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| Dr. Karen Jaffe: | 00:04 | Hi everyone. And thanks for joining us. I'm Dr. Karen Jaffe, I'm a member of The Michael J. Fox Foundation Patient Council. And I'm your moderator for today's webinar. I was diagnosed with Parkinson's disease in 2007. I'm also the founder of InMotion, an amazing wellness center for people with Parkinson's in Cleveland, Ohio. Um, so first, let me address a housekeeping issue. There is a question and answer box in the middle of your screen. You have any questions, write them down and we'll try to get to as many as we possibly can. Um, so we've got a lot to discuss today. So let's get started. We're going to be talking about the many sleep issues that come with Parkinson's disease. Some that even come before motor symptoms develop, we'll cover how to manage these problems today and new treatments that are in the testing phase for tomorrow. |
| Dr. Karen Jaffe: | 00:54 | Let me introduce, I'd like to introduce our panelists. First of all, we have Brian Duggan is the founder of Citizen Science for Health, a nonprofit dedicated to increasing patient empowerment and transforming medical research. He was diagnosed with REM sleep behavior disorder in 2015. We have Dr. Michele Hu who is a professor of clinical neuroscience and a consultant neurologist at Oxford university. She is a Parkinson's and REM sleep behavior disorder researcher. And finally we have Dr. Maria Cristina Ospina who is a movement disorder specialist in private practice in Phoenix, Arizona. She's also a medical director of the regional Parkinson's center. I want to thank all of our panelists for joining us today and welcome. |
| Dr. Karen Jaffe: | 01:44 | As a decade long Parkinson's advocate, I've met many people in the Parkinson's community, and I would have to say that it is a rare person who had Parkinson's disease, who seems to be able to escape being wrapped up a full night restful sleep. And so while we will discuss the management and treatment of these disorders a little bit later in the hour, let's, um, review some of the start with a conversation to review some of the more common sleep disorders in Parkinson's disease. So Dr. Ospina, can you help us understand what it is about PD that causes these problems, just how prevalent they are? And is there any commonality between these problems? |
| Dr. Ospina: | 02:22 | Hi, Karen, thank you for having us. As you said, sleep issues are very, very common in Parkinson's disease and are very difficult to treat. So just like constipation, that most patients have trouble with constipation, the constipation is there way before they're diagnosed with Parkinson's disease, with their motor symptoms like tremor, rigidity, bradykinesia, or slowness of movement, uh, constipation as part of the non-motor symptoms. And so, or sleep issues, things like insomnia initiating |

sleep or staying asleep, restless leg syndrome, REM sleep, behavior disorder, and sleep apnea. So in Parkinson's you start the medication, remember what happens in Parkinson's disease, that their cells deep in the brain that produce dopamine and for whatever reason, they're dying off. And we have to replace that dopamine with the medications. That's your carpet. Believe it, over that, leave it over. Turns into dopamine in the brain. And usually we're treating the patient during the day with mat or leave it over multiple times a day. And then at night they're not taking any medicine. So their levels of dopamine and they develop sleep. Fragmentation. Many patients are, have difficulty initiating sleep and staying asleep because their levels of dopamine are low. So many times we'll use once a day medicines like dopamine agonist, but then that brings other problems like excessive daytime sleepiness. Um, so what we want to do is we try to keep your levels of dopamine stable throughout the day and the night to reduce sleep fragmentation, to make sure that we're not giving you too many medicines during that day that make you sleepy. So that then you have excessive daytime sleepiness that can interfere with things like driving and going to work, commuting. Those sorts of things. The dopamine agonist are very common, uh, in having those side effects and just like RBD, which we'll talk about it a little bit later are less is part of, uh, sleep issues and Parkinson's disease that can be present way before the diagnosis of Parkinson's disease. Whereas more, you know, everybody has Parkinson's probably has restless legs. Um, but having restless legs early on does not believe you to have Parkinson's later on in life. Like we think that RBD has that chance to do. And then there's a central form of sleep apnea. That's common in Parkinson's disease. So many times your doctor or physician will order a sleep study. Uh, when you're first diagnosed with Parkinson's disease to see, do you have sleep apnea? Do you need something like a BiPAP or C-PAP machine? Uh, and then can, we can treat things like restless legs using again, dopamine agonist. And then we, it's the reason why your doctor's always looking to use the longest acting form of levodopa. So using things like Rytary, or once a day versions of your medicines, like the ones that eight versions of your dopamine agonist, so that we can better cover your dopamine tone throughout the night. So it's easier to fall asleep and stay asleep so that those Parkinson's symptoms don't return in the middle of the night. So you don't get rigid. You don't have Brady kinase, your slowness of movement, so you don't have trouble turning in bed. And so that you don't have dystonia, uh, that wakes you up and then keeps you from sleeping. And dystonia is an abnormal contraction of a muscle. So when your dopamine levels are low, those muscles start to get rigid and stiff. You

might have cramping in the foot that might wake you up. Then you have to go to the bathroom. You come back to bed and you can't fall asleep because your brain is not relaxed enough. Your body's not relaxed enough to fall asleep.

Dr. Karen Jaffe: 05:53 Well, this is a complicated issue. Uh, it's a little bit, um,

Dr. Ospina: 05:58 I mean, certainly if you're going to take a medication, that's going to keep you from sleeping, then you're going to be, have daytime sleepiness the next day. So one thing begets the other, just like, ah, we take medication to help our tremor. And then the side effect of the medication is unwanted movement. So, right. So, and it's really important in Parkinson's disease that all of our therapies, whether they're medical or surgical, they're purely symptomatic, they don't stop or reverse the disease. So our job is always to make sure that the benefits of the medicine outweigh the side effects of the medicine. And so that if you have a tremor that doesn't bother you too much, we don't have to keep increasing your medicine. And that we always want to be cognizant. Although the medicines help the motor symptoms of PD like tremor, rigidity, and slowness, they make the non-motor symptoms of PD worse.

