



YOPD and Parkinson's

with Dr. Rodolfo Savica

Davis Phinney Foundation

Note: This is not a flawless, word-for-word transcript, but it's close.

Melani Dizon:

Okay. So, Dr. Savica, how are you doing?

Rodolfo Savica:

Fine. Good to see you.

Melani Dizon:

Great. It's really good to see you too. I'm excited to talk about living well with young-onset Parkinson's Disease. So, let's just jump right into it. First of all, can you just tell everybody a little bit about who you are and how you got involved in this work?

Rodolfo Savica:

Sure. My name is Rodolfo Savica. I'm one of the consultants at the Mayo Clinic Professor of Neurology, and I dedicated the last 20 years of my, well, it's been over 20 years now, all my life to working with Parkinson's disease. Especially in the last decade or so, I devoted myself specifically to people that have Parkinson's disease, but they're younger. And I am spending time running a full clinic on people with, people that have early-onset Parkinson's disease. It's one of the few clinics that we have in North America devoted to Parkinson's disease affecting a younger population, as well as I am in my research lab and we are working on several initiatives and projects to try to understand, try to advance the knowledge on Parkinson's disease, especially affect in a younger population, and ultimately to cure, or at least to delay as much as possible, the disease and to ultimately help our patient population, making sure that everybody's having a full life. To be honest, I hope that one day I can, will be able to retire and my help wouldn't be needed. This means that we accomplish at least the goal of helping people with this condition.

Melani Dizon:

Right. That is a great goal. Let's keep that one going. Okay. So, there, there's been a lot of talks. There was a paper that came out called Age Cutoff for Early-onset Parkinson's Disease Recommendations from the International Parkinson's and Movement Disorder Site Task Force on Early-onset Parkinson's Disease. It came out and it is talking about people diagnosed before

the age of 50. And there was a blurb in the paper that I just want to read in case, you know, people haven't seen it yet, and I'll share it in the notes, but it said, authors who have first developed an interest in and published on this subgroup of PD have preferred the use of YOPD. However, there has been a shift, there has been a shift toward the use of EOPD in the past two decades.

There are no clear publications detailing the rationale behind this shift, but it seems motivated by an attempt to avoid age-related stigmatism stigmatization. Oh my gosh. Just the recommendation of the early-onset Parkinson's disease task force of the MDS is to use the term EOPD to designate PD with an onset of motor symptoms before the specific age that was agreed on. Now, the biggest concern I hear about the conclusion that this paper came to is that nobody living with Parkinson's was part of the task force. So, first of all, is that true? And then second of all, if it is true you know, how did the decision not to involve that community get made? And how was it determined that using the term young was an, you know, a negative age-related term?

Rodolfo Savica:

So, first of all, I'm guilty of the paper. I am the chair of the task force. Okay. And I want to clarify one point for every, many people. So, this task force is part of the Movement Disorder Society. This particular task force in this society is a scientific society. So, it's based upon a group of people, researchers, and people from all over the world, the globe. It's a global organization that has only scientific purpose, doesn't have any purpose of the legislation, doesn't have a purpose in the, you know, goal of the society, to have patient-centered care. This is scientifically based upon the idea of advancing science, not necessarily Ava changing any legislation all over the world. It's true the experts in the field who that participate in the task force are all physicians and PhDs of then Title Globe. They were a presentation of people from Africa, from Iran, from China, from Asia in general, not just China, from Australia, from Europe, from North and South America.

And this task force has been working heavily in the last two and a half years, ever since its inception to try to harmonize. So, the goal of this space, this manuscript, is to harmonize and try to help have, number one, a clear cutoff for the age because at least we know what we are talking about. And current cutoff is about 50 and below. When 50-50 fighters have some kind of grace time, we can think about it. Why we say that, because according to different countries, in some countries, early-onset Parkinson, young Parkinson's is considered below the age of 65 because of the need of the national system. In some other countries, it's 40 and below. But why this is important, because when we are pulling together data, we're not pulling too, we're pulling data when we are trying to understand what we are talking about.

If there are five different age cutoffs, it's impossible to know what we are talking and what is the actual number. Because it's true early-onset Parkinson's disease, young onset Parkinson's disease is on the rise. But if, as you can imagine, if we change cutoff for the age of onset, we

can have different chunks of result. So, the goal of this man, of this manuscript was to address the age, not to match the name to start with. Second thing I want to write about the name, the idea of using her onset is because it's working very well. Also, against the opposite. So, early versus late onset works very well. Young was the opposite of young, old, ah, you know what I mean? And this is English. This is a global organization. So, in some languages, and I tell you for example, speak few, but I'm Italian, even in Spanish, it doesn't work.

