

wHolistic!™ - Freeze, Shuffle, Fall: Parkinson's and Gait - Dr. Simon Lewis

Andrea Merriam: --Disorder Alliance, it's our pleasure to be hosting you today and to start with introductions I'll kick it over to you Dr. Subramanian.

Dr. Subramanian: Thank you so much. We're so excited to have all of you on. The numbers are growing, and we're globally connecting. You may hear some drumming in the background. I don't normally have this going on here, but I have a child who's got some music classes going on, so that should dissipate, but we'll have some extra noise in the background in my house today. Thank you so much, Simon, for joining us from literally across the globe. I'm so excited. I had the pleasure of meeting Simon a few years ago and have just been so impressed. He actually chaired a section of the World Parkinson Congress in which Dr. Mischley and Dr. Kluger and I were all in, talking about integrative medicine and have just been inspired by Simon and all the different things that he's been involved in ever since then. I'm really excited to have him and he's woken up bright and early along with some other Australians-- I think it's like 7:00 in the morning and on a Saturday so instead of sleeping in, he's joined us and has been kind enough to share his wisdom today, so we're so excited to have you Dr. Lewis-- Simon. I will tell you briefly about him but he has so many different things that he's involved in and interested in, it was so hard to come up with just one narrow topic, so we might have to have him back on. He is a consultant neurologist and a professor of cognitive neuroscience at the University of Sydney-- and you see that beautiful background there with the Opera House and the bridge and everything like that, and I had the pleasure of hanging out with Simon not that long ago-- it seems like years ago now but I think it was last September when Dr. Padmakumar, who's going to be on a little bit later on in the series, invited us to give some talks together at a fabulous meeting of minds with some geriatricians and some different folks from literally across the world. Really great to learn so much about how people are approaching Parkinson's from geriatrics perspectives, from neurology perspectives, and just an international collection of folks. We'll be bringing you some of those folks with the content that's coming up. Simon is going to talk a little bit about one of his passions to begin with and we might hop around. He has himself a fabulous website with a ton of videos and amazing content so we'll be sharing that as well so that people can get educated on his passion for Parkinson's disease. He's really such a patient advocate, so really excited to have him speak to us today. So Simon maybe I'll let you tell us a little bit about how you got into neurology and why medicine and specifically about Parkinson's disease and then the specific maybe a couple of passions that you've been focusing on with your research and clinical care these days and we can then have you speak about the specific topic of gait and freezing and then we'll sort of hop around.

Dr. Lewis: Well, good day, good morning, and good afternoon to everybody and thank you so much to the PMD Alliance for inviting me to do this presentation and connect with everybody. It's obviously a very difficult time for us all around the world. I know that, I can see that the people dialing in from all over the states and Europe and UK and obviously having it very tough compared to how lightly we've been touched by the pandemic here in Australia, so I realize it's a very difficult time for everybody. Indu, it's great to see you this morning, and I'm sorry that we can't do this in person. In terms of getting into neurology, I think I tried pretty much every other specialty and I was no good at them, and I realized I might as well be no good at something I enjoyed. I think neurology, it was good. Then in terms of the Parkinson's side, at the time that I went into neurology you couldn't get a gig, you couldn't get a training job, unless you'd done some research, the limited numbers. Literally the first job that came up was a study with Roger Barker in Cambridge-- he should definitely get on this platform as he can-- and Roger is a very vibrant guy, and it was literally the first job that came up, and the beauty that I had was that Roger had done all the hard work setting up a research clinic. He'd taken five years to set up a clinic there, and in that five years I think he'd seen about four people, and I said to him, "That's

not very many.” And he said, “Well that’s why I got the [maids?] to get you.” And so in the first four months of being in that job, I saw 200 patients through that assessment clinic. Most of them I went and visited at home because I couldn’t get the space in the clinic. That really did give me the passion for Parkinson’s because basically if you go through medical school you think about Parkinson’s very differently to when you actually start seeing it in practice. It’s funny because there’s a completely different view to seeing patients who come to see you in the clinic versus going to see somebody in their own home. When they come to the clinic, the wife will always say to you, “Oh he’s never like this at home. He can’t walk, he’s never like this, he’s always he very [inaudible], and of course they come to the clinic and they put on their best behavior, and you think “Wow they’re amazing.” And of course, the wife takes them home, and they want to beat them around the head, and it’s funny because it leads into this topic this morning. I remember it very distinctly I was visiting a gentleman in Norfolk in the wilds of England and [they had] one of those front doors which has this sort of frosted glass window. I remember seeing this shadowy figure coming up the corridor, and then it disappeared and then it reappeared and then it disappeared and then it reappeared, disappeared. And when the door opened, he turned and walked back down the corridor to let me in, I realized what was happening. He was freezing and falling down, And I’ve never seen anything like this before. And of course, he took it in very good part, very British about the whole thing. And he was like, “Oh I was doing that, bang, hit the ground, up, bang, hit the ground.” I thought, “What is this, he’s doing?” And I really must confess that probably was the passion to start looking at freezing. What I thought I’d do this morning is maybe take about 10-15 minutes or so and tell you not so much about the freezing but maybe about the angles of freezing where I think we actually might make some breakthroughs. Because clearly what you will know as a clinician and many others on this call will know is that we don’t really have any great treatments for freezing. What I want to do is to if you’re serious in the direction that I think we might be moving in terms of getting better treatments.

Dr. Subramanian: That sounds good. Maybe you could define freezing before we get into that too because some folks on call may not even fully understand what that means.