Dr. Ospina: 06:43 They can make you more constipated. They can cause a daytime sleepiness. They can lower your blood pressure, which leads to dizziness, which can lead to falls. They can cause confusion and or hallucinations. So our goal is to get that balanced just right, that you have enough meds on board that you're mobile, but not so much that you're dizzy. Every time you stand up that you're nauseous or that you're hallucinating or falling asleep at the wheel. Well, Brian, um, before preparing for this webinar, I always thought that, uh, the diagnosis of REM sleep behavior disorder was actually meant that you had Parkinson's disease, but you don't have Parkinson's disease. So can you please tell our audience your story, how it came about?

Brian Duggan: 07:26 Sure. Um, for me, um, it was really falling out of bed. I fell out of bed and my wife and I had common comment. Wow. That's kind of strange. Oh, it happened again. And then I would be moving during the night during my dreams and flailing a little bit, or I would punch and she would get hurt. And we began to think, wait, there's something more here than just some quirky, fall out of bed thing. And, uh, this was now some six years ago. Um, so I started researching and, um, you know, like you would call Dr. Google on, on the internet trying to understand what was going on. And in fairly short order, I realized I fit this perfect description of what they described as a REM sleep behavior disorder, where one acts one's dreams. My normal atonia had

stopped. I wasn't being paralyzed during REM sleep. And particularly if I was having a violent or stressful dream, I might hurt myself. I might hurt my wife. Um, and so we just realized, Hey, I have to do something about this. And in looking it up, you're also learn online that it's a harbinger of more serious neurodegeneration. So on one level, yes, RBB is not the same as Parkinson's, but there's a continuum here. And there's certainly people that would describe my situation as prodromal or early stage of Parkinson's,

Dr. Karen Jaffe: 08:56 But you

Brian Duggan: 08:56 Don't have any symptoms of Parkinson's disease. I don't have any motor symptoms, but as I researched this further, and my response to learning about this online was actually, I went to The Michael J. Fox Foundation website. I looked at trial finder, I found a clinical trial going on, um, where I was able to get a sleep study and get my personal diagnosis validated by it through a polysomnograph, which is really only way you really know if you have RBD. And, um, that was just really, really helpful as a, as a, as a first step on, on this journey. Thanks for the interesting introduction to RBD. So Dr. Hu Brian has gotten us off to a great start with this. Can you fill us in a bit more about, um, REM sleep behavior disorder, uh, what it is including the prevalence rates in terms of, you know, going on to Parkinson's disease. Uh, and I'm also curious whether it matters, whether somebody gets diagnosed or starts having REM sleep behavior disorder as a younger person versus an older person, somebody who's 40 versus somebody who might be 70 or 80.

Dr. Karen Jaffe: 10:13 I think Michele's she's muted. Michele. I think you're muted Michele. Yes. Now we can hear you.

Dr. Hu: 10:25 Thank you. So perhaps that to understand RBD or REM sleep behavior disorder, we just need to start with some really basics. The first style that we as humans have three vigilant States. The first is hopefully most of us on this webinar are all in the awake state. The second is non REM sleep, which can be divided into stages. One, two, and three. As you dive deeper into sleep, you go from an one, two and two and three being the deepest sleep, unless these types of anonymously called slow wave sleep, because the type of electrical brain activity is very slow REM sleep. However, which is when we dream is typified by very high frequency activity on our brain waves. And also by the absence of any muscle tone in our muscles that keep us upright, um, the eyes during REM sleep, Twitch and move. And if you've ever seen some deep dreaming, you might see the under their eyelids, the eyes, the eyes of jerky, often from side to side. And

the other thing is that in REM sleep, we can see muscle twitching, but not usually movement, uh, or speech. Um, and so REM sleep behavior disorder only occurs in when asleep. And it happens because there was a switch in the brainstem, which basically prevents you acting out your dreams when you're in this REM sleep. And this switch is located in palms of the brainstem, and it can be disrupted by a number of different conditions. So if you're unlucky enough to have a stroke or MS, with a lesion in the brain strand or a newer degenerative problem, uh, then that can start in this area of the brain STEM and the output will be, the end result will be that you will start to move in your sleep. Uh, typically the movements are recapitulating your dream. So we've seen many videos of people in sleep studies who box, you know, these sort of movements, or they're heading someone or shaking some more times often dreaming about sport, like kicking a football and then waking up because they have actually kicked the wall and hurt their leg, or maybe that they're nasty dreams, they're being attacked. So they're shouting and they're trying to push the bed partner. So this condition can be quite violent, not for the person who's having the dream, but for the bad partner. And I've seen this firsthand when I first became a consultant and a male patient with RBD was dragged to my clinic by the wife. And he was really oblivious to the problem, but she had had enough and was now sleeping in a separate bed. We know from population-based studies that RBD occurs around the world. It occurs in Western populations, Asian populations, and European populations, and using sleep studies to validate the diagnosis, which is the best level we have of making the diagnosis surround one to 2percent up to about 3percent prevalent in populations. And it increases over the age of 60 years. We do see REM sleep behavior disorder and a much rarer group of younger people who have, um, uh, a type of sleep disorder, uh, called narcolepsy with cataplexy. And these patients probably have a much lower risk of future conversion. So it's important to understand that RBD was only actually described about 25 years ago by a sleep neurologist called Carlo Shea, who was working in Michigan and who sold this happening to a person in the sleep clinic. And he thought there must be a way. And he went in and tried to, to sort of talk to them and they didn't respond. And then he realized that this was happening during that dream state. And it was his original description that is now being weak capitulated. And as people started to follow up people with RBD, they recognized over long-term follow-up, but there's about a 6percent charts per year of everybody with RBD converting to a newer degenerative condition. And that is most commonly Parkinson's disease. Second commonly dementia with Lewy body and third other

related conditions. So it's the highest or strongest risk factor we have for Parkinson's. However, it is important to realize that not everybody with LBD will convert. We still know of people who have had this condition who were living in their nineties without any feeder conversion. How long does it take on average, probably around 15 years. Uh, we know from following up these people that the earliest non-major symptom is loss of sense of smell that happens 20 years before conversion on average and the around 15 years is when the REM sleep sort of manifest.

