Dr. Subramanian: Great, well thank you Andrea. Thanks to the PMD Alliance for continuing to host this, and I know we're getting into the winter months in many parts of the country, and the world is you know continuing to be sort of-- the pandemic is raging in many parts of the world so hopefully everyone's staying physically distanced, trying to socially connect in whatever way you can-- picking up the phone. These virtual support groups are a great way to connect with each other and think about those that are less connected even than you, so think about how to reach out to them as well. So it's with great pleasure that I bring Professor Gershanik all the way from Buenos Aires, Argentina. I wish we were there together. I'm such a fan of so many things that are Argentinian, and I saw Professor Gershanik speak at the Movement Disorder Society, which this year was fully virtual. I thought it was an amazing meeting. I was just inspired by his talk there. I ended up connecting with him. I sent him an email, and he was kind enough to chat with me a little bit about some things that he's been interested in and was kind enough to take an hour of his time today and teach us all about dyskinesia, which has been an interest of his from a research perspective. He is a true Renaissance man. He does a ton of great things. He's very supportive of patients and advocacy groups there in South America. He really has some cool stories to tell about the history of Parkinson's disease. He's been taking care of patients for decades already, and even though he looks very useful-- he was there at even at the start of some of the therapies that we have, so he'll teach us a little bit about that journey. He was the president of the Movement Disorder Society a few years ago and continues to give some amazing talks that are really inspiring us as clinicians. So it's just been a lovely thing to hear him speak, and I wanted him to bring some of that wisdom and enthusiasm for patients here on this call today. So thank you so much, Oscar for joining us. And he is based at the Favaloro Foundation at the University Hospital in Buenos Aires, Argentina. And so thanks Oscar for joining us. Welcome. Maybe you could tell us a little bit about your journey to becoming first of all a doctor and then a neurologist and what inspired you about Parkinson's disease and why you take care of these patients this many years later.

Dr. Gerhsanik: Okay first of all I would love to thank you for the invitation. It's for me a pleasure to be talking to you and to all your group and all the patients throughout the US and different parts of the world. I'm very familiar with this type of conversations because I've been involved for many years with advocacy groups here in Argentina and also with the WPC--- the World Parkinson Congress, which is also more dedicated to patient interest than other meetings. If you want to know about my journey, it goes back to-- I would say to my high school years, because when I was a teenager, I was able to travel to the US as a foreign exchange student. I lived in Iowa. I did my senior high school year there. So that was my first contact with the US, and that allowed me to perfect my english, and that was a very good tool that was quite important in my academic years. Actually my interest in Parkinson's disease and basal ganglia disorders started very early on in my medical school. When I was in first year medical school, I had to write a kind of a monograph or thesis, and I was interested in the central nervous system, and I wrote on the basal ganglia function. The basal ganglia is the structure of the brain that is affected by Parkinson's disease. I was interested in the basal ganglia because of its complexity. When I was younger, I never thought I would go into medicine. I thought I was going to be an engineer. My uncle-- my mother's brother-- was a highly successful engineer, and he was kind of my role model. Whereas my father was a pediatrician, and I don't know why, I never thought I would go into medicine, even though I was used to-- in everyday life-- to be in contact with my father's patients and with his practice. When it came the time to decide on a career, I suddenly switched from engineering to medicine. When I was studying anatomy and physiology, the basal ganglia had this complex circuitry that reminded me of my interests in engineering, and so I decided to go deeper into the knowledge of the functioning of the basal ganglia. That's why in second year

