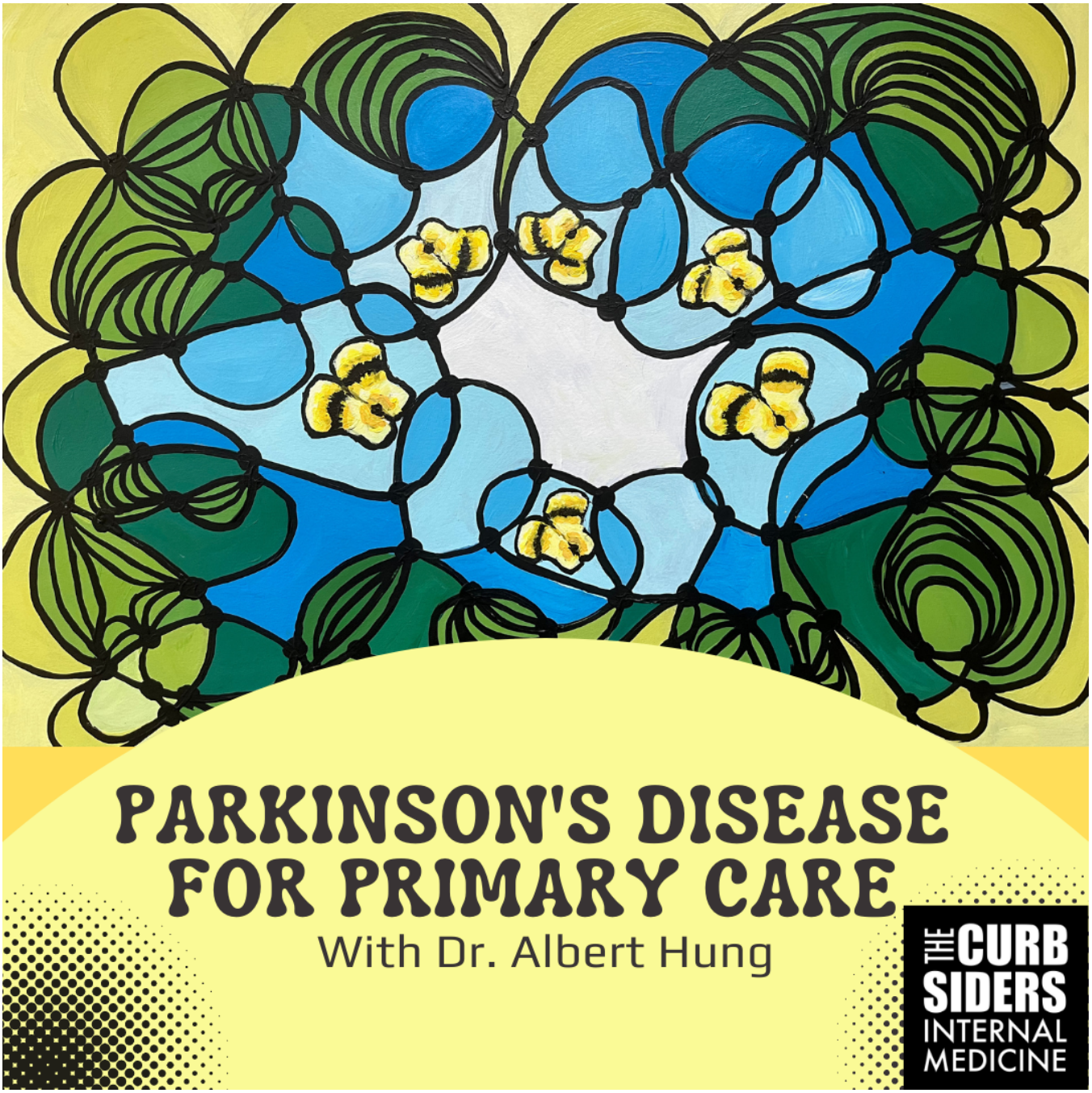
#370 Parkinson's Disease for Primary Care with Dr. Albert Hung



[Curbsiders Podcast theme]

Matthew: Welcome back to the Curbsiders. On tonight's show, we will be talking about Parkinson's disease with the great, Dr. Albert Hung. This was a fantastic episode. I of course am Dr. Matthew Frank Watto, here with my great friend whose birthday is this week, Dr. Paul Nelson Williams. Actually, not the week this is coming out, but as we're recording his birthday is coming up. He is going to be-- I won't give you his age.