Dr. Hu: 15:39 I've just got to get going. I'm going to let you finish. My research is really focusing on this group of patients because they are, um, a very homogeneous group of individuals. They've all been sleep clinic diagnosed. They've all had the sleep study and they can all give us the date in which their symptoms developed. So they are an ideal group of people to study how we can best prognose, uh, or prognosticate people. So how can we develop an individual whisk for that individual person with RBD of imminent conversion? Because this group of people I would argue are most likely to potentially benefit from curative treatments that we might use also for people with Parkinson's, but I think it's a spectrum and the RBD, or just the earlier phase of it.

Dr. Karen Jaffe: 16:33 Hmm. Is there a reason that it seems that, that it's the people that already have these violent dreams or, you know, you don't see anybody complaining that they're happy, birthday dreams.

Dr. Hu: 16:46 There are happy dreams. I've definitely seen videos of people laughing and having a really happy jokey time. Um, and the speech is often kind of sounds like you can almost understand the words, but when you listen a bit harder, it's actually quite slurred and it's difficult to make out. However, that it's probably true that the more dreams are quite frightening rather than pleasant. And a lot of people have wondered about why would you have, what is the biological function of dream sleep or REM sleep? And one hypothesis is that it helps the brain to consolidate memory of an unpleasant event. And when that memory is firmly fixed in the brain, through going through it in your dream, you then avoid it the next day and you survive. Your chances of survival are higher. So maybe in an evolutionary way, this gave some survival advantage.

Dr. Karen Jaffe: 17:45 Hmm. Interesting. Well, it doesn't take a diagnosis of REM sleep disorder, behavior disorder to ruin somebody's, night's sleep. Here's a slide that lists a lot of the conditions that many Parkinson's patients deal with on a regular basis, um, that are going to affect our sleep. Um, and, uh, it eludes us, um, I, I

blame my own sleep disorder on my medications, but, um, well, I I'd like to take a look at, um, what, what we, um, how often we see these things. Brian, are these, any of these things, part of your sleep disorder,

Brian Duggan: 18:26 Um, frequency of urination certainly wakes one up in the night. So it's part of the, part of the mix, I would say. And on the issue of, we just were talking about with different types of dreams, I think anxiety does play a role there. Um, you know, we'll talk later about management of this, but reducing stress, um, over the peer over a period of years, certainly has changed the character of my dreams. If you're acting out a dream and it's very benevolent and benign and some small thing, it's not really that big a deal versus a terrifying nightmare that you're acting out. So, um, I think reducing anxiety and stress reduction in general, um, again, has been part of the management of this, but it's certainly an issue that, that leads to worse sleep for me.

Dr. Karen Jaffe: 19:16 Dr. Ospina you're in clinical practice. So how often do you find that Parkinson's patients are that you are uncovering that the part of their sleep problems are due to some of these things that are on this list?

Dr. Ospina: 19:28 Yeah, so it's very, very common. Um, so like medication side effects, remember there's medicines like dopamine agonists that can make you very sleepy, then there's medicines that can keep you up. So things like selegiline and metabolizes into an amphetamine. And the reason why we have patients take it in the morning and the noon hour is that it can keep you up. And so it can cause, uh, insomnia that way. And then remember, remember that you've got the, your motor symptoms of PD, but you've got the non-motor symptoms, like the bladder issues, like the urgency and frequency of urination that can keep you up and anxiety, which can also be part of the non-motor symptoms of Parkinson's disease. So as you're leaving, a dopa is wearing off. Not only is the tremor and rigidity coming back, but so are the non-motor symptoms. And many times that is a free floating anxiety.

Dr. Ospina: 20:17 Some patients have a panic attack and that can interfere with sleep as well. If it's happening at that time. And many off periods happen at night. So pain and discomfort, you know, many PD patients go through one or two mattresses and the problem, it's not the mattress, it's not the bed, it's the body. That's lacking dopamine that can't relax and can't turn over in bed, can't get in and out of bed or becomes a headache. Dystonia the toes start to cramp up, you get a Charlie horse back pain and because your levels of dopamine have gone low.

So then your doctor in that instance is going to be trying to use the once a day medicines to get better cover your dopamine symptoms, uh, at night. So, or add a dose of levodopa in the middle of the night, so that your trough isn't so low and that pain and discomfort coming from an off period or a dystonia, doesn't wake you up and then keep you from falling asleep.

Dr. Ospina: 21:13 And fatigue is very common as well. So you can have fatigue because you're not sleeping. You're asleep. Wake cycle has been inverted. So you're up all night and now you're tired during the day. You don't have enough energy, but again, you can have fatigue because of Parkinson's. If you're underdosed, you don't have enough medicine on board, you're leaving. It was like gas in the car. So if you've run out of gas, patients have a lot of fatigue and they feel like, gosh, I just can't go through the day. One of our audience members is asking, does alcohol impact sleep? Yes. And probably if you can talk better about that.