Young wouldn't work. If you translate young in Italian is not going to work. It simply doesn't sound right and can increase the confusion. The way I see it is that we can use scientifically the word early-onset. So, at least we know what we're talking about. We know we are talking about this particular beast, but I think we can keep both. I have no problems in keeping young versus early. I don't have any emotional attachment toward one or the other. I think they're both equally relevant and they're both having good reason why. One is this one versus the other. One thing that we are taking advantage now after these manuscripts is that we won't like to make sure that the patients now are involved in a conversation. The task force is of the MDS, is moving into a study group, which is a different kind of nature that can be more inclusive.

Rodolfo Savica:

It can allow people to participate. We have an organization that reached out to me from the, from the UK that are working in trying to give a response, a scientific response or why, and is more important. And I think many patients can do the same. I think we have to keep both terms, but we should all agree that we know what we're talking about. Whether it's early or very young, as long as we talk about it. That's me. Very important. And again, I am not emotional about it. I am, I, as you can see, I go back and forth between early young. Yeah. It doesn't, it doesn't change too much to me as long as we know what we are talking about here.

Melani Dizon:

Yeah. So, it sounds, I mean, what I'm, what I'm hearing is it sounds like for sort of research and clinical reasons, having the term that is global, you know, every people do research from multiple countries together. Right? And so, if you're talking about saying it one way and someone else is saying it another way, right? It's like that's a challenge. And so, clinical research using early-onset, having that nomenclature that's common is, is important and great.

Rodolfo Savica:

Very important. Also, I want to tell you up to now, 2021, 2022, there were not such initiatives everywhere in the world. So, the movement, as our society took the problem, faced the problem, say, okay, we have an issue, we had to fix it. In the past we have had this, even this conversation. And as you can know, in the literature, people were talking about young, juvenile for a while or early, and it was a lot of confusion. And it was this condition, Parkinson's disease affecting the young, which was considered a rare disease affecting a small amount of the

population that has some familiar genetic problem. And it's not true. So, we have to do a lot of steps. And to be honest, we, and I, and that's why I'm here. But you know, that, you know me, you know, the way we, I think, but everybody knows the way. I think we need to partner up together in the right steps at the right time to lobby about the problem, to think about the problems, and to raise awareness. But first of all, we have to understand what we are talking about globally.

Melani Dizon:

Yeah.

Rodolfo Savica:

Globally, because we are using English clearly as the main language, and we should because it's the scientific language, but it's not working. Again, seem to be silly, but it's not working everywhere the same. Yeah.

Melani Dizon:

Yeah.

Rodolfo Savica:

And that's a problem. It's a problem because we had to raise awareness in entire continents where there's not too much access to information. North America, UK, all the, even Australia. So, all English-speaking countries and continents are taking the lead in this initiative. And these debates are fantastic about young, early or whatever. But we had to think about beyond that. Yeah. Because if you think globally is more meaningful to me, understanding, giving an idea and not a fixed strict cutoff, but of age. But an idea about what we are talking about knowing that we're doing something different than Parkinson's is a disease affecting later ages. That will be already the biggest message then we can call it young, early, whatever. It doesn't matter to me again because I don't have an emotional component attached to that. And based, we base, upon this decision on coding early, just because of the available literature, what was there was not based upon a decision made. I don't know whereby some bigwigs in their offices know, about what was already published in the literature.

Melani Dizon:

Right. Right. Well, yeah, I mean, that makes sense. And I'm really appreciative of, you know, talking through that because I know our, a lot of people in our community feel very strongly about keeping that term. And I think part of it is, you know, this, I know, you know, I, from my experience in the US and the UK, that is you a little bit in Australia, but it's just like sort of a cultural, they feel like they can belong to a YOPD community versus an early-onset community.

So, I think that's, that's part of it. Right. And it's absolutely, it's different for people who are I think that there might be a case, right, for keeping both the terms in play, one for clinicians, researchers, and one for those living with it, if they so, choose to use that, if that, if that,

Rodolfo Savica:

As long as we know what we're talking about.

Melani Dizon:

Right? Right. So, and so, part of that is let's, so, we're going to define that. So, in some ways, right, so, like you said, you've said before that YOPD and late-onset or early-onset and late on the sun are two really different diseases. And based on, you know, sort of where you landed with the age, how did, how were you able to get everyone to agree, and what were some of the different things that people are bringing to the table when somebody said, well, we call it's 65 years old because that's the retirement age. Well, we brought them down to 50. Like, how, how did those conversations go and where, how do they make sense? Right. Because I think in my head I'm like, so, if it's truly a different disease, does it truly a different disease? If I'm 54 and I'm 50, like how does this work?

Rodolfo Savica:

So, let me tell you your number one, that was not easy process. I am talking about years or years seriously, or multiple meetings where I remember the first meeting I said, oh, oh my God, what I what I've been through now, I don't know what to do because my role is to mediate the different, being the chair of the task force is to mediate a different solve of the problem and try to come with an organic plan. And it was tough. It was tough because, you know, people are coming from different background, different countries, a different way of calling, coding, identifying, reimbursing the diseases According to Different system. But I would say all my colleagues were quite reasonable about it. We tried to identify, and that's what we did. The biological underlying reason why 50 would make sense.