medical school I wrote this monograph on the intricacies of the basal ganglia. That was my first exposure, and from then on I decided that I would pursue a career in neurology, and not only in neurology, but in the sub-specialty of Parkinson's disease because at that time when I was studying there was no such thing as movement disorders as a sub-specialty. The sub-specialty of movement disorders came into being in the 80's, and I graduated in 1972. So there was no such thing as movement disorders. It was Parkinson's disease. In 1975 my mentor and the chairman of my Department of Neurology was invited to chair the meeting of the Argentine Neurological Society. And one of the faculty that was invited for that meeting was one of the pioneers in Parkinson's disease, Melvin Yahr. Melvin Yahr has the name of the Hoehn and Yahr scale, so he was one of the first ones to be interested in Parkinson's disease in a scientific and academic way and with true scientific methodology. Actually he was the first one to publish what happened to patients that were introduced to this new wonder drug called levodopa. He was invited to give a talk in Argentina, and there was supposed to be simultaneous interpretation of his lecture for the audience, and the interpreter approached Melvin Yahr and said, "do you have anything written?" and Mel Yahr-- who was kind of gruffy-- he was not very easy to get along with. He said, "I never write anything for my lectures. I have everything in my head." so the interpreter said, "well if you don't have anything written, this is a very specific topic. I'm not going to be able to translate your talk, so I quit. I resign." the chair of the meeting-- my mentor-- was kind of desperate and said, "Oscar, I know you're quite fluent in English. Do you think you can translate Mel Yahr's conference?" and I said, "yeah, I can do it. I cannot do simultaneous translation, but I can go up on the podium on the stage, stand at the side of Mel Yahr and do sequential translation." I did it, and it came out quite well. Everybody was surprised because the audience thought that that had been pre-arranged like this, as it went so smooth. Mel Yahr was kind of surprised that I was so knowledgeable about the basal ganglia-- I was just a very junior neurologist doing my residency training-- and he said, "how come you know so much about the basal ganglia and dopamine and levodopa?" At that time he was presenting Sinemet, the miracle of the combination of levodopa with dopa decarboxylase inhibitors. Everybody was fascinated with this new combination of levodopa that was so effective. He said, "are you really interested in the field of Parkinson's disease and dopamine metabolism and levodopa?" and I said, "yes this is one of the things I want to do." and he said, "why don't you come to Mount Sinai to work with me?" and I said, "well surely I'm interested in doing that." a year later I received an invitation, and I spent some time at Mount Sinai. I did basic research there, and I had the chance to meet-- I think-- one of the greatest guys in the field. Unfortunately, he has already passed away. Roger Duvoisin, not only was he a pioneer in Parkinson's disease, he was the promoter of the search for a genetic cause of Parkinson's disease. His group was the one that discovered the first genetic form of Parkinson's disease. When I finished my time at Mount Sinai, I came back to Argentina and soon after I arrived, I received a letter-- at that time there were no internet, no emails, no WhatsApp, nothing of that sort. Everything was via mail, regular mail. Roger Duvoisin invited me to go back to the States to the newly created Department of Neurology at Rutgers Medical School, what is now known as Robert Wood Johnson. That time it was called Rutgers. So I went back to the States. At that time I was not only invited as a fellow, I was invited as an associate professor of neurology and neuropharmacology, and I did teaching and clinical work and basic research in dopamine receptors. That was my beginning in the career in a dual or two-hat career-- on one hand my clinical interest and on the other hand my basic research interest. That's how I became interested in this field, and from then on everything was like a roller coaster. I started attending meetings, publishing papers. I got to know Stanley Fahn going to the American Academy of Neurology, and in the 80s I received another letter from Stan Fahn, inviting me to become a member of the International Executive Committee of the more recently created Movement Disorder Society. I started as a member of the International Executive Committee, and I climbed up the ladder within the Society. Later on I became the treasurer of the Society, and then in

2015 I was elected to become the president of the Society from 2015 to 2017. Still I'm very active in the Society. I'm the chair of the International Congress Oversight Committee. I'm advising the educational roadmap in our website, and I'm the advisor for the creation of the African Regional Section of the Movement Disorder Society. So this is in brief my career in the field.

Dr. Subramanian: Amazing! Well I think you know that's an amazing story of almost luck in some ways to have been in the place where the interpreter quit, but I think you would have shone anyway I think, and shot up in all of these ranks regardless of if you had translated for Dr. Yahr or not. But just such a cool story I think, so thank you for sharing that with us. Oscar, I think your work at the Movement Disorder Society has been really important, and we've had in these series of talks Omotola Thomas, who is very active with the PD Avengers and trying to get the African countries to have access to these medications. I think you've really put the South America and made the Americas unified in many ways. Some of the hopes that we're trying to create with the Pan American Society as well with the Movement Disorder Society, so I really commend you for your work and great causes that you've been behind and getting really great things done as well. So Oscar, I wanted you to have some time now to teach us a little bit about just kinesics. I think you've seen literally the history, and I think this pendulum even in the 20 years that I've been a doctor, of taking care of patients where we were having levodopa phobia for much of when I first started training, and now we're much more happy with using these dopaminergic medications. Then also I'd like to you to have a little bit of time to teach us also about some of the lifestyle and approaches that you think help patients in their day-to-day lives as well, so I'll give you some time to maybe teach us a little bit about your approach and the dyskinesia concept and what you think causes it and how we should approach that.