Dr. Hu: 21:50 I mean, having been a medical student in my time, but if we have a, perhaps more than we should, in terms of alcohol, our sleep quality is absolutely appalling. Um, and our dreams tend to be often a bit more vivid. And if you study somebody, a normal control person, their sweep, uh, that basic what we call their sleep architecture, which is that sort of nice cycle of what I mentioned going through sort of drowsiness through, you know, to, to, to, to REM and then non-medically, and then repeating maybe three times in a night, all of that is just totally messed up, uh, by alcohol. Uh, and it also reduces, uh, the restorative sleep. Uh, which many of us believe is so important for people with Parkinson's to maintain their memory and their vigilance and their attention in the day, which is the slow way restorative sleep.

Dr. Hu: 22:45 Um, I think it's also important when you're in an early phase of Parkinson's to also recognize that while dopaminergic medication can actually help sleep, uh, for Parkinson's, it can actually also make sleep worse. Uh, so in addition to alcohol, I have had patients who with simple Lipa diaper or doping, the agonists have actually rarely developed insomnia as a direct side effect where we've had to move the medication earlier in the day, because if they take it after six o'clock, they can't sleep. And this is also, you know, also the effect of caffeine, of exercising too late, perhaps of using too much computers and stimulation and blue light. So all of these things together for what we, uh, neurologists or sleep physicians call sleep hygiene, and it's really an important part of managing any sleep problem that a person with Parkinson's will experience. Uh, also we see

RBD can be triggered by medication or on, and the best evidence for this are for medications, such as selegiline and phenelzine and chlorpromazine, which has sedative medications, but it is also linked to SSRI medications used to treat of course, anxiety and depression in Parkinson's patients or RBD.

Dr. Hu: 24:04 We have looked at how non-major symptoms vary, and we compare the non-motor symptoms using standard questionnaires in 300 people with RBD, from our cohort compared to 300 aging gender match controls and around 800 people with Parkinson's. And the really surprising thing is that the person with RBD had an almost identical level of severity of non-motor symptoms, including anxiety, depression, mild problems with memory, sleep disorders, excessive daytime somnolence as the person we park in sentence. Uh, and they were both significantly different. The RBD and the Parkinson's cancer from somebody without Parkinson's. The difference is that the person with RBD has only subtle tremor, or maybe just can't swing one arm very well. So their motor symptoms and their motor signs are an order of magnitude milder than the person who has manifest Parkinson's

Dr. Karen Jaffe: 25:09 Can neither do Dr. Hu or Dr. Ospina address deep brain stimulation effects and how that affects the sleeping. A couple of our audience members are asking whether it makes it better. Does it help it at all?

Dr. Hu: 25:20 I mean that, so I have to meet there's really good wealth of data. Now that STN, which is subthalamic nucleus deep brain stimulation, um, significantly reduces non-motor symptoms. And that includes domains like sleep. Um, there is also I'm aware in Oxford, uh, of a study using, um, PPN (pedunculopontine nucleus), which is usually reserved for any gait freezing showing that that improves, um, autonomic problems. And we're going to be doing objective sleep monitoring before and after stimulation to see if it improves sleep outcomes

Dr. Karen Jaffe: 26:01 Dr. Ospina, is there anything that you

Dr. Ospina: 26:03 Yep. I agree. It's sort of remember that DBS deep brain stimulation, it gives you, it's a, it's a third, uh, surgical therapy that's on 24 seven. So unlike oral medicines where you're taking them every three or four hours, you're peaking and troughing the DBS is on all of the time. And so we're trying to increase your dopamine tone throughout the 24 hour period. It's not being pulse up and down, so it helps you with less rigidity, less

bradykinesia. So things like turning in bed or easier, getting in and out of bed are easier. If we can reduce that rigidity, you're going to be able to fall asleep and stay asleep easier. So it certainly has improved those non-motor symptoms and helps you sleep better. Or remember if you sleep at like Dr. Hu said, it's really, really important to patients with Parkinson's disease patients with neurodegenerative diseases, because what's happening in Parkinson's, you've got this misfolded alpha-synuclein that the cell can't get rid of and the slow wave sleep is part of when the brain does all of its housekeeping and repair work.

Dr. Ospina: 27:05 And it tries to get rid of this misfolded protein and it consolidates memories. So short-term memory turns into long-term memory helps you with, uh, cognition. Uh, so learning and memory are very important and are helped by sleep and anything that we can do to improve your sleep and the length of sleep as doctor, he was saying that you go through these stages of sleep throughout the night. We don't like to interrupt that because then you're not getting into that deep, slow wave sleep, which is restorative for the brain. And something like DBS that can have that continuous dopamine tone helps us achieve that, uh, as best we can much better than the oral medications. So I'm curious about DBS it's you hear about how it helps with motor symptoms and things like that, but you don't, I haven't heard much about people talking about the non-motor symptoms, like things like sleep disorders and stuff like that, for people who had DBS long time ago, D did those statements still apply to whatever how DBS was done 15 or 20 years ago? Uh, do they still have, do they also get the same benefits that current DBS people give DBS in 2021 would have?

Dr. Hu: 28:15 I mean, I think the first thing is that 15 years ago, we didn't really measure non-major symptoms and we weren't aware of it so much. So the initial people who got operated on 15 years ago probably wouldn't have had a non-motor symptoms, scale questionnaire, or an RBD screening questionnaire or the F-word scale, or which all of which look at different aspects of disturbed sleep. Um, I don't think we actually know the answer to that because the data that I was mentioning on the benefit of STN DBS came from Ray chowdry's group who's focusing on non-motor symptoms, only really been published in the last one or two years. Um, so I may be wrong, but I'm not aware of a really nice longitudinal study showing that the benefit of surgery is maintained at five and 10 and 15 years after surgery.