There's or mono reason, there's number of paper pub previously published on this particular different cutoff of age noticing on how things switch around 50 to 55. And I agree with you, this is an artifact, but using 50, this is an artifact because if I am having Parkinson's disease and I have been diagnosed and my symptoms started at 51, would I be not considered early-onset? No. I think biologically people need to be c considered early-onset despite their one ear above this cutoff. We had to try not to be dogmatic, especially in this particular cutoff and saying before or after, because it's not working this way, this is not what medicine, modern medicine is about. For sure. We know that somebody's young, and to me, somebody's young, as long as even the concept of young, we talked this in the task force is really different according to different culture.

I remember this was raised by a colleague from Japan. I said, A young in my country, something different than yours. And I say, you are right. That's why early would be working scientifically bit more better in your case. But it doesn't really matter to me and to us what is early on the parking. So, why is different, what do the difference of early-onset Parkinson's comp compare compared to people that are older in age, whether it's 50, whether it's 55, whether it's 47? Are there differences? Yes. And this goes to the concept that is currently developed by a number of colleagues, that there are no two Parkinson's disease, you know, lookalike. Clearly we can try to lump together things, especially as we get a little bit older, assuming that there is, the disease is caused by an accumulation of a number of products. The famous Laban is the famous art, and it's true as we get older, this is more likely the cause of the problem.

The common outcome is that accumulation of alpha claim, and the reason why it's accumulating comes from different sources. But when we are younger, this is not necessarily a common outcome. The common outcome is a damage, a dysfunction, whether it's temporary, whether, whether it's permanent of the dopamine activity in the brain. The vast majority is contained in the Bessel ganglia. But there are other areas of the brain that contained dopamine. So, it's not necessarily just in Bessel. So, the common theme of Parkinson's disease is that do activity doesn't work very much in, earlier on, in earlier, not even early, earlier on Parkinson's disease. The more we get close to our teenager area, eras is likely that we are dealing with a different disease that is not due to the accumulation of alpha nuclei is not due to accumulation of aging proteins that are present as we get older.

Because clearly my brain when I'm in my thirties, is not the same brain when I'm in my sixties or seventies or eighties. Aging is taken and removed out of the equation, which is a major driving force for degeneration. So, in earlier onset, Parkinson's disease, 50, 51, 52, 55 even 57, depends on what we see. What we need to be looking at is what are the, what is, or what are the underlying reasons? What is process of dopamine energy dysfunction is happening. And it can be metabolic, can be autoimmune, can be after infection, can be inflammatory. We know what happened afterwards. But the tension is to understand what happened at the very beginning. Because if I know what happened at the very beginning, not only increase my knowledge, but I may be able to impact the process. And with the current technology, we start to understand a little bit more about the situation. That's why I keep saying earlier, onset Parkinson's disease, Parkinson's disease, it is way different than later-onset Parkinson's disease.

Melani Dizon:

Okay. So, when, well, so, if we, if you, we do look at, you know, much earlier onset, and you said there can be a few different things at play. It could be an infection, it could be environmental, it could be all of these different things. How does that impact treatment?

Rodolfo Savica:

Absolutely. Excellent. So, it impacts for a reason. The main, the gold standard treatment of Parkinson's disease, as we all know, is to you, is to supplement carbidopa li dopamine with levodopa or with domine agonist. We know that unfortunately we don't have new treatment for that. Something that can help restore the cells, something that can help the dopamine to be reproduced. We don't have that yet, at least. But the treatment can be highly impacted because our knowledge on dopamine is a knowledge base on older individuals, not on younger individuals, means what we know the time to dyskinesia, time to fluctuations and response to the medication, even the response to the medication, even the absorption of the medication is based upon what we have been knowing for decades on later-onset patients. Earlier on. The patients are totally different. I have patients that do not respond well to the oral agents.

I had to use a different kind of agents. I have patients that do not respond well to the regular cinnamon carbidopa, use different formulations. I have patient where I'm not able, despite, I know there's a problem to easily replenish the do energy clause. Why? Because the disease is systemic. So, it's affecting, the absorption is affecting the way they respond to the drug. And if they have co coexistent problems, such as, for example, metabolic problems affecting some enzymes that are responsible for motility or for movements of the bowels or for whatever, we are not going to have the same kind of response. So, knowing these underlying causes, these concomitant causes, can guide me counseling what to do, preventing problems. And if I do, for example, a genetic test, and I see that people have specific genetic mutations, I know how they do I how they do, they will respond to the medication.

So, knowing that there's a difference between earlier and late and within early-onset, having a number of subtypes that we are still struggling to identify. But we all know there's a subtype. People that are in this field know people that are listening to us, for sure. They don't look alike. They have different background, they're different symptoms. They have different way that the disease is affecting them. We still have the same disease just because this is the name we call it, but ultimately it just quote unquote just, ah, re reduce. The common theme is a reduction of dopamine in the brain. That's what it's Personally, you think we should, we're talking about young versus early. I think we should call, we should, we should call the disease in a different name completely. If we could

Melani Dizon:

Completely, yeah. That's interesting.