Paul: Oh, let's just say old.

Matthew: Old. [laughs]

Paul: Well into middle age.

Matthew: Old enough that his med students don't understand any of his references.

Paul: [laughs] Yep, the Seinfeld jokes just don't sink the way they used to.

Matthew: So, Paul, can you tell the audience what is it that we do on the Curbsiders and then introduce our wonderful cohost corresponded for this episode?

Paul: Sure. Happy to. As always, Matt, we are *the* Internal Medicine Podcast. We use expert interviews from your clinical pearls and practice changing knowledge. As you mentioned, we talked to Dr. Albert Hung tonight about the workup and management of Parkinson's. Before you hear all about him, I'm going to introduce you to our other cohosts tonight, our producer extraordinaire, remarkable medical student, my future boss, [crosstalk] [Matthew chuckles] introduce, Malini Gandhi. Malini, how are you tonight?

Malini: I'm good.

Paul: Great, why don't you tell us about who we talked to and a little bit that what we talked about?

Malini: Sure, y, we had a wonderful conversation tonight with our guest, Dr. Albert Hung. Dr. Hung is the Medical Director of the Parkinson's Foundation Center of Excellence at Massachusetts General Hospital. He's Associate Director of the MGH Movement Disorders Division and an Assistant Professor of Neurology at Harvard Medical School. He specializes in the treatment of Parkinson's disease and other movement disorders and sees patients at MGH and Brigham and Women's Hospital. As a member of the Parkinson's study group, he also participates in clinical research trials to identify and develop new treatments for Parkinson's disease.

So, this episode Dr. Hung taught us a lot of wonderful pearls about diagnosis and management of Parkinson's disease including his approach to the initial history and physical, his framework for treatment, tips for managing non-motor features of Parkinson's like autonomic symptoms and cognitive symptoms and a lot more.

Matthew: Yeah, and Paul, before we get on to the episode, I just wanted to know, did you know why did the neuron like to sleep on the top bunkbed, Paul?

Paul: I feel I should be able to figure this one out.

Matthew: [laughs]

Paul: I don't know, Matt. Why would that be?

Matthew: You're not even trying. Paul, [Paul laughs] he wanted to have a high resting potential.

Paul: I would have never gotten that because [Matthew laughs] my brain doesn't work in that way. Great stuff.

Matthew: Well, yeah, I agree, Paul. It was great stuff. So, thank you to *72hilariousneurologypuns.com*.

[laughter]

Matthew: A reminder that this and most episodes will be available for free CME credit for all health professionals through VCU Health at *curbsiders.vcuhealth.org.* Albert, we've had some technical difficulties, but we're ready to go. The audience is definitely going to want hear a little bit about yourself a one liner and then throw in some hobby or interest that you have outside of medicine.

Albert: Sure. No, great. Thanks very much for the opportunity to be part of the podcast. I've been in Boston for a long time. Now, I'm actually a native Chicagoan, a diehard Chicago Cubs fan. So, it's now been a few years since we've had anything to brood about, but I'm really looking forward to sharing some information about Parkinson's tonight.

Matthew: Yeah, today while we're recording, the Phillies, Paul, are about to enter the World Series. I know, Paul's a huge Phillies fan.

Paul: Listen, it's nice when this grumpy city is happy for even just a brief moment in time. [Matthew laughs] So, if this is what does it, great, go with God.

Matthew: All right. By the time this comes out, we will either had probably some riots in the city. Joyous riots were-- [crosstalk]

Paul: There're going to be riots.

Matthew: Well, there're going to be riots either way. Well, who am I kidding? All right. Well, we have with us our super producer, Malini Gandhi. Malini, can you please start us off with a case here from Kashlak Memorial because we want to make sure we have plenty of time to talk about Parkinson's?

Malini: Sure. So, we have the case of Mr. Robinson. He is a 68-year-old man, has a history of hypertension and gout. He reports during his primary care visit with you that he's been experiencing this intermittent tremor in his right hand. He said he initially didn't think much of it, but over the past year, it's gotten worse and then recently has begun affecting his left hand as well. He said he thinks the tremor is worse when he's not using his hands. Additionally, he tells you that he has been feeling stiff and slowed down lately. He initially attributed it to aging, but tells you he's been having a lot of trouble doing little task with his hands like buttoning his jacket or tying his shoes. He also mentioned that his wife has been complaining that she can't read the shopping list that he writes out without her glasses because his handwriting has become very small. When you take review of systems, he does report some issues with constipation as well as some episodes of lightheadedness when he gets up from lying down.