Dr. Lewis: Well most commonly we talk about freezing in relation to gait, so problems with walking, and we define it as the inability to move your feet properly. Despite the intention to walk, either you’re walking along, and your feet stick to the ground, and you feel as they’ve been glued there. Or you’re trying to walk, and you can’t get going, or maybe you can only make very small non-purposeful steps. That’s the main area which we talk about freezing, but my own feeling is that it’s a phenomenon, and it affects a lot of other things. Some of the work that I’ve been involved in, we’ve looked at freezing affecting the upper limbs-- so people trying to do things with their arms and legs-- and also freezing with speech. I think the bottom line is that there probably is a common network, pathway, whatever that underlies the phenomenon of freezing, but of course we most commonly see it in the context of gait.

Dr. Subramanian: That sounds good, thank you for defining that. You can go ahead and maybe show if you want to start with your slides, is that--

Dr. Lewis: Yeah, so what I might do is I might try and share my screen and what do they say, this worked beautifully in rehearsal, so we’ll see how it goes, so hopefully my slides are about to show in a slideshow view. There we go, safe. I want to talk about defrosting Parkinson’s disease. This is the title of the paper I wanted to write, and Roger Barker never let me write it because he thought it’s a bit too jokey. But I thought freezing and defrosting went together so I will just say I just had a paper accepted which I love the title of which is “Shaken, Not Stirred.” It’s about one of those spoons that patients might use for tremor cancellation. Anyway, defrosting Parkinson’s disease. This is not the problem-- this is my family gate at home back in Wales with all the freezing on it, but that’s not the gait freezing we’re talking about. What we’re actually talking about is this. If you take a look at these panels, you can see panels of him starting to walk, so initiation, turning on the spot, the guy taking a left turn as he goes around the

corner, freezing, the video not playing so well. You can see the doorway freezing as well. Patients getting-- lots of different triggers to this phenomenon of freezing. It's common and it can affect basically pretty much the majority of patients especially as the disease progresses, which tells us I guess that probably the cell death that goes on in Parkinson's is playing a role, and we think mainly about dopamine and often patients will complain that their freezing is worse and their tablets don't work so well. But we do see other patients who say, "Look, my tablet seemed to be working, but my feet don't seem to want to move." So there are these sort of nuances that we don't really understand. What we really do want to focus on, as I say, is: what should we do? There's no doubt that exercise and physiotherapy is good for all Parkinson's disease. There is evidence that suggests that physiotherapy-- specifically taking sort of big movements, lifting your feet up-- This is work from Natalie Allen from Sydney suggesting if you do intensive three times a week at home and an exercise class once a month, there is a reduction in the amount of freezing the patients report. But unfortunately, that doesn't necessarily result in a reduction in falls, and that's one of the big things because of course falling over puts you into a nursing home, so that's a real concern. But definitely we think patients should be doing exercise and specific exercises where they make big movements and focus on their feet. One of the things that we recognize with their Parkinson's is that Parkinson's tends to affect automatic movement-- the things you don't think about doing. Obviously with gait you don't think about walking left right, left right, left right. What do you do with physiotherapy is you try and get people to use the thinking parts of their brain-- so the cortex because that area is less affected by the Parkinson's. So the deep areas which lose the dopamine, which are mainly involved in automatic movements like gait are absolutely ravaged by Parkinson's disease, but there's more compensation, if you like, from the thinking part, the gray matter. Our programs are really trying to make those thinking parts more automatic, but it's very hard, it's very intense for people to be thinking about their walking all of the time. It's draining. It's a bit like people who are driving. When you drive when you're driving tests in the examiner sitting next to you, your hands are in the right place, you're always looking at the mirrors and things, but as soon as you get on your own you forget about that-- you use your automatic systems. This is really what we try and do at the basis of physiotherapy for freezing is to try and make those more focused efforts more natural and automatic. And there are some more recent approaches to this to try and stimulate the brain. This is just one example of a study where patients were doing an obstacle training in a swimming pool. Walking around in a swimming pool is generally safer because if you fall over, you're saved by the water. What these patients were asked to do was to practice lifting their feet. It just sort of speaks to the fact that if you're worried about freezing and doing at-home exercises, then perhaps working out in the pool might be a good way for you to carry into some of those concerns, and it does seem as though it might help with the programming of the brain and reduce the freezing. One of the other things that people know about is the idea of cueing. This is a classic sort of video of a patient who sees lines on the floor and can walk very well when he's got a target, so he's focusing, so using that thinking part of his brain to focus on movement. There you see him sticking where he can't quite focus, and then he gets the lines and away he goes again. This is one of these examples of cueing-- we know that we can relieve freezing to some extent. There's been a whole bunch of attempts-- so visual like the lines or putting a light on the floor, attaching a drinking straw to your walking cane and stepping over it; audio cues like a metronome tick tock, tick tock, going away; and also tactile cues so vibration in the shoes just even some feedback to focus on. These have all been explored a little bit and one of the things I wanted-- I think you've had a Bas Bloem a good friend of mine on this program recently so Bas Bloem has been very important across a whole range of Parkinson's work but has been heavily involved in freezing of gait. I wondered if you had noticed, Indu, that when you interviewed him the very clear similarities between Bas and this guy-- this is Dr. Emmett Brown from Back to the Future, which of course has Parkinson's connections. I think you can see just a passing similarity between Bas and Dr.