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| Dr. Karen Jaffe: | | Great. Another audience question wants to know whether heat or temperature impacts sleep. |
| Dr. Ospina: | | So ideally you'd want to sleep in a slightly cooler room. Um, and so that, that you can sleep throughout the night, uh, the harder the room, the more likely you are to have more vivid dreams, just like having, um, you know, things like dopamine agonists, like Dr. Hu said, especially in young onset patients, they can cause your dreams should be more vivid. So certainly you want to be comfortable, not too cold, but slightly lower temperature. And certainly not too hot. |
| Brian Duggan: | 29:42 | That's certainly one of the things I've found too. Um, there's a researcher out here at Berkeley, Dr. Matt Walker, and one of his things as part of sleep hygiene is kind of shooting for about 65 degrees. Again, everybody's different, but that's, that's worked for me going for a cooler room. That's been part of a helpful regimen. |
| Dr. Karen Jaffe: | 30:02 | Okay, well, let's, let's move on to what we, the big topic here, and that is managing these sleep problems. Dr. Ospina, I'm going to start with you, and maybe you can tackle some of the things that are on this list. That's about sleep hygiene, especially, and some of the other things that are listed there as well. |
| Dr. Ospina: | | Yeah. So certainly so good sleep hygiene is key. So the last thing you want to do is be taking very long naps during the day, especially in the afternoon. And then you invert your sleep wake cycle so that you're sleeping most of the day and then awake at night, then that can lead to trouble with the insomnia, the sleep fragmentation. So always talk to your doctor about, you know, your medications and how well they're working. So sometimes you may need a dose of levodopa in the middle of the night to keep you sleeping through the night like Dr. Hu said, we want to avoid things like computers, tablets, you know, your phone because of the blue light, that's going to keep you up. Uh, and so we want to put those things away earlier in the day. And, um, I know there's this thing coming up on my screen, it wants to update. Um, and then we want to stay away from things like caffeine late at night. You know, we don't want to be taking coffee late at night, like Dr. Hu said, not a lot of alcohol because it disrupts that sleep architecture. We want to be going through all those stages of sleep to get the benefits of the sleep, which are consolidating memories and consolidating learning that has happened during the day. Um, and then exercise is very |

beneficial. So if you want to do some exercise early in the afternoon, that will help you with sleep.

Dr. Ospina: 31:42 And then just like you want to have a well-balanced diet. You want to have a well-balanced exercise program so that you want to do some aerobic exercise, which we may think that it may be restorative for the brain. Keep you keeps, it keeps your brain young and healthy. And then we want to do some resistance training to help you with the muscles and the bones. So in Parkinson's disease, there's nothing wrong with the muscles. They're just bradykinetic. There's moving slowly. If you're not moving those muscles, they tend to atrophy and waste of way. And then if the muscles aren't pushing and pulling on the bone, it doesn't tell the bone, Hey, I need to stop that calcium from my diet or my supplement into the bone to make it strong and healthy. So if you happen to fall, you're less likely to have a fracture.

Dr. Ospina: 32:24 So you want to have a well-balanced exercise program. So you have aerobic exercise for the brain to keep it young and healthy, and then resistance training to keep your bones and muscles strong and healthy and Parkinson's disease. And that you want me to go into complimentary or alternative things are here. And then cannabis is always something that's asked about here in America, since so many States are now legalizing it. Uh, and so some pay so cannabis, we've got two forms, the CBD oil, and then the THC. In Parkinson's patients, you usually want to stay away from the THC because you're already on psychoactive medications. Your levodopa already causes hallucinations. All of your dopamine agonists can be, uh, hallucinogenic as well. And so we don't want to add in one more thing that can cause you to be confused and hallucinate. Some patients have found that the CBD portion that CBD oil can help with sleep.

Dr. Ospina: 33:19 So insomnia initiating sleep and can help with pain. Uh, there's still not enough data on that. Uh, light therapy can help. So especially patients with seasonal affective disorder, they can use light therapy to help not only their mood, but to reset their clock and reset that 24 hour circadian rhythm things like acupuncture. So anything that helps you with the rigidity of Parkinson's disease, like a massage Tai Chi yoga acupuncture, again helps relax the body so that I can fall asleep and then also relax the brain. So it's not only the brain and the body that stiff and rigid, but sometimes your brain is going a mile a minute and making tons of lists. And that can be a reason why you can't fall asleep and why it keeps you asleep. Uh, so meditation Thai sheet helps you to retrain the mind so that you can fall asleep easier,

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| Dr. Karen Jaffe: | 34:16 | Uh, in regards to cannabis and the CBD oil. How are patients to know how much, how often, uh, it seems that, um, everybody has a different formulation of it, or, um, how is there any guidelines that are out there for people who want to try this? |
| Dr. Ospina: | 34:33 | Yeah, so that's very difficult because there aren't any guidelines and it's, you know, depending on the state, you know, some have regulations and some don't, so it's not a very regulated sort of, sort of like, you know, vitamins, you don't know when you buy some vitamins, you know, how much vitamin D is in it. And, uh, is it actually vitamin D it's not regulated by the FDA and neither is cannabis. And so it's something that, and it's re it's different from state to state. Uh, so everybody has to sort of see, try it and see what works for them. So some patients, you know, in Arizona, gummies are very popular. You know, some patients say, well, I only eat the head of the gummy bear and that's enough for me. Uh, so I think that there's a lot, much, yes, you can have too much so you can have, so it can lead to confusion, hallucinations, uh, you know, remember you're mixing with all of your other medications. So we want to be very careful with that. |
| Dr. Hu: | 35:39 | I was just thinking that, um, in all of these treatment trials that we have for sleep disorder, there's very little good evidence base. Um, one of the problems is that particularly with complimentary therapies is you don't have a placebo-controlled trial and a placebo benefit, which is that you're you think you're taking a drug that's going to work for you and could be massive in somebody with Parkinson's up to a 50, 60, 70 percent benefit just simply because they have that sense that they're taking something that's working you're much more positive. I have recently reviewed a paper that actually was the first ever that I'm aware the CBO control trial using cannabidiol versus a placebo. And that actually used patient diary as endpoints for RBD, as well as, um, the overnight sleep study. So I am bound by confidentiality. I can't tell you the results. However, um, it was showed some promising benefit for overall sleep quality, uh, but not necessarily for our BD, but I think we need more studies of this nature to really kind of tease out what works in terms of treating RBD. We have some, the CBO control trials of short duration in small numbers of people with Parkinson's and idiopathic RVD. These are people who have not converted to a condition, uh, that show benefit with clonazepam, which is a benzodiazepine like Valium, um, and also melatonin. However, the one melatonin study I'm aware of the actually use sleep on a tree as the endpoint, which used melatonin and up to a dose of four milligram was negative in Parkinson's. However, I believe |