Matthew: So, to start off with this case here, I think really we always start with the history. Albert, can you talk us through how you think about it when you're talking to a patient? What are you listening for as you're getting this history from the patient and his wife?

Albert: Absolutely. I will just underscore that for most movement disorders including Parkinson's disease, the diagnosis is going to be made largely on the history and on the exam. We don't really rely that much on other tests. And so, that makes the first time you're discussing the particular symptom with the patient all the more important. When I see somebody and we're thinking about, well initially, presentation with tremor and a question of Parkinson's, there're a few things that I'm really listening for. One is the tempo of the symptoms. Somebody who has a Parkinson's tremor is likely not to really notice it or complain about it at the start. But it's something that comes on very gradually. Oftentimes, because it generally is a rest tremor, the family member or the PCP may be the first one to mention it. Sometimes, the patient themselves downplay it because it doesn't necessarily interfere that much with their activity.

Tremor is one of the main symptoms, but not the only symptom that we look for in terms of trying to make a diagnosis of Parkinsonism. And the tremor in this case, an asymmetric rest tremor is probably the most typical type of tremor we would associate with Parkinsonism.

Matthew: We did an episode on tremors like 300 some podcast episodes ago, Paul, which it was called a tremor and it was one degree of Kevin Bacon, Paul, which is a title you should be very proud of.

[laughter]

Paul: Yeah, great stuff.

Matthew: The cover looks like the cover of the *Tremors* movie. Can you talk a little bit about when you're taking the history about tremor in Parkinson's, which sort of things do you ask for that maybe make you more suspicious as a Parkinson's tremor rather than an essential tremor, which is--? I usually pray it's an essential tremor when a patient comes to you with tremor because then you could just be like, "Oh, it's maybe bothersome. We can do some stuff for that, but it's not Parkinson's."

Albert: Sure. So, I think that all the time that you are talking to the patient in the office, you're watching them, because most of movement disorders is diagnosed based on observation. And so, when a patient complains of a rest tremor, in the office you may not see that much more than a twitching of the thumb or a little bit of a shaking of the hand and it can come and go. What I'm really looking for is oftentimes if it's a very large amplitude tremor, asymmetric rest tremor, the diagnosis of Parkinsonism is not difficult to make. It's that subtle tremor, a little bit of shaking, a little bit of twitching that really makes you pause and think about, is this really Parkinsonism that I'm dealing with?

One other important aspect of the tremor to realize is that patients with Parkinson's disease can also have a postural tremor. When you ask a person to bring their hands up, it can shake. One of the distinguishing features between the postural tremor of Parkinsonism and say ET is that somebody with an essential tremor, you put the hands up and they'll be shaking right away. Somebody with a Parkinsonian tremor, when they bring their hands up in may be quite still, but when they're maintaining the position, the hand will start to shake or even wind up. We call that a re-emergent tremor. And a re-emergent postural tremor, again, should make you think more Parkinson's disease, whereas the tremor that's there from the start and especially if it's bilateral should make you think of ET.

Paul: What questions should we be asking to assess for bradykinesia? I feel I have less of an illness script for that necessarily. So, how are you assessing that especially in the history portion of the show?

Albert: I think the point brought up in this case is a really good one and that is that oftentimes bradykinesia can be fairly subtle and bradykinesia can often be attributed to other issues say, age, or arthritis, or depression. People will just slow down. And in the absence of a tremor, identifying that bradykinesia can sometimes be difficult.

Some of the things that I will ask for are essentially changes in a person's daily routine. If you're asking for appendicular bradykinesia using the hands, you can ask about handwriting, the micrographia that was described in the case is a common symptom. People will often describe bradykinesia with buttons, or zippers, or trouble cutting food, putting their arm into a sleeve. Now, you always have to rule out that there's something else, arthritis, a rotator cuff something like that. It's interesting there's been actually lots of reports about people who eventually were diagnosed with Parkinsonism initially being diagnosed with frozen shoulder-

Paul: Right.