Dr. Gershanik: Okay, well there are many ways to look at the problem of dyskinesia. One is first to understand that this is a very very complex clinical phenomenon from a phenomenological point of view because people try to think about dyskinesia as a uniform phenomenon. It's very complex, very diverse. There is a range of clinical phenomena that have different pathophysiology and different forms of presentation, so I think it's important for the patients to understand, first of all, that dyskinesia is a long-term complication of the exposure to levodopa. This is not a symptom of the disease. It’s an abnormal reaction to the effect of the medication on the brain. This is a very important concept to bear in mind. Second is that dyskinesia, as I said before, is not a uniform phenomenon. There are very different types of dyskinesia. You have what is called the on-period dyskinesia and the off-period dyskinesia and the diphasic dyskinesia. These are quite different. The off-period dyskinesia coincides with a period of absence of the effect of levodopa, and the phenomenology is quite peculiar because it's mostly dystonic-- dystonic meaning muscle contraction. It's a sustained muscle contraction, and the most common of the off-period dystonias is the early morning foot dystonia. People wake up early in the morning, get out of bed, try to start walking, and as soon as they start walking, the most affected food goes inward, and it can become painful. This is what's called off period dystonia. The on-period dystonia has very different forms of presentation, the most common being the great type of dyskinesia. This is kind of a dancing like movement, oscillations of the trunk, oscillations of the limbs. That's the most common type of dyskinesia that occurs during either the maximum benefit of each levodopa dose or during the entire on-period, where the patient is under the effects of the medication. There are also other types of on-period dyskinesias, like jerky movements of the limbs, jerky movements of the head, etc. Then there is one peculiar type of on-period dyskinesia that is called peak-dose dystonia. This is characteristically affecting the perioral muscles-- the muscles of the mouth. People, when they reach the maximum effect of levodopa, experience a contraction of the muscles around the mouth. That interferes with speech and articulation. And then you have the diphasic dyskinesia.

This is a very complex type of dyskinesia, and it appears at the beginning of the effect of a levodopa dose, disappears during the period of maximum effect of the drug, and then can reappear in the period where the effect of the drug tapers off. This is the most complex, the most debilitating, the most incapacitating because these are very complex jerky movements that predominantly affect the lower extremities, like repetitive movements of the legs. They are very very debilitating and incapacitating. Every time we face with a patient with dyskinesia, we have to be aware of these different types of dyskinesia because the mechanism of production of these dyskinesias is quite different. The off-period dyskinesias are due to the lack of effect of the medication. The on-period dyskinesias are because of an excessive effect during the periodic effect of the medication. The on-period or peak-dose dystonia is very difficult because it appears at the peak of maximum effect of levodopa, and it's very difficult to manage. The diphasic dyskinesias that some people associate with an excessive effect of medication-- the fact of the matter is that these dyskinesias are because the patient cannot achieve enough levels of levodopa in plasma to have the full effect of the levodopas. So these diphasic dyskinesias actually respond to increases in the dosage of levodopa. So we cannot lump together all the dyskinesias and think this is a very simple problem, and it's because of an excessive effect of the medication, and just by reducing the medication you solve the problem, because this is not the case. It's not also such an easy explanation that it's an excessive effect of levodopa because sometimes patients develop dyskinesia with very low doses of levodopa. So this has to do with what is called the therapeutic margin or the therapeutic window. The therapeutic margin or the therapeutic window is the difference between the dose that provides benefit with a dose that produces side effects. If that distance is very narrow or very short, the dose that you need to have to benefit is the same dose that produces the side effects. So that's why sometimes it's very difficult to manage dyskinesia. This is an overview of the clinical phenomenology. Concerning the factors or the risk factors for the development of dyskinesia, we know for a fact that younger people are more prone to develop dyskinesia than older people. In younger people, one has to be particularly careful with the use of medications because they tend to develop dyskinesia very easily. Second, lower body weight-- females that have a lower body weight than males-- are also more prone to develop dyskinesia. It's an important factor, duration of the disease is another important factor. In my experience, another important factor that people do not consider as important, but there is significant evidence in this regard, is the way you will administer levodopa. This can be a controversial issue because the manner or the mode of administration of levodopa differs from one part of the world to the other. When levodopa was first introduced into the market, the mode of administration was suggested as three doses a day, and there was no explanation or a scientific background to decide that this was the correct way of administering levodopa-- three times a day. The other thing is that when you say three times a day, it may be not the same for one person or the other because sometimes the doctor doesn't tell the patient, you have to take this at regular dosing intervals. So you find patients that take one dose in the morning, one does at noon, and one dose late at night when they go to bed. We know through our research in the mechanism of action of levodopa and the dopaminergic system that oscillations in the stimulation of dopamine receptors-- what is called pulsatile stimulation of dopamine receptors-- is one of the mechanisms that leads to all the changes that take [audio cuts out] level and at the structural level in the cell that lead to the development of dyskinesia. If you administer levodopa in a very pulsatile and irregular way, the chances of developing dyskinesia are much higher. There has been a lot of research done in other ways of administering levodopa at shorter intervals-- three and a half to four hours-- so at least four times a day or five times a day, and to be very precise in the way you adhere to the intervals. You have to take it every four hours, and you have to be very regular, and you have to take the lowest possible dose. These are things that diminish the risk of developing dyskinesia. In my experience this is something that is not shared by many people particularly in the US and Canada, but it's shared by people in Europe and in the

