactive. We have to do everything we can in our power not only to be proactive but also to try to find ways, alternative ways to try to halt or delay the progression of the disease. So I always say, and you guys have been great on that, everybody should be lobbying, everybody should try to help the governments, and the agencies to provide more research, because this is something that we



are seeing. I want to tell you this is not to scare you, but we will see a triplication, you hear me right, triplication on the number of patients that have Parkinson's disease with dementia in 2050. Why? Because of the aging population, because people are getting older, and because these diseases, for reasons that are beyond our understanding, are still on the rise and it's something that is clear, so, in other words, we will face this problem as we get older and it would be better to face now rather than when it's too late. That's what I would say.

Melani Dizon:

Right, thank you. Well thank you again for being with us today. It's always, I always learn so much from you, we love having you here today. Yeah, everyone said thank you so much I really appreciate Dr. Savica's breadth of knowledge. Absolutely, this is so great. I want to thank our peak partners again for making this possible. Adamus, Amneal, Lundbeck and Sunovion. And if you have any questions, you can always email us at blog@dpf.org and always definitely check our website dpf.org to find out about new webinars and events coming up. Thank you so much everybody. Bye.

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