Rodolfo Savica:

Well, drop part it disease and talk about something else.

Melani Dizon:

Because that brings up this, you know, idea that you know, later-onset there's, you know, you get a clinical diagnosis, you have two out of the three of sort of the cardinal symptoms. Often those symptoms are not showing up for right. Younger onset. And so, is how, how do you diagnose somebody who is really doesn't present like what we think of as somebody with Parkinson's? And what is the sort of clinical bright line that says you have Parkinson's, or you have on young onset at early-onset Parkinson's?

Rodolfo Savica:

So, unfortunately, I have to repeat myself in a sense that the clinical criteria that we use are the one used, you know, as you say, later in life. And as you say, very well, they don't necessarily are present the same way they are in early-onset Parkinson's on a young onset Parkinson, they're not and people present in very different way, in a very different way to the point that sometimes, and there, there's some studies that are showing up. We don't have yet this data. I cannot say very much about it because we are, we yet published this data, but there is a huge, massive delay from onset to diagnosis. our,

Melani Dizon:

I know a lot of people will get diagnosed with like an orthopedic issue, right? They're totally, they

Rodolfo Savica:

Have one of most common presentation is the presence of dysfunction, for example. Virtual DYS after a marathon, people are thinking they have a muscle sprain, and they go to the orthopedic surgeon. But it's very difficult to make this diagnosis very difficult. We unfortunately need to yet use the famous cardinal signs. But together with the cardinal signs, I think is imperative for experts on the field to look beyond and start to use that scan, PET scan, MRI other diagnostic tests, lab works, genetic tests that can confirm what we're dealing with and especially in early-onset Parkinson's is young onset Parkinson's. We need to make this extra effort to confirm what's going on. because,

Melani Dizon:

So, for, does, does a DAT scan always, you know, when somebody young, and so, what can you, for the people who don't know, what is a DAT scan checking? And then what if it, if the DAT scan doesn't say anything, what, where do you go? What do you do?

Rodolfo Savica:

A DAT scan is a particular test that is ordered by your physician that is talk, talking and showing the activity or some specific nuclei of the brain called basal ganglia. And this particular test is,

should give you two set of answer. Yes. No. So, either you're positive or you're not positive. Unfortunately, still based on visual representation. So, is the radiologist the review and say you are positive or you're not. Many times, I see negative results that actually are indeed positive or vice versa.

Melani Dizon:

And that's because of training on the-

Rodolfo Savica:

I think so-

Melani Dizon:

-part of the reader. Okay.

Rodolfo Savica:

Because of training. And also, we have now some abilities, for example, amino and in many other centers where we can quantify the actual loss. So, getting a more objective measure of the loss of the activity. The test is quite specific and sensitive, but it's not telling the full story. Because if it's positive, it's telling us one thing, what I told you before, the dopamine energy activity is at lower, but if it's negative, not telling you that you don't have Parkinson, yeah, it's more likely that you don't. But it shows only one piece of the equation, not the full piece. So, it cannot be the only test that people are coming. I say, I have a suspicion of Parkinson, let me do the last, again, it's negative. You don't have Parkinson's. It's not likely, but I cannot yet exclude it. In Italy, where I'm from, we use this technique ever since the late nineties. It's been around for a long time. And I remember when I was a young, a young doctor, people were coming to me with a piece of paper without saying a word, with a dopa scan result and say, doctor, what do I have? Do I have Parkinson's or not? That's not the way you have to make a diagnosis. You cannot base upon one testimony what this test should be part of a bigger effort involving multiple aspects to try to understand what's going on.

Melani Dizon:

Okay. Okay. So, one of the things you talked about was response to medication. And sometimes, you know, young onset there, they don't respond to normal levodopa interventions. And this is interesting because for a long time I want to get into deep brain stimulation and why it can be beneficial for young people. But at the same time, you know, the argument was always, well, if you respond to levodopa, you're going to respond to D B s. And that's not necessarily the case because, so, this is confusing.

Rodolfo Savica:

Oh, under percent I am confusing is a dynamic and constant changing word. But it's true. In the past when I start to train, they were saying, oh, you can get if stimulation you can get the same response, the [inaudible]. So, it's crucial that you have a good response and it's still valid if you have a good response, even if it's fluctuating response to carbidopa-levodopa, you know, the likelihood that a d stimulation works is done properly is higher. But it's also, true that some people cannot tolerate carbidopa-levodopa and not necessarily, they don't respond. They simply cannot tolerate it, or they don't respond or whatever. They cannot use the drug in these circumstances. Deep brain stimulation can be a very good alternative as well as a Duopa pump. Let's not forget about the pump. The pump is saving some problems with absorption in the small intestine getting a faster constant absorption.