that Brian has his own anecdotal experience, that might also be helpful to listen to.

Brian Duggan: 37:23 Yeah, true. Yeah. When it comes to managing RBD, it's a unique sleep problem because on one level, the first thing you need to do is reduce the chance for sleep related injury. If you're moving about in your sleep, if you're falling out of bed, if you're punching your bed partner, there's a big chance for injury. So for my wife and I, it was really about moving our bed low to the floor, getting a larger bed, putting a lot of pillows around, um, when traveling doing a lot of those same kinds of pillow, uh, pillow things to, uh, create a safe environment. Otherwise you feel stressed going to sleep because you wake up out of a dream into some violent incident. It's a terrifying thing for the patient and for the partner who's trying to manage this. Who's often the one getting hurt. I mean, I, you talked about sports dreams.

Brian Duggan: 38:13 I used to dream about a basketball rolling out of bounds. I have to get this basketball. I have to get this. I woke up one time and I was holding my wife's head in my hands. And she was calmly talking me down out of this, but it, so it, it's, it's a lot to deal with just from the sleep related injury side. But then you get to the fact that there is a of ongoing neuro-degeneration here. And like you said earlier, doctor who, you know, I had lost my sense of smell 10 years earlier. So you're having a constellation of symptoms that do look like they lead to further neurodegeneration. And so the one does everything you can to try to, or my approach has been to try to do everything I can to reduce the chances of neurodegeneration. Melatonin has worked very well for me at a higher dose again, in the groups and people I talk with clonazepam is also something that often works for folks.

Brian Duggan: 39:13 Um, but it's really in a constellation of, um, what one neurologist talked to me about as the basics are basics for a reason exercise as Dr. Ospina was talking about, um, including Hyatt and high intensity interval training, um, and diet stress reduction, overall sleep hygiene. Um, I, my, my approach is to do any experiments I can, that will help me be part of the, uh, percentage of people that don't convert to something more serious, or don't develop more serious motor symptoms. I will just comment on the CBD. I have started experimenting with, uh, CBD oil here. Um, the, what I think is, you know, getting a high quality product is important using a full spectrum product, often as a tincture, maybe the best way to do it. And then starting with low number, maybe five milligrams and trying to

work your way up. But I've found that that's been a little bit helpful in my sleep as well.

Dr. Karen Jaffe: 40:15 What do you mean by a full spectrum product?

Brian Duggan: 40:17 Well, see, there's a lot of products out there where they isolate CBD, and there's a lot of cheap products where it's just isolated CBD on its own or in a tea and a solvent of some kind. And that's not really what you want there. The value of the plant of the CBD seems to be when it comes with all of the terpenes and all of the things that are in the plant itself. Because again, all of this is very experimental from a, from a scientific standpoint, we don't know what these things do yet, but the full value of the plant can be found with one of these high quality full spectrum, uh, uh, tinctures and, and, um, yeah,

Dr. Ospina: 41:00 As Brian says, Oh, you know, over the counter, we use a lot of melatonin, uh, for patients. And then as a prescription medicine, we use clonazepam, a low dose clonazepam to suppress REM. And then we do things like if there's, like Brian said, you make the pillow for some patients sleep in separate bedrooms, some patients where they're falling out of bed, they'll use a bed rail or put the mattress low to the floor, or we'll put the patient into a sleeping bag so that when they're fleeing about they're sort of, self-contained, they're not hitting the lamp. They're not hitting the wall, they're not punching the bed partner. Uh, so there's, you know, many behavioral things and or medications that we can use to treat RVD to make it less violent.

Brian Duggan: 41:45 Interesting. Just to give a little bit of a helpful, um, note on this. My experience has been that the combination of higher dose melatonin with all that, some of these other lifestyle choices and good sleep hygiene going to bed early, so that those deep sleep hours can take place or minutes. Maybe they're not hours. Um, it's all accumulated for me into much less RBD over time. And I have not yet converted to more serious. Um, motor symptoms

Dr. Karen Jaffe: 42:18 Definitely is, is all melatonin the same? Is there one of the audience members is asking whether there are different forms of melatonin or this melatonin.

Dr. Ospina: 42:31 That's the thing. So again, it's not regulated by the FDA, so you always want to get your vitamins and your things like melatonin by when you look at the bottle to see that it was looked at by another independent laboratory saying, yes, what's truly in this pill or gummy is melatonin. And that is three milligrams. So

again, it's one of the problems with our FDA that it does not regulate over the counter medications, including vitamins and things like melatonin.

Dr. Karen Jaffe: 43:01 Okay. So on our last slide here, Oh, look, there I am my husband and I on our anniversary. He surprised me with a private sailboat cruise at night. Um, so obviously these things don't impact just us, but impact our family members, our care partners, our spouses, um, Brian, you mentioned a little bit about how you have changed your environment to adjust, uh, and to keep yourself and your spouse protected. What other kind of struggles or challenges have you guys faced because of your REM sleep behavior disorder?