Brown and then when you look at Bas', you can see that he's probably been inspired because this is work from Bas Bloem with laser shoes-- so these are little lasers that fit over your shoes and project that line onto the floor. This is work published suggesting that patients can get a cue from these lines, and I am told this is the prototype. I think this is going to be the next level of laser shoot. I don't think they've got this one quite in full production yet, but to see our idea of tapping into this cueing. One of the other things of course that Bas is very famous for is his work as a Dutchman with bicycles, and as you know the Dutch got a strong traditional bicycle. This was work published a few years ago now, where a patient from the Netherlands really struggled with freezing, but of course you put him on a bicycle and he can cycle very well. Of course Bas again has his own passion for bicycles, this is him just going to work, this is normal attire for the clinic I gather, and in the Netherlands this is pretty standard. He's translated this idea of a walking bike or a balanced bike as we say, and this again is another way of trying to get patients mobile in their own home. It's got to be pointed out these cueing techniques-- and this is work from Alice Noble from Belgium-- they've got modest benefits on freezing, this cueing stuff, so maybe a five percent improvement, often unsustainable. You need this constant cueing. People habituate, so they look at these lines or they look at the lights on the floor or whatever and the effects or the benefits wear off. We don't have very much data on those commercial devices yet to suggest that they are going to be beneficial. What about other approaches? Well this is work from my own team, the idea that perhaps if we can get the brain working a bit better. This is the idea of using cognitive training to improve processing speed and in terms of improving freezing of gait. Indeed, we did show that if we could give people cognitive training to work on their ability to think faster if you like, that they're freezing was improved when they were off their medication. There are definitely links between freezing and cognition, for example, as well as anxiety and mood, so these are all things that we should be thinking about more in terms of future therapies. People always want to know about medications, and really I guess the headline story is that people have tried various medications. This is Ritalin methylphenidate, Amantadine which is a Parkinson's drug. Really they're very limited in their benefits. A more recent study using a drug called istradefylline targeting not dopaminergic therapies-- this was published just at the end of last year-- suggesting perhaps this drug might have some benefits at reducing freezing but again, this needs more work. It doesn't look like we have a tablet that is simply going to fix freezing of gait. I noticed already somebody had asked about surgery for freezing, and it is true to say that the normal deep brain stimulation surgery that's done can improve freezing of gait in Parkinson's disease, especially if patients are mainly getting their freezing at times when their tablets aren't working so well, what we call off periods. If you've got a real indication to have that kind of surgery because your tablets don't work consistently during the day and you have freezing during those bad periods, the surgery can certainly help. But people have been looking at targeting other areas of the brain and there's an area deep in the brain called pedunculopontine nucleus, which effectively is very deep, lower in the brain than we normally operate down in the brain stem. There have been a number of experts who have been advocating this surgery-- such as Thevasathan who's based in Melbourne now but did his work in Oxford-- and targeting this area of the brainstem. These studies have been pretty small, and they've been a bit mixed in terms of their results. It's difficult to know whether we should advise this for all of our patients. This is a video of one of the patients I've seen. This is him having had this stimulation to this deep part of the brain. They've turned off the stimulator in this video and you can see his feet sticking there as he tries to turn. Then when we turn on his stimulator-- and this is one of Paul Silverstein's patients here in Sydney-- so you see him sticking there with his stimulator turned off. But when the stimulator is turned on you can see what looks like a pretty major improvement. I think perhaps in the right patient, targeting this region of the brain may be an efficient strategy, but it is very major surgery. This is deep brain stimulation surgery, but targeting's a pile of rats, very deep and much more risky, I would suggest unless we knew good evidence that it was going to work. What's less risky is the idea perhaps of monitoring the brain

from the outside. This is a patient wearing a cap with electrodes on the top of it, like an ECG where you'd have a heart recording but effectively a brain wave recording. We can slim this down-- this is a video of one of my patients wearing a headband. [The headband on the brain, it's really listening?] [loud audio with video obscuring words]. You can see him freeze here as he gets to the box. That headband is recording activity in his brain. What we've been able to show across a number of different studies now is that we can actually detect signals from these brainwave recordings that reflect changes that occur in fact about five and even two seconds before people stop walking. Before the freezing happens, there are these changes in the brain areas which we think might give us a way if you like it detecting freezing in real time, which of course might then be hooked up to some kind of cueing mechanism-- maybe a biofeedback system where you have a headband that by Wi-Fi alerts a patient that they're about to have a freeze and at least gets them safe so they can stop falling over. That's something that I think is less invasive, but just going back to say there's a bit more invasive. This is work that we published I think at the beginning of this year. Again, going back to the operating theater and looking at patients having deep brain stimulation surgery. What you're able to do during that surgery because patients are awake is to actually do some recordings directly from the deep parts of the brain-- the brain parts that I mentioned, which we think are affected and by freezing. One of the things that I've developed over the last decade or more is a virtual reality system where patients basically can use foot pedals like this to walk through corridors. Here you see a freeze episode as he gets that doorway. This is a paradigm that we've used now multiple times and correlated the amount of freezing that patients get in our virtual reality environment with the amount of freezing they get in the real world to show that they can actually correlate with each other. We think it's a mirror of what's happening in the brain in real freezing, and I mentioned freezing as a phenomena. Here's work that we published now. This is a patient awake in the operating theater. You can see my team there at the bottom with some foot pedals. The patient is awake, and he's looking at those screens that are in front of him. You can see that corridor there. We're able to actually get the patient to walk down the corridor whilst we're listening, as it were, to the brain with the electrodes that are going in as part of the surgery. There's a screen there. What showed was that as patients are freezing, there's a different firing pattern that happens just before the freeze starts, and then a different firing pattern again just when the freeze ends, so when the feet get moving again. What we're optimistic about is that this might be a way of detecting freezing in real time in patients who've had surgery. Now we normally don't do surgery because of freezing. One of the big questions we wanted to know the answer is, well what about just stopping? Clearly when people freeze, they stop walking but what we actually found was there was a very different signal-- the red line here is what happens during freezing, versus the brown line which is what happens when somebody voluntarily stops their feet when they're walking. So you can see there that there's actually a difference between this band of signal coming out of the brain. We think that there might be a very sophisticated way in real-time of detecting freezing. We have got some studies out there that suggest if we could just change the deep brain stimulation pattern for just say a few seconds leading up to when that was going to freeze, perhaps you could stop or abort freezing episodes in real time, which would be a whole new way of using deep brain stimulation, which we normally use just to control tremor or these bad off periods. There we have it. I think we obviously need to rely on physiotherapy and the other techniques we have. We might look at some other medications, but I think the idea of ambulatory EEG, which is non-invasive-- therefore, every patient you could wear a headband maybe hooked up to some kind of biofeedback. I always thought perhaps if you could detect a freeze in real time, and then have a recording of your wife's voice saying something like, "Lift your knees, you're going to freeze"-- something that would stimulate you in real time-- maybe that you wouldn't habituate to it. Then there's other potential for what we called closed loop deep brain stimulation, where you'd have a surgery, the electrodes would be in place, they could detect in real time that you're about to have a freeze, change the stimulation