So, those are two things that we should consider. Not only brain stimulation, but I'm saying brain stimulation can be a good alternative even in absence of a developer response. But telling the patients, hey, we are not sure. I have patients that despite my best attempts that didn't respond to anything, my next step is that, okay, you're getting worse. I need to be doing something. We need to be doing the breast stimulation. Knowing that maybe the response is not optimal, but is one of the last, one of the few things I have in that circumstance. The question you had to ask, say why you didn't respond, why we don't know. There are some people that have some genetic makeup, some environmental problem, some disease that is different, still causing a damage in the be ganglia, but is different that does not add the same rate response or responding at all to carbidopa-levodopa.

And not because you had not because you have complications of, or in, or immediate, immediate dystonia or dyskinesia. So, abnormal movement simply, there's no response and it's a problem. But let me say something about deep deeper stimulation. We have to be very careful there. There's some data that are surfacing that do not necessarily warrant the use of stimulation early on, even in early on, say Parkinson's, unless it's really needed. So, what I don't want, and I want to people think, okay, and the I going to, I am destined to do breathe stimulation is not true. I'm doomed to do the stimulation. It's not true. And I will need breath stimulation for sure. It is not true. It's something that can be used as a tool in some selected cases. And especially I would say in early-onset individual young onset people, we had to be extra careful, even extra careful.

Melani Dizon:

Do you think it's gotten to the point where it's being used too much?

Rodolfo Savica:

No, not necessarily. But I'm worried that we're going to go there and it's not going to be good because we have some data that support that is not always great to be, I can this data been presented to the society that by my group showing that surprisingly people that ever with early-onset Parkinson's disease, young onset Parkinson's F five 50 and below that underwent

the debris stimulation that had an increased light as light increased risk. I content decline, which I don't like the idea and I wasn't expecting that. I'm not here to say, to hide the data, to meet the data need to be out there because they, we had to be saying, okay, we had to be careful means that we can do it. But we had to be careful. It's not something that we can jump to conclusion very easy because it's still a procedure and is not, there's a lot of moving pieces. And again, we are as usual adopting technology tested in all than individuals in younger individuals, which is not exactly what we would like to do but is the way it works.

Melani Dizon:

Right. Okay. So, can we talk a little bit about how progression looks? Sure. For both different groups?

Rodolfo Savica:

That's one of the most difficult question because if the groups are diff, I mean, if we do ma to macro groups later-onset, early-onset, I can give you some solid data.

Melani Dizon:

Yeah, yeah, yeah. That one. Let's do that one

Rodolfo Savica:

So, later-onset, the data that we have, survival, so, in other words, time to death after the diagnosis, it generally speaking about 12 to 14 years after the diagnosis. So, if somebody is diagnosed with Parkinson's disease, 75 he or she will look about 1992, which is not bad. You are getting old anyway. And the causes of that are the usual one for the western world. So, cardiovascular diseases, cancer, pneumonia, so, those stuff in early-onset Parkinson's, totally different from diagnosis to death to last to last encounters is 48 years.

Melani Dizon:

That's amazing.

Rodolfo Savica:

So, this is the, and two, I'm giving you generally speaking numbers that encompass a full array of different individuals. Clearly. So, there are people that may be having a shorter duration, people that have a longer duration, but so, their exception to the rules, we're talking about large numbers here, but this is an, an attestation to show the major biological difference between the two conditions.

Melani Dizon:

Yeah.

Rodolfo Savica:

For 48 years. And I tell you, I always tell my patients if they come to see me, they know that if you're a woman and you have tremor, that's the best you can be being a woman.

Melani Dizon:

They know that you know that you are later-onset because you have that MO, is that right? Because there,

Rodolfo Savica:

Whether you're late or when you're young being a woman and having tremors is great. The prognosis is much better.

Melani Dizon:

Mm.

Rodolfo Savica:

And a woman makes sense. I mean, and not to do with estrogens. I wish she was with estrogen. Well, women currently speaking they've been exposed to a higher level of estrogen throughout their life. Clearly, you know, man is on the opposite of testosterone. If you ask me, we have that little information about the role of testosterone in the degeneration of any sort of degenerative disease. We are trying to fill this gap as well, but it's not going to be easy. But what makes a difference? There is one little gene that is very important.

Rodolfo Savica:

Chromosome x. Chromosome X is crucial for our life. There's no life without at least one chromosome X. You have condition with X and zero turner syndrome, but you're not conditioned with Y and zero. There's stillbirth birth. So, chromosome X is the most important single most important chromosome that we have is one that is not necessarily studied formally. Even with the whole genome sequences, the studying, the full genome is not always studied because it's very difficult to study. There's other redundancy, it's a nightmare for our colleague in genetics, they, they hate the chromosome X to be studied super difficult to explore. But that is single handedly the most important of good protic factor for Parkinson's disease being a woman. And again, I'm talking about gender here, I'm talking about chromosomes. Yes. X, X, X, and Y. That's what it is.