[inaudible] region, and in some people in the UK too. I sometimes prefer to delay the use of levodopa in younger patients, and in my own experience, when you talked about this cycle with levodopa, I started in the field in the 70's, when levodopa was just introduced into the market. I treated patients before Sinemet appeared in the market, so we had levodopa without dopamine decarboxylase inhibitors, so you had to give huge amounts of levodopa-- 12, 16, 20 grams of levodopa. Patients did not tolerate levodopa very easily, so the titration had to be very slow and in low fractions of levodopa, but we thought this was a miracle drug. It was the first drug that specifically addressed the biochemical disturbance underlying the clinical features of Parkinson's disease, so we were going to solve the disease. We were very careless in the use of levodopa. We gave levodopa to everyone, and we climbed the dose until we reached maximum benefit without any consideration about the risk of developing dyskinesia. Soon enough people were having these complications. In the late 70's and early 80's, we had the best descriptions of dyskinesia, and all these complications due to the careless use of levodopa. That coincided with the development of dopamine agonists. Dopamine agonists were thought to be less powerful in the sense of achieving clinical benefit, but also less powerful in their ability to induce dyskinesia. People started developing what is called levodopa-sparing strategies. We started patients on low doses of dopamine agonist, and we delayed the use of levodopa. Some people started also to claim that levodopa was not only capable of producing these side effects, but also was toxic to the brain. On one hand it improved the clinical symptoms of the disease, but on the other hand it could be toxic to the cells, to the remaining cells in the brain. I think this was promoted in part by the pharmaceutical industry trying to put a wedge into the levodopa field and promote the use of dopamine agonists. But there were many scientists that truly believed that levodopa was toxic. It was in fact in my own research lab that we demonstrated for the first time *in vivo* that levodopa was not only not toxic for the cells, but it promoted to some extent the recovery of dopaminergic cells. From then on, the myth of levodopa toxicity was not claimed anymore, was disproved. So people started back again to get more confident with levodopa. We arrived to 2019, 2018, where we've gone full circle. Now we have some of my dearest colleagues in the world and some people that you have interviewed in your series, Indu, that say levodopa for all, no matter what-- whether they are young, they are old, etc., etc. 'm still a firm believer that in younger people we have to be quite careful. I base this not only on scientific evidence, but also on my clinical experience. I've been in the field for 43 years. I'm not just a consulting neurologist. I see patients on an everyday basis and some of my patients, I have followed them for 30 years now. I have seen them from day one until today, when they are 30 years into the disease, so it's not that I see a patient every two or three, four years, referred by the primary care physician. When I started in the field we used to see this very severe incapacitating dyskinesis. We had to admit the patients to the ward because it was so severe the patients got dehydrated. We don't see that anymore. In the last 10 years, we don't see as many patients with severe dyskinesias as we saw before, and I think this is because three things, three factors that influence that. First, we are careful with the introduction of levodopa in young patients. Second, if we use levodopa, we use it very carefully at the lowest effective dose, and we are very careful with the mode of administration. We try to use it at very regular intervals, trying to make the patient understand that the more stable the levels of levodopa in the brain, the less chances of developing dyskinesia they have. So these are some of the factors that lead to the development of dyskinesia. Another thing that I would like to underscore or underline, is that once you develop dyskinesia, it is very difficult to go back. It's very hard to make them disappear, not only because there are molecular changes, but because there are genetic transcriptional changes in the cells and structural changes. The cells modify their structure. Cells contact each other through what is called dendritic spines. These are small protrusions in the harborization of the neurons. When you get Parkinson's disease, and you lose dopamine neurons so there is less dopamine in the brain, there is a change in the structure of your cells. When you try to introduce levodopa to alleviate the symptoms of the disease, you do