Brian Duggan: 43:37 There are phases to it, right at the beginning when one first falls out of bed or first lashes out, it's kind of, you look at each other like, Oh my God, what's going on here? I mean, and, and, um, I don't know how many folks that followed Alan all does, um, diagnosis, but his, his experience was much the same. He was, he was, uh, throwing a pillow at his wife during the night and, um, then went and did online research and, uh, an article by Jane Brody, I think, and learned about RBD. And that led him to find out he had Parkinson's. So at the beginning, you're in this violence at night sort of struggle. Um, um, in our case we did spend some time in separate beds, but then found a way to make it work, to be, um, all together, um, in a safe environment. And, um, but it's a, it's a challenge for the partners as much because I

Dr. Hu: 44:32 Will wake up out of a dream, but I don't know what's been going on. I don't know, I've been foiling until I wake up and they've had to live with the talking, the noise, punching, whatever it is.

Dr. Karen Jaffe: 44:46 Yeah. Um, for me, you know, I don't see my sleep problems as, as a problem. So, because I don't see it as a problem. Um, and basically I don't get enough hours of sleep, but my husband does and it doesn't pack the, the family member, especially the spouse. Um, one of the, one of our audience members is asking whether a person who's having a REM sleep bad dream should be woken up during it. Well, how do you, how do they manage that and how, how do they, um, proceed with when they're in the middle of it? Dr. Hu, you want to take this one?

Dr. Hu: 45:22 Yeah. I mean, I think so what I tend to say to the partner is that they're often very aware that this is happening and they can see and know from experience whether this is going to escalate into something that is a really big full-blown attack with movement

and, you know, potential for injury. And what I would tend to say is it is probably in my experience better to wake up the partner. If you can sense it's going up to that. And then the person will wake. Um, in fact, actually, if you wake someone up during that episode of random sleep and RBD, they immediately know the dream. Um, and they remember it, but if you let them sleep through, they might not remember it the next day. So they will wake up. Obviously the realization will then slowly door, and this is just a dream.

Dr. Hu: 46:11 They can get some reassurance and they can hopefully then just go back to sleep. But this time go through the sleep phases without going into an episode of RBD. Um, I'm interested to know what Maria's thoughts are on this. Um, and just one other question, which was on the chart is, is mindfulness or meditation helpful for sleep. Um, certainly insomnia, which is delayed, sleep onset, lying in bed with your mind, really racing and not being able to go to sleep is one of the common asleep problems for people with Parkinson's. And in the UK, we have an app called Sleepio S L E E P I O, which was developed by, uh, researchers in the sleep and circadian neuroscience Institute, which is available for patients to download worldwide. And it is providing cognitive behavioral therapy approach to insomnia, and it has been tested and shown to be effective. Uh, so I would certainly recommend that. Um, and that's a very similar approach to mindfulness, um, and can help you get back to sleep if you wake in the middle of the night, um, Maria, do you ask your, um, your patients bed partners to wake them up, uh, in the, in the middle of an episode, if it looks to be escalating?

Dr. Ospina: 47:30 Yes. If it looks to be escalating, so there's going to be self-harm or there the bed partner's going to be punched, then they can be woken up if it's just mumbling or talking, or sometimes even screaming, and it's not going to, there aren't any movements, you could let them sleep through it because they won't remember any of the dream whatsoever, or if they're in another room. Um, and so really RBD is really a problem for the more for the bed partner than it is for the patient, because the patient sleeps through all of that. So unless they're getting out of bed or sleepwalking or punching, or you're in a hotel, so yeah. Or, you know, tells her if you're screaming and then somebody's calling the hotel manager because they think there's a murder happening in there. Then you want to wake them up. And then, and another thing that's interesting is that during the day, the Parkinson's patient is very hyper phonic. They have a low whispery voice, they have trouble getting their voice out, but during REM sleep, you know, they're yelling and screaming and it's a full-throated voice. And it's sort of interesting to see how,

why does that happen? You know, why can they get a big scream out at night? And then during LSVT or big and loud, they can barely get their voice out.

Dr. Hu: 48:40 The videos show that the movements are very quick, easier. And so the question is what's happening in REM sleep is different than accessing different motor pathways to generate movement. Um, and it's an absolutely fascinating question. Really, isn't it to think about. It's just generally people with, um, RBD don't generally make it outside of the bedroom, um, because the movements that are needed to walk and the empty gravity toad is just not there. Um, and so they usually kind of fall out of bed, uh, or they'll take a few steps and then fall and wake themselves up on the floor, um, as opposed to a non REM parasomnia, which is the sort of night terror that you get in much younger people when they do actually sleep, walk very effectively and go downstairs into the kitchen and get, and make a sandwich and go back to bed.

Dr. Ospina: 49:38 Right. Yeah. It's super interesting. Now I've had Parkinson's disease for 14 years and I've just in the past year started having, you know, screaming out violent dreams, things like that. What percentage of Parkinson's patients develop, uh, RBD?

Dr. Hu: 49:53 Yeah, so, um, we looked at this in our cohort of a thousand people. Um, we didn't have obviously the logistics and the resources to do, um, polysomnogram or sleep study in everyone. So we just use the RBD screening questionnaire. So that is, um, limited. It's not a hundred percent accurate for RBD, but it's, um, about 80 to 90 percent. So using that screening questionnaire and around a thousand people with Parkinson's who are within a mean of one year from their pockets and diagnosis, 38percent were positive for having active, uh, RBD in the previous six. Uh, we've now actually tracked the frequency of RBD, uh, in each individual with Parkinson's over a mean duration of about six to seven years, which is the length of follow-up we have in our Oxford discovery cohort. Um, and the reason for this is that anecdotally I've talked to a lot of patients and fat and bad partners who sort of say, well, the RPD seems to have got a bit better.