Melani Dizon:

That's interesting. Okay. So, let's, let's talk about women for a minute.

Rodolfo Savica:

Sure.

Melani Dizon:

It seems that you know, so, many of the biological processes that women experience, menstruation, pregnancy, breastfeeding, menopause, hormone fluctuation, all of those things that the distinction between YOPD and later-onset and women is probably even more important. Right. So, what are, what are some of the biggest differences you see for your early-onset women versus later-onset women? And is there you seeing a big difference between post-menopausal and regardless of age, right? Like later menopause, early menopause, that kind of thing?

Rodolfo Savica:

Let me tell you first one. So, spot is that women as been absolutely underrepresented in sci in scientific literature early on, the women as well with Parkinson's has been very much not represented non necessary studied. There's number of studies shows the women are living a delay, a four third delay in getting to a specialist compared to men for Parkinson's disease in North America. So, we're not talking about any countries that are developed. I'm talking about North America there, you know, the most important country could, could form of in this moment in the western world. But clearly there's a lot of needs and a lot of things that needs to be done, because I tell you something shocking, women and men are different. Okay? Women and men are very different. And the disease, and I talk about social rights here. No, no, no, no.

Rodolfo Savica:

They're biologically different and even the diseases are looking different because I give you a practical, very simple example. We're talking about estrogens. Okay? Women need more levodopa compared to men to have the same effect. And these increase the risk of dyskinesia women compared to men. Why? Because the circulating estrogens that women have more are displacing the amount of levodopa in the blood. So, they need more. But, and these changes as we get older. That is why, and many, many women can tell you that with early-onset Parkinson's during their menstruation, during the menstrual, period, things can get definitely worse. it's like their medications don't work at all. Perfect. And then better and then worse again. And then maybe after menopause. And menopause is again moving target. We cannot tell you talk about when it's going to be early or menopause is difficult to say, but after the say, let's say after the age of 45, where many people start to enter, at least in some biological changes, things level up a little.

Rodolfo Savica:

But to the point they're not. Another thing I want to mention, women are different pregnancy and Parkinson, a complete abandoned field that now we are trying to fill the gap with calling me the Netherlands doing a PD registry for women that are in pregnancy. And actually, I want to mention this name, Dr. Sterban, she's a gynecologist from the Netherlands. She had Parkinson's disease, she has Parkinson's disease, and she had two pregnancy without Parkinson's and third pregnancy with Parkinson's. So, not only she has, she is a physician, she has a patient, but she's firsthand experienced that. And we always been very careful. But this is another topic that has been abandoned and has been neglected in the literature. And we need to do that. We need to study more. And other things seem to be silly. Still above women veteran and women, women that are in the army.

Rodolfo Savica:

There's, there's nobody many data about early-onset Parkinson's in the army. And I'm pretty sure that something that we need to be looking to that. But I'm pretty sure there are even less for women, and we need to fill these gaps. So, there's a number of gaps, but from a standpoint of seeing patients every day and doing research on the topic, there's massive difference between men and women in terms of responsible medication, because women require more in terms of role of estrogens, I always ask for menopause. I always make sure that people are, are not taking estrogen. Sometimes they're taking estrogen, say, take progesterone instead. And I try to involve whenever I can and whenever there's something, let me pass a term fishy. I'm always involving somebody in the women health clinic because we need to be understanding that. But another thing I say about women that is very important, autoimmune diseases, women are definitely more prone to about immunity compared to men. And that is to be, be the fact that women are able biologically to grow a parasite in there, there, in their body, which is, you know, having a pregnancy. So, women financially have the tendency to be more autoimmune disease compared to men. And this is an important role of neuroinflammation in development of early-onset Parkinson's or Parkinson's in general. And men do not have this issue.

Melani Dizon:

So, are you saying there's a link between people who get autoimmune early and then develop Parkinson's? Or not necessarily. So, common for them to have

Rodolfo Savica:

Wanted to say that linear, but clearly there are some types of Parkinson's disease that have been ignited by inflammation. it means started or at least manifested earlier because there is an, an immune response. And this means that clearly immune response as a role in the

developmental disease. And there's a difference between men and women there under percent. There's a difference.

Melani Dizon:

Wow. Okay. Let's chat a little bit about this,

Rodolfo Savica:

About women and Parkinson, another neglected topic. Sexuality, it's being neglected, man is easy. Quote, quote, I'm a man, man is easy. You ask your patient, hey, do you have an erectile function that is easy? That is not a question to ask. And sometimes you see Viagra saline in the medication list, so, you already know the answer. But how many physicians are asking the same to women are asking a and not talking about erectile function? It wouldn't be working in women, but what is the correspondence of erect dysfunction is dryness.