not go back to normal. You do not re-establish a normal functioning of the brain. You make further modifications in the molecular cascades and further modifications in the structures of the cells which are not normal anymore. They are a different abnormal that allows the patient to feel better, but it's the stepping stone for the development of dyskinesia. These structural changes do not disappear. These molecular changes do not disappear very easily. So when we are faced with a patient that has developed dyskinesia, it's quite problematic. This is another myth that I would like to address. Again, some of my dearest colleagues, as I mentioned before, think that dyskinesia is not truly a problem. In fact they go as far as to say that dyskinesia is a measure of success in your treatment of a Parkinsonian patient because it means that you have achieved a sensitization of the brain such as to provide more benefit. This is absolutely not true. I mean I don't think that developing dyskinesia is a measure of success in the treatment of a Parkinsonian patient. Parkinsonian patients with dyskinesia, first of all, they do not feel comfortable. They feel discriminated. I can tell you some of my patients taking public transportation have been forced to oscillating and dancing all the time, and people tend to discriminate people that look different. When you're talking to somebody that is moving and gesticulating and doing bizarre movements, this is easily confused with mental incapacity. This is a kind of a factor that stimulates social discrimination. We're not talking only about social discrimination and discomfort. People with dyskinesia find it very difficult to dress when they have these movements because it's not easy to button up a shirt or to zip up a a sweater. It's difficult to use your fork and knife when you are eating and you're moving. Sometimes it's difficult to chew the food when you have all these gesticulations. So I don't think dyskinesia is a measure of success. There are many publications addressing quality of life and dyskinesia. Very few say that dyskinesia does not affect quality of life. In fact I would say that there's only one that is often cited by those that promote the success that dyskinesia means in terms of therapeutic objectives. But most of the other publications talk about all these other issues that really reduce quality of life in our patients. So we have to be very careful in the way we use our medication and try to prevent dyskinesia, because once dyskinesia is there we only have two or three possibilities. We can reduce the dose of levodopa, which sometimes is not very easy because of what I talked about-- this narrow therapeutic window. When you reduce the dose of levodopa, you get rid of dyskinesia [audio cuts out] benefit of the drug in terms of your motor performance. You can do fractionation of the dose of levodopa. So instead of taking three or four times a day, you go up to six or eight times at lower doses, but that sometimes is not very effective. You can give amantadine, which is the only approved drug in the world for the treatment of dyskinesia, but amantadine reduces only 60 percent of dyskinesia, and it has another problem. It's not only that it's not effective in a hundred percent of the cases, but it has an anticholinergic component to its effect, and that can affect attention and cognition. In patients that are old or of advanced age and have dyskinesia, you have to be very careful with the use of amantadine because amantadine may contribute to further deterioration of the cognitive status, so it's not for all. The other possibility is advanced therapies-- DBS surgery or levodopa infusions. Levodopa infusions are not very easy. They have to put a tube in your intestines. You have to carry a huge pump at your side. It's very very expensive. It has limitations in the things you can do in everyday life. You cannot swim, for example, you cannot get into a jacuzzi, you cannot get into a swimming pool or the sea because you have this tube in your stomach, and you're carrying that pump. It's not a very good solution. It's a solution in a relative sense for patients that cannot undergo surgery. Then you have surgery. This is something whenever I give a lecture at society, I always remind our colleagues that we are an international society, and the world is not uniform. The world is not the US and Western Europe. The world is wider, it's more complex, it's more diverse not only in culture but in resources and access to medical care. We cannot take for granted that when we give a talk about, what are the opportunities for a patient with dyskinesia, oh he can have duodopa-- levodopa infusions-- tell that to a patient in Africa or in central America, where levodopa infusions are not available, not even DBS, not

even surgery. So we cannot talk so easy about we have all the resources to treat dyskinesia because we have advanced therapies because these are not available worldwide, and even when they are available for some countries, they are so expensive that not many people can afford to have the type of therapies of advanced therapies. So this is something that we have to take into account when we talk about, dyskinesia is not a huge problem. It is a problem. So I think I've said enough, Indu. Maybe you can make some remarks or questions or some things that you would like me to talk about.

Dr. Subramanian: Yeah, so I think a lot of what you said is resonated in the chat a lot. People are really appreciative of hearing about the different types of dyskinesia and dystonia, the understanding of that. The way that you explained it I think has been very helpful to people. And I think a lot of people have been trying to get a better sense of things for themselves. So one of the questions is that some people say that they experience dyskinesia and dystonia at the same time. Could you speak to that? is it possible to have both at the same time?