Albert: -because they come in with stiffness. And so, those types of symptoms are important to ask for other signs of bradykinesia that I will often ask difficulty getting in and out of bed, in and out of a car or a chair. And so, these are the types of questions I ask and again I'm probing without trying to ask too many leading questions to try to get a sense of whether there's a symmetry that would make a diagnosis of idiopathic Parkinson's disease more likely.

Matthew: The non-motor symptoms are something that I have to confess. They were not so much on my radar. I knew about orthostatic hypotension, but I didn't realize that they often proceeded and when reading through the list of these, there's bladder problems, constipation, like I said, the orthostatic

hypotension. Paul, we see these commonly in primary care. So, now we would be paranoid, everyone has Parkinson's, but can you tell me what constellation of those non-motor symptoms make you start to wonder could this patient have Parkinson's?

Albert: I think this is actually one of the hottest areas in Parkinson's research these days because we really want to be able to identify who's going to be at risk for developing Parkinson's motor symptoms before they develop them. I would say that the three premotor symptoms that are most helpful. One is hyposmia, changes in smell, another one is constipation, and the third and the most specific is REM sleep behavior disorder. So, REM sleep behavior disorder or RBD refers to a sleep disorder where people during the REM phase of sleep are active. Most people during REM sleep, all that moves is their eyes, rest of their body is still, they're atonic.

And so, people who have REM sleep behavior disorder during that phase of dream sleep will actually act out their dream. They'll yell, they'll scream, they punch, they kick. Oftentimes, the person themselves aren't aware of it. It's the bed partner. Other people in the house who will say, "You know what, my partner's doing this. I've had people tell me that they thought they were being chased and they threw themselves out of the bed. And so, they found themselves on the floor a couple of times unexplained. When you get that history of REM sleep behavior disorder, you should pause and ask yourself, "Are there any other signs to suggest Parkinsonism?" Because there's quite a high rate of phenoconversion from RBD to Parkinsonism over the course of years.

Matthew: Yeah, Paul and I were talking ahead of time. There's a movie, I don't know if you ever heard of it. It's called *Sleepwalk with Me*. It's about this comedian Mike Birbiglia, who had REM sleep behavior disorder. As I was reading this, I was like, "Oh, no, I hope he doesn't develop Parkinson's," because in that movie, I think this was a true story and how he figured out what he had. He was in a hotel room, and he was dreamed he was being chased or something, he ran through and jumped out a glass second story window and landed in the yard of his hotel. So, scary stuff.

Albert: A lot of the cohorts that are actually being collected for research purposes these days are not people with Parkinson's disease, but either people who have RBD or people who have family histories or genetic risk for Parkinson's. Again, this is the group I think that from a research standpoint, we may be able to intervene on to change the course of Parkinson's whereas once a person has motor symptoms, it's possible that it might be too late.

Matthew: There was a JAMA article that Malini had sent us. It was a review article from a year or two ago. They were talking about with Parkinson's it seems these non-motor symptoms may be present for years ahead of time, and then the motor symptoms develop, and then eventually as the disease progresses, these cortical symptoms develop where people are getting dementia, maybe hallucinations things like that. Is that widely thought about now how things progress and is it a late diagnosis? Is that pretty typical or the immediate like they're in the middle of that range where they're just having the motor symptoms when most people are diagnosed now?

Albert: I think that when we try to think about how Parkinson's develops and progresses, it's an increasingly interesting question. What is Parkinson's disease and when do we make a diagnosis? Do

we make a diagnosis when the motor symptoms appear? That's the way we do it now. But I think that the disease process like you point out, Matt, starts years before. If you look for the premotor symptoms, they can start a decade or more before. If we look for biochemical changes of dopamine loss based on functional imaging, we know that that predates the motor symptoms.

As we're thinking about the way that Parkinson's develops and progresses, there's this idea that the pathology largely based on this protein called alpha-synuclein that that gradually spreads through the nervous system. So, the core feature pathologically of Parkinson's are Lewy bodies. The main protein component of Lewy bodies is aggregates of alpha-synuclein. But by the time we get involvement of those parts of the brain that cause motor symptoms like the substantia nigra, we can already see alpha-synuclein aggregates elsewhere in the nervous system. We can see it in some of the neurons in the gut, we can see it in other areas, nuclei in the brainstem.