Melani Dizon:

Rodolfo Savica:

, vaginal dryness, pain during intercourse. How many people are asking that? No, not very many. And that's an important thing to do. But this comes to a question, a topic. I want to talk to you about education, educating the new generation of physicians, of colleagues and so, forth. That will be something you want to talk maybe later.

Melani Dizon:

Yeah. Oh, there's so, much to consider. Right. Okay. Let's talk a little bit about exercise. Sure. Because such an important topic and I want to get your sense on the value of it. Is it the same for people with young onset as it is late onset? What have you found? I think it's even more important. You do you give the people the same recommendation no matter what age they've been diagnosed? So

Rodolfo Savica:

Yes, everybody should move. Okay. Because if you reduce the risk of having cardiovascular diseases strokes hypercholesterolemia and everything else, clearly your brain would've a better wellbeing and you will live longer. That's a fact. Any age. But in early-onset is even more important. More important. Why? Because it's possible that some of the major changes are indeed mitochondrial are working on a mitochondria. And we need to activate these little organa somehow. An exercise is one of the way that we activate the organs. Always say, especially in patients or to patients that are young and are on top of their life. I said, okay, do

you like to do boxing? Do you like to do rock study boxing? Which is great. Just do regular boxing. Just do regular, regular exercise. You have to compare yourself with people your age. Because clearly if you're 42 and it is not fair for you to compare with somebody who's 72 to start with is not fair because there's aging there and you are not aged yet. You will because you are going to, we are going to be, but you're not age well. So, it is good to make sure that you compare yourself with somebody your age rather than somebody with a disease affecting you later in life. But all my patients, I say to engage in exercise and sometimes to tailor the medication intake according to the requirement of their exercise.

Melani Dizon:

Can you give me some examples?

Rodolfo Savica:

Sure. If somebody is training for a marathon, the requirement of dopamine, it should be higher during the marathon. So, I always say to my patient, let's try to find a threshold that works for you daily. Imagine like insulin, right? People are having an, in their diabetes, they're taking insulin in a baseline level. That is that one, I don't know, 100 units, let's make it easy. But there are moments of the day, maybe because you're working out, maybe cause you're busy, that your requirements are higher. So, the sensor is telling the diabetes patient, hey, you need to take more because your insulin is maybe you need to take extra 50 units and so, forth. Same story with Parkinson's. Somebody's taking, let's say one tablet or part of dopamine, doesn't matter what three times per day. Maybe on the particular day that they're training for the marathon, they need one and a half, maybe four times per day, maybe an extra dose in between the intervals.

And then on the weekend when maybe they're not working out or they're chilling out with their family, they need less than one. So, the amount of medication can change according to the needs. And exercise sometimes makes you require more. and people need to be taken more. I don't want people to grind through that because my biggest concern is falling. If somebody falls and breaks a bone, breaking bones is not good. And so, the biggest concern is making sure people are not falling. Because if they do, we have a problem. and the trajectory is going to be different then.

Melani Dizon:

Yeah. So, somebody actually told me, they wrote in and said that they, a lot of people will tell them, hey, you have to have your medication same time every day and you know, no matter what. And she says, I don't listen to that. I just take it when I need to take it. And she said, you know, I can see where for some people it needs to be more regimented because you know they're going to do it. But, but what is your, what is your opinion on people taking this into their own hands and saying like, well, I'm just going to take it when I think I need it.

Rodolfo Savica:

First of all, nobody knows their body better than yourself. Right. Your own, what your body requires and what body needs. So, I'm not, I don't know, I don't feel what neither you do, but nobody feels what a patient feels. So, they know better than anybody else. So, I tend to listen when they tell me number one, number two, that is an important thing. There's truth in both clearly. That's why I told you before, a threshold is good to know. It's good to know if levodopa works for six hours and then you need again. So, clearly you need to be taken every six hours because otherwise there's a drop that is too substantial attempts or five hours and so, forth. But it's also, truth that some people, again, within young unsafe Parkinson, their different subtypes. Some people do not have these massive wearing of or not having worn off at all, but they still require the medication. So, this patient, I agree with this patient, I don't feel the need of taking the meds. I need it only when I know I feel that I'm fine with that. But he or she start to wear declines wearing golf, then you had to have, you had to do both. A little bit of a regimented, stable, same time every day, more or less. Plus, some extra that people may need in some specific circumstances.

Melani Dizon:

Okay. Great. We are almost out of time, but I have to ask you this question. Hopefully we can do cover it. Just a general, general, general coverage of it, dementia and cognitive decline, young onset versus late onset. Sure.