pattern so that perhaps it isn't controlling your tremor but for a few seconds it's controlling your gait, and then abort the freezing episode. So an on demand system if you like, and hopefully this would reduce falls and keep people out of nursing homes. I want to take this opportunity to thank the people that did all the hard work-- and there's just a few of them listed on there-- and importantly the people that pay for the work, and I'm really grateful to those people that pay the work that we do. But more importantly I just wanted to put up this slide which was taken in 2017 from our charity walk here for Parkinson's. This is my research team dressed up in attire to celebrate the 200-year anniversary of James Parkinson's first description of the disease. Basically just to remind me that none of this work can happen without the efforts of all the team and the students and the nurses and the junior doctors that I train, so I wanted to thank them for putting in all their hard work. They really appreciate all the patients that we work with and to try and improve the quality of life with these problems like freezing. With that I'll stop my sharing and pause to take any questions you might have. Somebody needs to unmute Indu, because I have to say, she's got beautiful lips, but I can't quite work out what she's saying.

Dr. Subramanian: [laughter] I think I'm unmuted now. That was really great, so interesting. We'll take a few questions in a minute, but just to make it quite simple, if you're freezing so your feet are not moving when your brain tells them to do. It sounds like maybe the first thing to figure out is if the pills-- so your Parkinson's pills, or as you call them the tablets-- are working at that time or if they're not working at that time, or if you're basically what sometimes we describe it as an on phenomenon or an off phenomenon. There's this on time-- what we call on time gait freezing-- and there's an off time gait freezing. If it's when the pills have worn off, then it sounds like we could adjust the medicine and maybe fill in the gaps and maybe that would help. But if the pills are working well, and you're still freezing, then the algorithm would probably be next to try maybe to work with the therapist to see if we can work with some of the strategies with the bigger movements and walking more and things like that that you've described in that first slide. Are there other things that one can do environmentally in the home maybe in the environment that people are in? And you've been-- it's so cool that you've actually-- I didn't realize that you had actually spent time going to people's homes, and I think that's very revealing. We actually had Jori Fleischer on earlier in this series, who also has been doing home visits as part of an intervention that she's been doing. I think now that many of us are doing these telehealth visits, I'm seeing sort of glimpses of the background of my patients' homes. Maybe you could just speak a little bit about the environment and how it might contribute to freezing as well.

Dr. Lewis: Yeah, I think it's pretty obvious that one of the reasons that patients do well when they come to see us in the clinic is that hospitals generally have wide corridors with very little going on. There's very good work there from people like Quincy Almeida from Canada, which has actually objectively tested this, if you cluttered the environment. Just to give you some idea again of how simple the brain can be and how beautiful, if you think about driving again and you're listening to the weather forecast, and then you see the potential for a child to step out into the road you have no idea what the weather forecast said because all of your attention-- there was an attentional steal, and your brain did that for you without thinking. The more cluttered your environment, your brain is looking for the threat, and that threat essentially occupies resources that otherwise would be dedicated to keeping your feet moving. So there is no doubt that simplifying the environment, making sure there's less clutter-- the classic place to freeze of course is the toilet because you walk into that room, and you normally have to do a 180 degree turn if you want to sit down. A tight turn is one of the things that will trigger a freeze, so again we need strategies to help patients. So if you're going to do a tight turn, what we often will say to patients, is where you stand on the spot, ideally have something in your hands, a handrail, and lift your knees and count, so 1-2-1-2. And you're lifting your knees marching style, very very much not what you do normally, not an automated movement, but a goal-directed movement to try and reduce that freezing.

Dr. Subramanian: That sounds good. And also sometimes even if in certain spaces-- so if people go to the farmers market or the airport or the theater, and people are moving about, sometimes just that a lot of things happening in the environment can also trigger a freezing.

Dr. Lewis: Yeah, it's a potential steal. People can try and override this, and people have done things like putting lines on the floor of their own house, and the old dance patterns where you cut out the footprints and you walk on the footprints. These things can be tried, but often they habituate, so people get immune to the benefits.

Dr. Subramanian: Yeah, that sounds like it could happen, certainly. Just taking a few of the comments-- and I just wanted to say that it sounds like you're having a lot of fun with these dress-up parties for the 200th anniversary-- [laughter] We actually had Ray Chaudhuri on earlier this week, and he surprised me on this presentation showing. I knew it was leading up because he showed the picture of the pub, and then he had a picture of me holding a glass of wine because I ended up going out for the party in Parkinson's home, which was just magical. I think we can all attest to how nerdy we are with James Parkinson and his description of the essay, but I think we're all quite drawn to this disease for many reasons, and hence the need to celebrate many victories but also to keep fighting the fight with looking for these things that are unmet needs. One of the questions here is about using a technology program called Clock Yourself that is a balanced gait training and cognitive training that somebody's husband is using. Have you heard any results using this program? And if not this program specifically, you were talking a little bit about the cognitive training, maybe you can speak a little bit about that as well.