It's this idea that the alpha-synuclein pathology gradually spreads from one synapse to another through the nervous system. Usually, it from a caudal to a rostral approach, starting low down, coming up into the midbrain, where you get involvement of the nigra and develop the motor symptoms, and then it spreads to the cortex, and then people start to develop some of the later features like dementia or psychosis.

Matthew: Yeah, I guess, we'll get to treatments later, but reading about the monoclonal antibodies trying to target the alpha-synuclein, Paul and I were talking about this ahead of time. It reminds us of the Alzheimer's trying to target amyloid and they're speculating, maybe the trials were negative because you're intervening early enough and there's too much damage by the time. I'm not sure if that's widely believed, but it's interesting to think about this. I had no idea. I just thought Parkinson's was like cogwheeling rigidity, which [Paul laughs] is not. I learned even that wasn't as pathognomonic for Parkinson's. So, yeah, this was very eye opening to me.

Albert: It's really interesting as a Parkinson's specialist how the way that the field has changed over the last 5 ,10, 15 years. It's really gone from being your quintessential movements disorder really now being a multi-system disorder that affects much more than just motor systems.

Matthew: Should we talk about exposures and little bit about how that maybe informs the differential or the risk for Parkinson's? You ask about any of those things like I was reading pesticides and head trauma medications. What else do you ask about in that initial visit?

Albert: The point that you bring up is, how do we decide that somebody has idiopathic Parkinson's disease or what we typically think of as PD as opposed to some other form of Parkinsonism? Parkinsonism really is more of an umbrella term. It has four cardinal signs. Tremor, bradykinesia, rigidity, and postural instability. Bradykinesia is actually the most important one. Even though, people always think about PD and tremor, you really can't make a diagnosis of Parkinsonism without evidence of bradykinesia.

When I see a patient, the first thing I try to ask is, am I convinced that the patient is Parkinsonian? Do they have some combination of these symptoms? Once clinically I've convinced myself that they have

Parkinsonism. The first one is this, like you said, drug-induced Parkinsonism? That's a cat miss, because drug-induced forms of Parkinsonism are reversible. They can be very difficult to distinguish clinically from neurodegenerative forms of Parkinsonism, but it's really crucial to do that. Most of us think about the anti-psychotic medicines, the older generation ones like haloperidol. But even the newer generation dopamine antagonists that psychiatrists think should be better in terms of causing extrapyramidal side effects. Medicines like risperidone, olanzapine, aripiprazole, all of them can cause symptoms that look like Parkinsonism.

When I am seeing a patient that's the first thing I do. I take a good look at their medication list. If they have any history that suggests that they might have been exposed to a dopamine antagonist in the past, I'll actually probe their recent history because symptoms of drug-induced Parkinsonism can sometimes last for months even after the medicine is stopped. That's really important too because sometimes, patients come off their medicine for a week or two, they say, "Well, my tremor didn't go away or my stiffness didn't go away. Therefore, it wasn't the medication." That's not true. We want to make sure we first exclude drug-induced Parkinsonism, rule out being on a dopamine antagonist.

Also, one of the medicines that we or the group of medicines that we sometimes forget about are medicines like metoclopramide or prochlorperazine, the antiemetics. They can also cause extrapyramidal side effects and look like Parkinsonism in some people.

Paul: You talked a little bit about this, but I would love to hear a little bit more detail about how you evaluate for tremor on an examination. I feel there's always a characterization of Hertz, which is not a value that is of any meaning to me specifically. So, I guess, what are you looking for when you're assessing a patient who reports you with tremor and how? You talked about some of this, but if you could summarize your overall approach, that'd be very helpful to me at least.

Albert: Sure. When I'm teaching my trainees about the exam of a Parkinson's patient, you'll sometimes hear this MDS-UPDRS acronym. What that means is Movement Disorder Society Unified Parkinson's Disease Rating Scale. Even as a general neurologist or as an internist, you don't need to know all the elements of the MDS-UPDRS. But the reason why it's useful is because it helps you give a framework for all of the different aspects of the exam that are important for anybody that you're evaluating for Parkinsonism. With this evaluation, just starting from the head down, you're looking at their facial expression, you're listening to their voice, often patients with Parkinsonism will have hypophonia or a bit of hoarseness in their voice. When you're checking rigidity, you're checking for tone in their neck and each limb separately.