Dr. Gershanik: Yes, of course. In the benefit of those [inaudible] dyskinesias, they can be not only co-reactive, but they can have dystonic jerks, and they can have peak dose dystonia in the head because these are dyskinesias that appear during the period of symptomatic benefit of the drug. So there can be a combination of choreatic movement, jerky dystonic movements, and contractions of the neck, of the arm, of the head. It can happen, yes.

Dr. Subramanian: Okay and then there's another question here about, is it possible-- would it be helpful to measure blood levels of levodopa, like we're doing in diabetes, for example? we can measure glucose levels and check them. What is the utility of that?

Dr. Gershanik: Well it's not useful because the absorption of levodopa is quite erratic, and the variability in the plasma levels of levodopa is great, and it does not reflect what happens in the brain. If we were able-- via some mechanism that doesn't exist at present-- to measure the levels of dopamine at the synaptic level, that would be interesting, but we cannot do that. But measuring the plasma levels of levodopa doesn't make any sense.

Dr. Subramanian: Yeah because it's just a reflection of what we're seeing in the blood, not actually what's going on in the brain level. Okay and then talking about somebody's asked here about when they have stutter stepping, so their feet are moving fast. Is that a dyskinesia example or is that something different?

Dr. Gershanik: Are you talking about propulsion and fascination?

Dr. Subramanian: It sounds almost like freeze, like their feet sort of go like this [makes fast alternating motion with hands]. Is that an example, I think they're asking, if that's sort of a question.

Dr. Gershanik: Yeah. Well no, that's not a dyskinesia. Some people when they get stuck on a place-- what we call freezing of gait-- sometimes they experience a jerky movement of the legs, and that's a myoclonic phenomenon, and it's not a dyskinesia. That's a totally different phenomenon.

Dr. Subramanian: And somebody here has written that they don't enjoy their dyskinesia at all. They would not call it a success from a patient perspective, so they're resonating with your comment about how it can really affect quality of life. I think a lot of people have felt similar with

that. So a couple of questions. I think one is getting a sense then, Oscar. Your algorithm. So let's say when you're talking about young versus old, or younger versus older, I guess, what is your cutoff? is there a way that you define that in a number? or is it something that you-- what do you take into account when thinking about that cut off?

Dr. Gershanik: Well when you decide the type of medication-- first of all, it's very hard now to say who is young and who is old because the life expectancy has expanded so much in the last 50 years that now a person that was considered to be in advanced age 20-30 years ago now is a middle-aged man or a middle-aged woman, so it's very hard to define that. I would say biologically young more than chronologically young. When I talk about very young, I talk about people under 50 for example. People under 50 are very young, and we have to be very careful with the use of levotoba. Between 50 and 65, it's a matter of being biologically young versus chronologically young, and there you can sometimes decide whether this person will benefit with levodopa because of the severity of the disease or we can postpone the use of levodopa. When a person is above 65 or 70 sometimes, it's not sensible to postpone levodopa because the complications of levodopa tend to appear after 10 years, and so if life expectancy is around the 80s you cannot deprive the patient of one of the best drugs we have for the symptomatic treatment of PD. It's a matter of experience. I cannot give you strict rules. In the very young, yes. In the very young, yes. I would like to make a comment about the treatment of dyskinesia that I forgot to talk about.

Dr. Subramanian: Sure.

Dr. Gershanik: This has to do with diphasic dyskinesia. As I told you that diphasic dyskinesia or end-of-dose dyskinesia or beginning-of-dose dyskinesia, paradoxically they can be resolved with rescue therapy, for example apomorphine or inhalable levodopa. Whenever a patient has one of these bouts of diphasic dyskinesia, you can give a shot of subcutaneous apomorphine or a puff of inhalable levodopa. Now you have the Kynmobi-- the film-- and you can rescue the patient from this severe diphasic dyskinesia because they are caused by low levels of levodopa or intermediate low levels of levodopa.

Dr. Subramanian: And Oscar, in your practice when you're trying to understand these things from a patient-- the timing of day and when they're getting-- is there some sort of-- do you use a diary for example, and have people fill things out, or is it verbal? How do you get a sense of when these episodes are happening?