Dr. Lewis: Yeah, I think the trouble with a lot of these packages and it's the same with the cueing devices is that they look like they should work, they're packaged very nicely, and they often are sold at a price to excite-- so they're not too expensive. The fact of the matter is that I think that you can definitely get benefit out of most of these packages if they are challenging you to do stuff that you would not ordinarily do. Doing something is better than doing nothing. In terms of cognitive training, we generally recommend Lumosity.com or BrainHQ as packages that have got quite a good breadth, but the headline story for all of these things is a bit like medicine itself. They always say the best medicine tastes terrible. If you're doing a package and let's say you love Sudoku, then stop doing Sudoku and go do something you find challenging, because what you really want to do is to tap into the circuits that you don't normally use. This is the same with gait and balance. People who want to work on strength because they like that, it's great, but you need to be working more on balance and vice-versa. It's really about a holistic package, and one of the things you touched on earlier was we should use the medicines first and then use these other strategies, that the advice that we give patients-- and you do this I'm sure all the time-- is do not wait until you get bad.. You start your exercise programs, your balance therapy, your speech therapy from the day you get told you have Parkinson's because what you want to do is have as much reserve in the system as possible, so that if it was to get worse that you'd go from a high point rather than a low point. One of the other things which do you, you're very involved in is the concept of mindfulness. Now I'm not an expert-- I'd be silly to comment on it with you, but the idea of focusing one's attention on the specific problem at hand is very much what I think about with freezing because what you're trying to do is normally multitask, and if you slim down and focus on one thing and calm your brain-- is it worth more other distractions-- I think that's going to be your best strategy. But it is exhausting to do it all the time, just like trying to drive like you're on a driving test.

Dr. Subramanian: Absolutely. Wow Simon, you said the word mindfulness. I'm so proud of you! [laughter] Next I'm going to get you to say yoga and then I'm going to send some chocolate over your way.

Dr. Lewis: Lattes!

Dr. Subramanian: There's been some questions just about the type of exercises that you're generally recommending for your patients. I agree, we've had Bas on, we've had a number of--

Becky Farley who's the power physical therapist, so many amazing people speaking about the wonders of exercise. Maybe you could tell us a little bit about your prescription for exercise, and you were talking about this holistic package. What kinds of things are you including in that? Maybe teach us a little bit about Australia. Are you having people meet a physical therapist actually on the day of diagnosis like they do in the Netherlands, or what is the role of physical therapy along the course of the disease in Australia?

Dr. Lewis: Yes, so just like most countries in the world, although we have a very good health system it's not all-singing all-dancing, so it's very patchy. A lot of medicine here is done in private rooms and not connected to various other facilities, so you really are in a bit of a lottery. Especially in regional Australia, where we don't have as many of the therapists or the setups to go to, but I recently posted a video on my website about the COVID pandemic and really tried to highlight the number of good online resources that are free that are out there, whether it's speech therapy, dancing, all of those things. In terms of the balance of exercise, you need everything, and the bottom line is that Bas' work on exercise and getting your heart pumping in cardiovascular aerobic exercise really is targeting, does this slow the progression of the disease? Whereas you definitely need to work on balance, you definitely need to work on strength, you definitely need to work on flexibility and range of movement. It's a bit like, effectively you're preparing for the decathlon. You're not preparing for the high jump, you have to prepare for everything with Parkinson's. As I say, the danger is that people pick and choose the bit they want to do.

Dr. Subramanian: Yeah, I can't agree with you more. So there's been a couple questions. We'll talk a little bit more about deep brain surgery because these were some early questions that people wanted to make sure we got in right at the beginning so that we didn't miss them. So what are the benefits of deep brain surgery from your perspective in Parkinson's disease on gait, shuffling steps, freezing, things like that. Could you speak to what you think could help?

Dr. Lewis: Yep, for sure. So there are two indications for surgery. One is uncontrollable tremor that doesn't respond to medications, and the other is periods where you don't have good control because your pills aren't working, so wearing off versus periods where they're working too well where you're having the involuntary dyskinetic movements. Those are very much the indications. Now in terms of the best predictor of how your surgery will go, the answer is if your symptoms respond well to dopamine tablets-- so levodopa therapy-- then you would expect them to do well with surgery. We know, for example, that balance does not seem to be improved by having levodopa. Those balance mechanisms don't seem to be improved by the tablets. But if you're slow and just your steps are shuffling because you're stiff and you're slow, and that does respond to your Parkinson's drug for periods of the day, then you'd say yes that surgery should help. But if you feel that it doesn't improve with your Parkinson's therapy-- even at your very best-- the likelihood of the surgery doing the better job is very low, very very low. This is why I'm saying that with freezing, which doesn't seem to respond well to tablets, pills, the truth is that we really need to find a new therapy. Which is why it may be targeting deep brain stimulation, but not all the time, not having it switched on for freezing, but just changing the settings at those times when you're about to have a freeze would be the strategy that I would advocate.

Dr. Subramanian: Sounds good. There's also a question here about falls and fall prediction. Are abnormalities in gait and fall prediction tied together always, or are there other things that influence falls?

Dr. Lewis: There are lots of other things that influence falls. One needs to rule out other causes-- so obviously fainting, which is one of the things that we see as a postural hypotension. We see that in advanced Parkinson's. I think the question is that there is an overlap between falls, balance, and freezing, or gait, but it's not that tight. I've seen lots of patients with freezing who have fantastic balance. What happens is that as you're moving forwards-- your momentum is carrying you forwards--if your feet then stick to the ground, your center of mass still goes

forward, and you can't correct your balance because your feet can't move. The classic example, as I say, is turning so you go into the toilet, your back's turned around, your momentum's taking you one direction, your feet can't compensate, and so it's not necessarily the balance mechanism, but the combination of not being able to move your feet that's the problem. So we really need to get into the bottom line of what it is that's driving the balance problems.