The way that I check for tone is it's important to remember that rigidity is something that is velocity independent. When I'm checking for stiffness in somebody who I think has Parkinsonism, I'll usually stabilize one joint, move their hand or their wrist very slowly. Sometimes, if you move it too fast, people will resist you. But you have to remember that Parkinsonian rigidity should be independent of how fast you move the hand. You can move it faster or slower what you're checking for is resistance.

When we are assessing for rigidity, another trick is that you can do some maneuvers that will bring out or augment the rigidity. If you're moving somebody's arm, so let's say I'm testing tone in the left arm, I

can have somebody do some maneuvers in the right hand. I can have them open and close their fist, draw some big circles with the arm, and those type of reinforcement maneuvers will bring out subtle rigidity in somebody whose resting tone may be normal. So, I go back and forth side to side try to see whether or not one side has more rigidity than the other. You can do the same thing in the legs.

Then when I'm checking for bradykinesia, it's important to remember that somebody can be slow with one task and not necessarily with all tasks. And so, again, as part of this MDS-UPDRS, there's five different tasks that we do. We have people tap their fingers, open and close their fist, pronation, supination, turn your hand back and forth, you keep your heel flat on the floor and tap your toes and then you tap your whole foot. The way that the scale is set up, you want to have people do a minimum of 10 movements of each, because there're different aspects that can characterize the bradykinesia. Sometimes it's just slowness, sometimes its detriment. If you have people do it 10 times, they may look very normal at the beginning. By the end of the sequence, their movements may be quite small and then you can look for hesitation. So, those are some of the core features of the of the bradykinesia.

Then, Paul, you're mentioning the tremor. Tremor is tricky because tremor can be quite variable. And so, most important thing when you're checking a rest tremor is to make sure that the arm is totally at rest. Sometimes, people think rest tremor that means the hands not moving. But if their arms are lifted, that's a postural tremor. That's not a rest tremor. And so, you're looking for both the amplitude of the movement, you're looking for how much of the time the movement is there, and it can be really quite subtle. Sometimes, when you distract patients, you ask them to do other tasks, you put them under a little bit of stress, you can bring out that tremor a little bit.

Matt, you'd actually mentioned cogwheel rigidity. So, cogwheeling is essentially somebody who has increased tone and then superimposed on that they have a tremor. So, if a person has no tremor, they may have rigidity without cogwheeling, but that's still Parkinsonism.

Matthew: Yeah, I found it funny that cogwheeling is one of the main things I remember about Parkinson's and then I was reading that it's not specific to Parkinson's and not everyone has it and I was like, "Oh, well, this is not the thing I should remember about this." Now I know this. That's why we do the show, right, Paul?

Paul: [laughs] Sure.

Albert: Then the last part is that you want people to walk because oftentimes, especially in a busy clinic and a crowded clinic, you don't always get them up to walk. But for somebody who you're concerned about Parkinsonism, you want to see their ability to stand up, see if they need their hands in order to do it, you will have to look at their posture. The classic walk of somebody with early Parkinson's maybe just a little bit of slowness, but the posture might be a little bit stooped and the side that's more affected by the Parkinsonism may have less arm swing. That might be all you see. What we think of as freezing of gait or shuffling gait, those may be signs of Parkinsonism at more advanced stages. But the earliest ones, the ones that you may see in your primary care office is the person who has a slight bit of tremor on one side. When they walk, they seem just a hint slow and that arms not swinging.

Matthew: Asymmetry is the rule with idiopathic Parkinson's disease, right? If there's too much symmetry and I guess, maybe this whole transition is what we'll talk about next. But that's something that goes against that being the diagnosis, if there's perfect symmetry to what you're seeing?

Albert: Yeah, I would say that if this is idiopathic Parkinson's disease, it really should start asymmetrically. If somebody has very symmetric symptoms that would be one of those red flags that would make you wonder whether or not they have a different flavor of Parkinsonism.

Paul: Are you checking for postural instability? We were talking before the show, I guess, there's a test for you. You go behind the patient and just yank them backwards and they fall down, they failed the test?

Matthew: [laughs]

Paul: I'm not sure I'll be trying it. Maybe I'm oversimplifying here. I guess, a better question is, how do you assess for postural instability on physical examination?