Dr. Hu: 50:52 It seems to have responded to dopaminergic therapies. Um, you know, maybe it's burning itself out, but actually at a group level in over probably an hour, 750 people who've been followed up every 18 months with the same screening questionnaire, the RBD frequency keeps going up, um, during their Parkinson's duration and people like you, Karen, who develop it only after that diagnosis, I definitely, um, recognize so, you know, not

everybody gets it before. Um, and some people get it, uh, doing, you know, the first five years, some will only get it following five to 10 years of diagnosis

Dr. Karen Jaffe: 51:34 And it never goes away.

Dr. Hu: 51:37 I mean, I do have individuals who have said to me, I don't think I've ever had an episode of RVD since I went on to this treatment. But the problem with it is that you're reliant on their knowledge of their sleep or the bed partner. And many people can be having like mild episodes of RBD that you might only pick up during a sleep study. So I think that's not possible to say definitively and just say that I feel like I have my RBD symptoms quite well under control these days, but I have probably some degree of RBD, some degree of movement, most nights, maybe every night, and I still will have violent or thrashing movements that I sleep through. And so it doesn't bother me so much. And my wife and I have arranged, so it doesn't bother her so much, but it's not gone. It's just controlled.

Dr. Karen Jaffe: 52:37 Um, Dr. Hu, is there anything else that you can share with our audience about the current research that's happening with RBD?

Dr. Hu: 52:43 So, um, yeah, I mean, I think to mention, obviously this is The Michael J. Fox Foundation sponsored webinar. So the PPMI prodromal cohort I think, is really going to help us because it has the resources to really follow up large numbers of prodromal Parkinson's individuals, including those with RBD. And so in Oxford, we're going to be part of the first wave recruiting people who've had a sleep diagnosis and they're going to go in alongside other people who may have higher risks through family history of Parkinson's through genes, to, uh, having the poor sense of smell. And they're going to be seen, uh, quite very regularly every six months, but importantly, also going to have a number of different tests or biomarkers that we hope to be able to put together in combination to pick out those who are at the highest sort of 10 percent risk of converting and that those individuals, we would want them to be maybe having a 50 or 60 percent of chance of imminent conversion in the next two years, because those are the individuals that would most benefit from high risk treatments designed really to try and prevent you will slow down or delay the onset of your Parkinson's.

Dr. Hu: 53:59 So this is, this is the sort of way that I think research is going now. Um, and through the PPMI, we'll be able to combine imaging by your scans with very clinical simple digital measures,

like a smartphone or a home sleep measure, uh, with a very sort of clinical bedside task and maybe a blood test as well, uh, to throw into that mix. And I think those combinations biomarkers, which is really what we've been looking at in Oxford, uh, will help to refine that. And, and that's really, I'm excited about going forward into trials now with people with RBD. And so, you know, we're really keen to get patients with RBD like Brian involved in as ambassadors so that people can hear what the experience is like of living with RBD. And that patient voice is also recognized by pharmaceutical industries because people with RBD, they're not asymptomatic. They do have a lot of symptoms, particularly on the non-major side, and that can be worse than somebody with Parkinson's. I think the other thing is there's a number of new compounds, new drug compounds now being tested. Um, and when you looked at this recently, uh, we have six compounds, uh, through either Biogen, Jazz Pharmaceuticals, uh, looking at either GAPA, uh, agonists or different, uh, histamine uptake or dopamine reuptake inhibitors to look at the benefit on sleep. Um, and I think that, that if we have something that is really effective, that will be a big breakthrough because as we've said already, improving someone's sleep will have a big impact on them, but also on their family not just on their quality of life, but on their motor symptoms the next day and on their ability to think and retain information, et cetera. Um, and I think that's, it really, that's all I have to say at the moment.

Dr. Karen Jaffe: 55:59 Brian, was there something you wanted to add?

Brian Duggan: 56:02 Just on that point about, you know, the importance of sleep? I mean, on the one hand sleep hygiene, sleep, something to do to, um, take care of oneself, but it's also potentially a way to prevent neurodegeneration, right. And to increase neurogenesis and to, um, stop one's progression, you know, for moving on. So this is speaking as a patient in the RBD community, you know, this recognition that, okay, this may be a prodromal stage of Parkinson's. How do we, um, keep ourselves from moving forward and keep, you know, keep our, keep ourselves from neurodegeneration. We're, we're excited to be part of the research and part of the PPMI and to, um, contribute to an understanding of, uh, of a constellation of symptoms that we're all experiencing over a, of a wide continuum. Even those of us that don't have motor symptoms.

Dr. Karen Jaffe: 56:57 Well, and for people who are interested in the PPMI study, if you go to the resource section on the website here, links for more information about that PPMI study, it should be in the resource box. I also wanted to bring up in the resource box. Uh,

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| | | I didn't get a chance to talk about this earlier, but the Fox Foundation has created something new called the Parkinson's Buddy Network. It's also listed in the resource portion of the screen. Um, and this is a network where it's creating, um, you know, one-on-one connections for people who maybe need to want to have a little bit more support that they they're not getting, or having a conversation with somebody who understands what you're going through. It's still in the beta testing phase. So you, if you want to get involved, you can click on the resource box and, and sign up and have some input into how that buddy system gets developed. |
| Dr. Karen Jaffe: | 57:50 | So those are two important tools that you could use. Well, it looks like we've come to the end of our time here. I want to thank everybody. I know we had a big audience today for being a part of our community and for joining us today. And of course, thanks to our panelists for sharing their time and their expertise. Dr. Hu, Dr. Ospina, Brian, it was great to meet you and hopefully we'll see you in the future. We'll be sending a link to this webinar on demand to listen again and share as you would like. We hope that you found it helpful. Uh, and may you stay safe and stay connected and be well. |