Dr. Subramanian: That sounds good--

Dr. Lewis: --and [inaudible] tablet surveillance-- if we had great tablet surveillance, I'd take them. The truth is that we need to get people to do those physiotherapy and balance exercises. Of course we all have a home gym. It's called chair. If you stand behind it on one leg with your eyes closed singing the national anthem backwards, you will be challenging your brain. These are the sorts of things that everybody can do. But of course what happens is that patients will look at you and go, "Well that sounds like hard work, can't I just have a tablet instead?" Well no! No, no, there's no side effects from this. Do this instead!

Dr. Subramanian: That's very very funny and sad but true, that is definitely true. What about the role of music in walking and gait and freezing?

Dr. Lewis: Yeah, that comes back to that audio cueing. People do use metronomes, they do use - music to improve their walking. The important part is to try to get the right rhythm. The fact of the matter is the faster you walk in Parkinson's, generally the shorter your step, and the shorter your step, the more likely you are to freeze. You really want something that's got a nice even rhythm that you can lift your knees and get that longer step rather than try to go fast. Most people are familiar with the idea of listening to the Bee Gees' "Stayin Alive" to do cardiopulmonary resuscitation, but that's too fast. We really need something that's got a nicer beat to it that people can keep walking. But the difficulty is again habituation. You really need something to mix it up. I think people find their own favorites.

Dr. Subramanian: That sounds good. One thing we haven't really mentioned too much of is a walker. Chuck says that he manages his freezing pretty well using a walker all the time. He's not fallen in five years, but recently he's noticed that the hands freeze and it sounds like they won't release from the walker when he stops using it. He's managed this quite well by sliding his hands one at a time off the handles. "Strangely my fingers don't grip the handles." Maybe you could just speak to maybe the walker and a little bit more on the upper limb freezing situation.

Dr. Lewis: Yes, so it is something that we see. It's not that common. I think the fact of the matter is that when people say I've stopped falling because I use the walking frame, that's great, and what they're often doing is paying a lot more attention to their gait. The walker is slowing down, they're not taking that risk, they're not trying to take off in a certain direction or turn without recognizing that they need to be more careful, so I think those are positives. One of the things that I've done with a number of patients in the past with freezing is attached a drinking straw about 30 centimeters or maybe a foot from the ground at a level that patients can see it and aim to kick it as it were. One of the other things-- I don't know there's those things that children used to wear on their head with springs that make a ball on the end or something with flashing lights-- something that's visual and novel, can be changed in there. This business of the hands freezing, often what will happen is it usually goes hand in glove with anxiety. We know from some of the research we've published that anxiety is a major predictor of who freezes. It not only predicts who's going to freeze in the next 12 months or two years, but also at-the-time freezes because when you get anxious, you actually steal away some of that resource we were talking about before and the hands will freeze. So the idea of again practicing mindfulness-- my goodness twice in one lecture-- focusing on those movements and saying, "Okay, I'm going to relax, I have one thing or two things." Counting strategy, very very sensible way forward. The great thing about patients is if you listen to them, you actually learn what you should be telling the other patients. I'm always grateful when you hear these things.

Dr. Subramanian: Do you guys have the U-step walker in Australia? It's the walker that has a frame that's like a "U" and then it has a laser that you can activate with the basket and a seat.

Dr. Lewis: We possibly do. I haven't seen many of those come through the clinic. It sounds a little bit like the forearm walker, where you put forearms on and you're sort of more encased in it. These things can be beneficial that-- you're talking about much more severe cases who require that.

Dr. Subramanian: Okay yeah. It's not exactly a forearm walker, it's just a walker. I can certainly send you a picture of it. It's made by a small company here, and it's pretty Parkinson's-specific. It is expensive as some people are saying, but it's covered sometimes with Medicare, which is the insurance that we have here. I think because of the laser, it can be helpful, and they have a metronome feature as well. Somebody's asking about Nordic poles and whether they seem to help with freezing of gait.

Dr. Lewis: It depends a little bit. If you've got somebody who is very good at using the Nordic poles to regulate their stepping-- so you think about Nordic poles, they're a little bit-- they're very unusual to walk with. They're much higher, and you have to make a very definite placement with the Nordic pole, and theoretically you then have to make a very deliberate step with your feet. It's very hard to use Nordic poles subconsciously, and that's going back to this automatic gait versus not automatic gait. The problem I've seen with the Nordic pole walking is that people sort of phase out, and they try to use them a bit quickly, and effectively they then lose the benefits. Everything has to be slowed down and focused on one task at a time. It's a bit the same when patients freeze. Once you are frozen, and you can't break the freeze, you need to focus all of your attention on making that first step so you can break the freeze.

Dr. Subramanian: You mentioned anxiety. I think this is quite an unmet need in the nonmotor realm, which I know you're also passionate about many of these non-motor symptoms as well. What are maybe a couple of pearls that you have for an approach to anxiety in Parkinson's patients, maybe in the setting of freezing and maybe even outside the setting of freezing.

Dr. Lewis: Let's talk about a few do's and don'ts. Alcohol is often used as an anxiolytic by people, to reduce the level of anxiety, but the problem is that alcohol of course is it's very good at dumbing the balance organ of the brain. So this is something that again, one wouldn't advocate alcohol as the treatment. The other thing that goes into that category of course is cannabis, and I'm amazed I've been on a talk for this long and nobody's talked about cannabis yet, which is fine. But the role of cannabis-- and I think you may have had Benzi already on the program, which is great-- it's difficult to have objective data about the cannabis because the effects of cannabis. Well I would just say-- and people who are thinking of considering if they haven't already done so-- is there's a nice study from Israel that points out that about 10% of patients on medicinal cannabis-- that is to say the cannabis that shouldn't make you go funny-- about 10% of those guys develop hallucinations. So you have to be very careful about using cannabis, but certainly as a way of that anxiety and therefore helping gait, there are strategies around this, and there's good data. In terms of other things-- in terms of reducing anxiety, clearly time pressure is one of the things that patients with Parkinson's often fall over with. If you're trying to rush-- and you mentioned busy environments like train stations or airports-- not we can go to airports or train stations that much currently-- but effectively those are areas where you're trying to rush, that's when you get more freezing because you get more anxiety. I think if you can slow things down and try and if you focus as I say on the one task, that's going to be your best strategy.