Dr. Gershanik: Well there are many diaries that are used out there to try to record off-time, on-time, time of sleep, time of dyskinesia, but there's no single diary that properly differentiates off-period dyskinesia or dystonia, diphasic dyskinesia, on-period dyskinesia. So what we do is we try to make patients understand, try to pay attention to not only the time of day in which the dyskinesia appears in relation to the time of the dosing of the levodopa, but we also give them instructions as to the recognition of the phenomenology, because you can tell whether it's a diphasic dyskinesia or a peak-dose dyskinesia by the type of movement. Diphasic dyskinesia predominantly affects the lower extremities, are repetitive [audio cuts out] movements whereas [benefit-of-dose?] dyskinesias are choreotic or dystonic. Off-period dyskinesias are muscle contractions. So we instruct the patient to recognize these different phenomena in order to identify them, and we also talk to the carer of the patient because one of the curious things about dyskinesia is that sometimes the patients that have [benefit-of-dose?] dyskinesia, if these are not too severe, they do not realize, they do not perceive that they have dyskinesia. It’s the carer, it’s the relatives that tell them, “you're moving all the time, can you be still?” and the

patients do not realize they are moving all the time. Sometimes because there is a tendency to develop what is called levodopa addiction or what's called dysregulation-- dopaminergic dysregulation syndrome, these patients that have dopa addiction have severe dyskinesias, and they think that they have dyskinesias because they do not have enough effective [audio cuts] levodopa and they worsen the dyskinesia because they are addicted to the levodopa. So these things you have to take into account, too. Some patients become hooked to levodopa, and it's very hard to tell them, “well all these movements that interfere with your activities in everyday life, they are caused by levodopa.” you have to reduce levodopa.

Dr. Subramanian: Yeah, it is very complicated, and even within the same patient sometimes, the 24 hour discussion is very interesting. So quick question, when you're starting levodopa, let's say, you had talked about the judicious use of it.

Dr. Gershanik: Well sometimes I ask a patient to [audio cuts out]

Dr. Subramanian: Can you hear me? Is this okay?

Dr. Gershanik: I was saying that sometimes we ask the patient and their families to register through a video recording the phenomenology of the dyskinesia.

Dr. Subramanian: Yeah, that's very helpful. So when you're starting levodopa you were talking about the judicious use. Can you give us a sense of what your average idea of starting dose would be when you're starting it? you talked about starting low, starting it multiple times a day. Let's say you had a 65-year-old woman of relatively small size before you. What would you start her?

Dr. Gershanik: I'll give you an example of the way I start levodopa on a patient like the one you talked about. If I see a patient in which I have to start levodopa, first of all, I do not give four doses from the beginning. I start introducing levodopa very slowly, trying to adapt the patient to each dose. For example, I tell them-- we have here Madopar, which is the brand name of levodopa benserazide, that has 200 milligrams of levodopa. I encourage the patient to fractionate the tablet in fourths-- 50 milligrams, start with 50 milligrams at 8 am the first week; 50 milligrams at 8 am and 4 pm the second week; 50 milligrams at 8 am, 12 noon, and 4 pm the third week; and the fourth week complete the four doses with a fourth dose at 8 pm. Why do I do that? not only because my experience [audio cuts out] titration of the levodopa, but there is a reason. Parkinson's disease is an imbalance of basal ganglia function. If you try to modify that imbalance very rapidly, you cause a very tremendous shift in the stimulation of the dopaminergic receptors that leads to these molecular and genetic transcriptional changes. So I try to adapt not only the patient to the tolerability of the levodopa, but adapt the brain to new levels of dopamine in the brain. Many of my patients can go on with just 200 milligrams of levodopa divided in 50 milligrams four times a day for one or two or three years without the need to modify the dose. If I have to modify the dose, I try to modify it gradually. Again, if the patient is taking 50 milligrams four times a day, and I have the need to increase the dose, I tell them-- the first week you increase to 100 milligrams in the first dose of the day, the second week in the third dose, the third week in the second dose, and the fourth week in the four dose, and you reach 400 milligrams. If possible, try not to go beyond four mil 400 or 500 milligrams per day because the chances of developing dyskinesia are very high when you go above 500 milligrams. The other thing is that there is something that-- it's not well studied from the basic research side of things-- which is a phenomenon that I call induction. The more you give levodopa, the more you need levodopa. That's a type of phenomenon in pharmacology, and

people that experience not only dyskinesia but experience fluctuations that need to shorten the intervals between each dose of levodopa. You start shortening the intervals and increasing the dose, and the patients keep fluctuating more and more. It's kind of a no-win or catch-22 situation.