Rodolfo Savica:

So, let's start with dementia. Dementia is a memory decline that clinically defined as memory decline that people patients may or may not realize they have, but pa but family members, they do realize they have, that has a significant interference in the activity living. So, in other words, when somebody is demanded, he or she is not able to function independently. That's the clinical definition. As we get older. Let's talk about late onset Parkinson's. As we get older, after the age of 75 years of age, 40% of all of us human beings are accumulating plaques and tangles in the brain that are the same plaques and tangles that you see in Alzheimer's disease. So, as a function of aging, and it's true that the data on Parkinson's disease letter, a letter phase are pointing at about 35, 40% of patients may have some sort of memory problem from very mild to very severe. But the memory problem that people with Parkinson's they have is not the same memory problem that people with dementia of Alzheimer disease they have has to do with do energy clause is affecting other circuit on the brain. Usually the executive function, the planning function, what we call the visual spatial abilities. So, the ability to know where your body is in the contents of space and the ability to, as I mentioned before, executives to a plan, a multitask plan is going to be tough. Clearly also, memory process, short-term memory can be effect.

Early-onset Parkinson's is totally different because there's no aging as far as we can tell. So, the plaques and tangles are not there. And it's true depending on what part of the circuit is involved. We may have a different form of memory disorder. And one thing I will, I said, I say in the past, I say it again, the first treatment is to optimize carbidopa-levodopa dopamine because sometimes memory decline is because the medication is dropping. So, increase in the medication to potentially provide some massive benefits. So, I do not treat memory disorder in late or early if I not at first optimizing the medication, number one, because that is a problem. Number two, memory is ordered in the young, the more the most, the most common complainer receive is I have brain fog. I have problem in a at times during the day I struggle I feel like in a cloud.

And this can again be a functional fluctuation of the medication, but sometimes it's not. Sometimes that has to do with the different circuits that are involved. The different frontal circuit are involving earlier onset Parkinson's disease. Because if you ask me about the frequency of dementia of clinically defined dementia in early-onset, Parkinson's disease is not very common. It's not very common, the clinical define. So, if I do a formal test, I look at the biomarkers and I have a diagnosis of dementia is not very common. But the complaints of brain memory disorder are very high, and they can interfere substantially with employment, work, and social life because it's almost always fatigued. I mean, this burden, this at least what my patient told me, and I tend to listen to them. So, that's what they told me, a burden on top of their head.

That's the most difficult one. And sometimes it's not easy to treat, but I think it's worth doing it. It's worth treating it. Again, most of my, some colleagues don't, don't even know about that. And it is a problem because those are concerned that are raised by the patient. Typically, the neurologist will do the maneuver, see their tremor, and say, oh, you're doing good. But that is a tip of the iceberg. There's so, many more things that if not task or if they're not reported by the patients are having massive role. And I don't know what you I, what my patient in front of me, what is the main problem with my patient. They yet to let me know. But I had to ask. Cause if I don't ask for sure, the tremor is under good control, fantastic. But that's not the problem. There's way more a memory decline. Brain fog memory issues seem to be one of the big ones in spite of normality, normal results for dementia. Because remember we talk about it before the Louis bodies are not necessarily there. And if they're there, they can be a common outcome coming from different sources. But it's not necessarily the main drive of the symptoms that we see in earlier younger patients.

Melani Dizon:

Okay. Oh gosh. I have so, many more questions. Hopefully we can do it again. We can do it again. Is there anything that you're really excited about in the research or work that you're doing that you want to tell us about before we say goodbye?

Rodolfo Savica:



Yeah, yeah, sure. No, absolutely. So, the initials are very many, very, very many. What I'm excited about is that there are a couple of potential targets, medication targets to try to help a specific subtitle, Parkinson's Disease. We're working with a number of we are working with some to some biomarker, blood biomarkers that can be also, targeted for potential medications that are already available in the market. They should be reported to something different. So, that would be something quite interesting. There are maybe a couple of trials coming out. But my problem with the trials is that there are not many trials, and I'm trying to be diplomatic here. There are not very many trials only on early-onset Parkinson's. There's not, and he is, and he's wrong, but he's also, wrong to lump early-onset Parkinson's together, we had to divide, we had to differentiate.

So, one of the things I'm excited about, that my team is trying to, really trying to understand the different, what we call phenotype, different types of disease to see how we can potentially customize the treatment for different people. That would be another thing. What I'm excited, about I hope that there will be some grant called some research grant calls from NIH, from Michael J. Fox, from maybe you guys, from anybody, doesn't matter who there will be devoted. This is my wish devoted only to early-onset Parkinson's. That is to me the biggest, biggest weak link that we have at this moment because all the current research is not necessarily devoted to early-onset Parkinson's, but to Parkinson's in general, which is okay, don't get me wrong and not say is not right. But we have spent an hour and everybody here in this call knows that what we talk here is completely different. And this means that the approaches that have been used so, far, and I'm not saying anything that we don't know, they have not necessarily led to advanced science. So, I hope that my wish will be indeed and this what excite me if we will have one day at one point something specifically for early-onset Parkinson's.

Melani Dizon:

Yeah. That's great. Well, I hope it comes, I hope the day comes sooner rather than later. Thank you so, much for being here. I'm so, grateful and I can't wait to share it with everybody.