Dr. Subramanian: Yeah and sometimes even taking a timeout, a little bit. There's a lot of things going on. I say from the mindfulness or even some of the yoga background, just kind of closing your eyes for a second. If you're sitting or if you can, just taking a few deep breaths and sort of disconnecting from the environment and then resetting and then restarting sometimes-- kind of when we're sort of failing let's say to stand up from a seated position, and you're getting frustrated by trying to move your feet at the beginning, maybe just taking a minute or two and then resetting and restarting sometimes can be helpful as well.

Dr. Lewis: Absolutely, absolutely.

Dr. Subramanian: A few quick questions. Since Simon you wanted me to put you on the spot a little bit, this I think was a hope for you, to be kind of grilled a little bit by me. I wanted to ask you we've been doing a lot of things about advocacy, and we're really thinking outside the box in this series. We're not talking about standard things that we would be approaching patients with in your average meeting. I think we're thinking outside the box. So if you were to pick maybe three things that patients should be advocating for around the world when it comes to Parkinson's-- and since Bas is a friend of yours, we have been talking a little bit about the *Ending Parkinson's*- - Ending PD book-- maybe you could just tell us, in your mind, having been leader in this field for a number of years, what your thoughts are on how patients can advocate for themselves and what the main things are that you feel are important.

Dr. Lewis: Well I think the first thing is that one of the big problems with having Parkinson's and often across a lot of diseases is that you often feel as though somebody else-- this is a big problem and someone should do something. Well that someone is you, and nobody else is going to write to your local politician, your local hospital. When I think about the support group movements across Australia, they generally have membership, but the membership is a very small percentage of the patients out there in the community that have that [commission?], but even in that membership of motivated people, it's very hard to get them motivated enough to be a loud voice. We're currently seeing a whole range of terrible events across the world, which have actually galvanized people and because that's why we haven't done it before, various protests and rallies going on. And I think, I don't want us to become too political, but I think the bottom line is that if we all take the opinion that somebody should be doing something and forget the fact that that somebody is you, and really patients being that person-- the politicians if you talk to them-- and I spend a bit of time talking politicians-- they're worried about votes, and the bottom line is-- you know this yourself-- if you have one compliment, it doesn't rank the same as one complaint. The fact of the matter is if 10 people are complaining, it's a real problem for a politician or a hospital, so if you don't have a service like, "Well how do we get access to Parkinson's nurses, physiotherapists, a coordinated package of care, which everybody would agree is going to improve the quality of life of people out there living with Parkinson's. Let's not forget the impact is not just the patient, it's the families, the caregivers, the wives, the husbands. An actual fact-- we just need people to be a bit more galvanized. Now how we get them all on the same page, it's tricky because everyone's got a local problem. In America, you can say, "Well we don't have a universal health care system that's going to serve everybody. And you go, well that's possibly different to say in the UK, where they've already got a network of Parkinson's nurses. Their challenges might be that they want access to the advanced therapies. We do need people to be coordinating things, and this is where I guess one of the things that I've always felt-- and I think my wife regards me as a show pony because I'll go on television for anything to do with Parkinson's-- because I feel like I have a voice, and a lot of patients don't. So effectively, we need to set the agenda, but we need to listen to patients to say, "Look, we think this is the important thing. Hopefully, you're with us. If you're not, tell us what the important thing is." I think that's one of the roles that we have. In actuality, the heavy lifting here isn't the number of patients and their families that are out there. The great thing about social media is it's very much easier now to get a movement going.

Dr. Subramanian: That sounds really interesting. Karen says here, Professor Lewis is right. We got funding for a movement disorder center by going to our legislature and telling them our needs. It sounds like Karen's from New Mexico. So starting local, but connecting through support groups like this, and we've got a global connection here. I agree. I think that we are fighting for many things and resetting many ideas. The world is sort of on pause a little bit, and maybe we can really think about silver linings to move forward with in helping our patients and in healthcare in general, so I think that's exciting. Okay, well that was a good answer. Simon, you've been treating Parkinson's and the motor symptoms and non-motor symptoms, all these

different things. What are your top three unmet needs in the symptom world of Parkinson's? What do you say?