Dr. Subramanian: I see, that's really interesting. It's good to hear how you start that. There's been a few questions just on leg cramps at night. Could you speak to that, Oscar?

Dr. Gershanik: Yeah well leg cramps at night are in fact off-period dystonia in most of the patient that sometimes is solved by giving control-release formulations of levodopa at bedtime.

Dr. Subramanian: Yeah that seems like a very reasonable approach. So I want to give you the last few minutes, Oscar, to just tell us a little bit about some of the more holistic approaches. I know you and I spoke a little bit about the tango dancing that some of your communities are doing in Buenos Aires. Maybe you could tell us a little bit about your kind of approach to those sorts of things, what you think the tango dancing may do, and if there's another secret or two maybe that you've thought about we have about three minutes left to inspire our patients here. And I wanted to give you a chance to teach us any of your secrets.

Dr. Gershanik: Well, just a couple of things. You know that I'm a fair advocate of lifestyle changes in Parkinson's disease. I'm a firm believer that you need social interaction, [audio cuts out] [sleep at?] night. You have to have a good healthy diet because a good diet like the Mediterranean diet promotes a healthy microbiota, and a healthy microbiota prevents neurodegeneration, and it modulates your immune system. You need to be psychologically well and accepting the disease because if you do not accept the disease and share with the disease your journey, you're going to be unable to do the things that you need to do-- to accept taking a medication in a regular basis, to to do exercise every day because exercise is very good. So I'm all in favor of this holistic approach to the treatment of Parkinson's disease. It's not just the medication. It's also the contention that you provide to the patient every time you see him. Try to make the patient learn to live with the disease in a friendly way. Try to make amends with the disease. I just saw one of the patients saying, “Don't all porteños dance tango?” You know porteño are the people that live in Buenos Aires. Not all porteño dance tango. I do not dance tango, and I'm a porteño. But coming to tango, I was telling you before we started this interview that tango has been shown to be very effective in Parkinson's disease. I believe that the reason why it's very effective in the rehabilitation of Parkinson's disease, particularly balance and gait, is because tango is something that is not done by rote. It's not something that you memorize. It's something that you have to do it very consciously and very attentive. Whenever you increase your attention, you improve the performance of your gait and you improve your posture. So that's why tango is so successful and effective as a mode of rehabilitation in Parkinson's disease.

Dr. Subramanian: That's amazing!

Dr. Gershanik: And it's not true that all porteños dance tango! And it's not true that all Argentinians drink maté either.

Dr. Subramanian: Well this has been such an amazing session. It's so great to connect with you through this

Dr. Gershanik: And it's not true that all Argentinians have dinner at 10 pm!

Dr. Subramanian: [laughs] You're dispelling many myths here. So thank you so much for your time and all of what you've done. I mean it's just an amazing career that you've taught us about, spanning from when levodopa was first introduced. Really it's so fascinating to see your description of your evolution of thought over these many years, and it's just amazing to also hear about these patients that you've followed so closely. At your stage of your career, it's very easy to say somebody else can do the daily phone calls and the follow-up, but I think it really makes a huge difference when you are the one to know about the intricacies of the patients and are the one to see them so often and for so many years. I think it's really telling. So I really appreciate you coming on the series, Oscar, and appreciate all that you've done for the Society and for inspiring people like me. There's many many kind comments here hopefully the gang from PMD Alliance will forward to you. I'll just give you a second to wind up here if you want to say a message of hope to our listeners out there and thank you again, Oscar, for spending the hour with us.

Dr. Gershanik: Oh I thank you very much, Indu, for the invitation. I really enjoy talking to you, and I think it's a wonderful opportunity to talk to people with the disease, people with Parkinson's and give different outlooks as to the experience that many of us share. I can tell you there are not many people that are fortunate enough to have lived through the whole evolution of the processes-- the introduction to levodopa to what we know presently. So I feel fortunate to have been a witness of that evolution. I thank the opportunities that the societies have given and my mentors have given to me. So thank you again.

Dr Subramanian: Thank you. Back to Andrea for a goodbye wave.

Dr. Gershanik: Bye

Andrea Merriam: So, Professor we always show our gratitude by turning on our video and doing a wave, so if you want to look in gallery view and see all the faces saying, “thank you for educating us and all of the work that you've done over your long illustrious career.” so thank you for joining us and thank you to all of you for tuning in and great questions and great discussion as always, and thanks Indu.

Dr. Subramanian: Thanks, bye guys.

Dr. Gershanik: Thank you bye bye, everyone.