Dr. Lewis: I think the truth is that, I guess if I was going to say these things--if you look at what puts people in the nursing homes, it's dementia, psychosis-- which essentially is hallucinations and delusions-- and falls. We've already talked about falls in the context of freezing, but the other side of it-- which we talked about briefly-- was the fact that we don't have much that will improve balance. Are there mechanisms whereby we can deal with this? Psychosis, hallucinations-- so patients with delusions believing that their wife is having an affair or someone's taking their tablets or breaking in-- we have very few medications that can deal with this, and there's very little appetite from industry to go down that path. There's lots of targets in the brain in terms of the neurotransmitters that we could go for. Obviously cognitive decline and dementia is huge. I think if you're going to wrap that up, what you'd say is, look, what we really need is to stop cells from dying at the earliest time. Even if we can't stop them from dying, if we can slow cell death-- so for example, if I had a drug that could stop people getting any worse or if you change their path so they-- We currently see patients, and maybe over the first five years, if we said, well if that's as bad as it was going to get over the course of your next 15-20 years, I'd take that deal tomorrow, I'd take it today, it would be fine. So the idea I guess is really around disease-modifying therapies. One of the great things in the last 20 years that I've been doing Parkies is that we've now moved to an era where people are actually talking about doing trials to see if we can cure, slow the disease down. Now just like Alzheimer's, we're going to see a lot of negatives along the path but I'm excited by the fact that we're starting to see the trials happening and some thought behind the processes. We talked about trying to mobilize things globally, and the Australian federal government has supported this to the tune of 30 million Australian dollars over the next five years. Now that's probably in U.S. terms about \$15 million. It's a drop in the ocean compared to what Pfizer could spend on this problem, but the key part is they're actually talking about it. In terms of the unmet needs, dealing with those non-motor features-- and gosh let's not even talk about things like apathy or anxiety or sleep disorder or bladder-- and the things that put you into a nursing home like psychosis, hallucinations, dementia, and then the idea of saying, well okay how can we deal with all of these problems? The answer is instead of fishing people out of the river downstream, whether they've got hallucinations or dementia or whatever, we need to get upstream and see who's pushing them in. And so eventually have a disease-modifying therapy from the day you're diagnosed or indeed-- as part of my research-- involved in predicting most people who are going to get that disease and treat them. But we need obviously those breakthroughs, and that's kind of an exciting area at the moment.

Dr. Subramanian: That's great. We have about four or five minutes left. Maybe you could just tell us a little bit about that predicting who's going to get the disease and how to help them research because I think that's quite exciting and it sounds like it could be sort of giving hope for the future of catching this early so we can prevent progression.

Dr. Lewis: So most people on this call will be aware of things like constipation and losing your sense of smell as features that we see that as you get those in later life, you seem to be at increased risk of getting Parkinson's disease. In terms of what we talk about, we say well your odds ratio-- your hazard risk ratio is increased-- and by losing your sense of smell, it's maybe two or three times higher than the background population. But one of the things that we've noticed over the last 5-10 years, maybe more, is people who start acting out their dreams and during dream sleep, what we call idiopathic REM-- rapid eye movement-- sleep behavior disorder-- and they are people who, if they don't have another cause for why they're acting out their dreams, over the course of the next 15 years the vast majority-- like ninety percent plus-- will get Parkinson's or Lewy body dementia, so these people have got maybe five ten years before they get diagnosed. In that period-- maybe longer for some of them-- where you go, well we're pretty confident you're going to get the disease, if we had a disease-slowng treatment,

then you're going to get it now before you get the physical symptoms or the dementia. It's an exciting area. There is an international study group which we're part of here, which effectively is collecting these patients who act out their dreams in the hope that one day, we'll have a breakthrough in the Parkinson's [space?] that we'll be able to say, okay well let's take these people that we know are likely to get the disease and treat them at a time when they don't have it, and see if they never get it, so that's where we're at.

Dr. Subramanian: That's fabulous. I wish you the best of luck with that. Well I just wanted to thank you,, Simon. I'm going to give you a minute to say something inspirational, something hopeful and then we'll hand it back to the PMD gang, but just before that, I wanted to thank you so much for waking up so early on that side of the world and joining us and bringing your wisdom and your inspiration. People are asking about your website, and we'll give them the links and the videos and stuff because I think they're pretty spectacular. We will hear from you now for a minute or two before we close.

Dr Lewis: I'll take the opportunity to say thank you, not only you Indu, but the PMD Alliance for basically being facilitators and advocates. I mean the truth of the matter is that, as I said earlier, we really need leaders to help us to bring us together. But the truth of the matter is that we've got I think 200 people on this call, and perhaps there are more out there who will watch a video recording of this later. Really to you, you are the inspiration. The fact of the matter is that I showed you that photograph of my research team, and everybody in my team is smarter than I am-- it doesn't take much, they're all smarter than I am. Thankfully they're younger than I am, they're smarter than I am. But the fact is I take them all into the clinic with me to meet families with Parkinson's because I want them to understand the problems that you face every day, just to get on a call like this. I want them to understand that the effort it takes for you to get through your standard day, living with this 24/7, compared to us who are doing a bit of research two hours or whatever with you and then you're gone back to your own home. I can tell you from my perspective that we're inspired by you. The fact of the matter is that I think you're often looking up to us and going, "oh you do good things." And you kind of go-- I used to have a slide in my slide deck which basically had a picture of hamsters. I can't do the research that I do with hamsters. They don't get Parkinson's disease. So the truth is that we rely on people, like the people on this call, to help us to do the research that we hope will bring benefits back to the community, so I thank you all for providing that opportunity.

Dr. Subramanian: Wow. Well that was lovely, Simon. Thank you so much. There's a lot of positive, exciting comments. People think you're hilarious. They think your humor is very important. It's such a breath of fresh air to hear very serious subjects discussed with an injection of humor, and love how you think outside the box. Andrea will send you all these comments because I can't read them all at this point, but thank you so much for joining us. It really means a lot to me and we'll have a few more Aussie's on the next few episodes as well of this because you're all very fun and funny and it's just been a pleasure. I will send Bas a copy of this video, and I'm sure he will be amused as well. And so again thank you for taking the time and for your hard work and inspiration and look forward to your future research outcomes and things like that. To everyone at home, be safe, be well, and have a great weekend and thanks again the PMD Alliance for hosting and we'll hand it back to you Andrea.

Andrea Merriam: Yes, thank you Simon and Indu. I think we have some new people joining us today. We always close with a goodbye wave, and so turn on your video, and we have some across the ocean I contact. I love scrolling through the video if you put it in gallery mode and hit the blue arrow on the right, you can see dozens and dozens and hundreds of friends smiling and waving from across the country. So good to see all of you. Thank you so much for joining us and have a great weekend! Bye everyone.

Dr. Subramanian: Bye.

Dr. Lewis: Thank you.