Albert: The test that you're describing is a pull test and you're checking for retropulsion. When you're checking somebody, you have them stand up and you stand behind them. The teaching is that you should have a wall behind you, so that they don't topple you over. The way I tell people is, "Okay, I'm going to give you a little pull, okay? I want you to do whatever it takes to keep yourself up on your feet. If you need to, you should take a step or two back." Because that little love tap that doesn't cause people to move their feet. That's not a good enough tap. In order to really test retropulsion, you have to pull hard enough so that a person with normal balance has to take at least one step back.

Give them a little pull, make sure that they know what they're in for and then you say, "Okay, I'm going to pull a little harder now." And then you pull a little harder and if they can catch themselves in a step or two, that's normal. If they have to take 3 or 5 steps or 5 or 10 steps, then that's what we describe as retropulsion and then obviously if their postural instability is pronounced enough, you'll have to catch them.

Matthew: Well, that sounds terrifying.

Paul: [laughs]

Matthew: I probably have someone else there with me, Paul, make sure that I don't have the patient end up on the floor.

Paul: That seems like a good tip.

Matthew: Yeah, we were transitioning here to talking about-- You mentioned red flags and perfect symmetry would be one of the red flags. This is another concept that I wasn't really aware of that there's all these exclusions or red flags that make you think this could be something else. Can you talk about those?

Albert: Once you've ruled out drug-induced Parkinsonism and you have narrowed down your patient to having a neurodegenerative form of Parkinsonism, what is important is to try to figure out what the likelihood is that they have idiopathic PD versus some other form of neurodegenerative Parkinsonism. Because this affects their response to medication, it affects their prognosis, and it affects the way that you counsel your patient. I just gave you a couple of examples. Somebody has PSP, progressive supranuclear palsy that is a person who's going to come into your office often with early faults. People with idiopathic PD don't fall early. They may be a little slow, they may shuffle little bit but they don't fall. If you have early falls and you look at their eye movements and their eye movements don't look very normal, they stare at you and their eye movements are very slow, you should think about PSP.

If somebody Is Parkinsonian, but they come into the office because they had a syncopal episode, because they had profound orthostatic hypotension or you get a history, especially in guys that they've had urinary retention or erectile dysfunction that's not explained by prostate or other issues, that combination Parkinsonism with significant autonomic dysfunction should make you think of a diagnosis like multiple system atrophy, MSA. If they have a lot of cognitive issues very early on, again, people with Parkinson's, they can develop cognitive problems, but they're usually not early. If you get a history of somebody who is a little slow, a little stiff, but has some early executive or visual spatial dysfunction, maybe you get a sense that they have occasional hallucinations, especially if they got tried on some Parkinson's medicine, then you might think about a diagnosis like dementia with Lewy bodies. So, these are some of the red flags.

They're really flags that point to another diagnosis. Early cognitive impairment, early severe autonomic dysfunction, early falls, these are red flags that should give you pause about whether or not somebody has idiopathic PD. And then we'll get into more of this in a little bit but when you're talking about treatment, their treatment response is going to tell you a little bit more about their diagnosis as well.

Matthew: I know multi-system atrophy seems like it's a challenging diagnosis to make because we just talked about earlier the non-motor symptoms, constipation, and hyposmia, and some of those things that can precede idiopathic Parkinson's by years, but it sounds maybe just the tempo of those things is much different in multi-system atrophy. Is that how you differentiate them?

Albert: They tend to progress more quickly. I think that when we think about "rapid progression" in the neurodegenerative field, you have to take it with a grain of salt. But somebody who is asymptomatic and then gets to the point that they are needing quite a bit of help, or having significant functional limitations, or needing a cane, or a walker, or something within a few years, that's too fast for idiopathic Parkinson's disease.

Now, one of the tricky things is oftentimes, your history is not always accurate. So, sometimes somebody can look like typical Parkinson's disease based on the tremor they have, the absence of other red flags. You get the history and they tell you, "Oh, yeah, no, they were totally fine until we were on vacation" and then they couldn't get off the plane. And so, people can mask a lot of Parkinsonian symptoms for quite a long time, because again it is something that usually changes slowly. And so, if

there's some disconnect between what you see and what you're hearing on exam, it's good to try to probe a little bit and convince yourself as the clinician how long this has really been going on.

Matthew: Now, Paul, you would like to order a lot of neuroimaging. I know that's your thing. Did you have any questions about that?

Paul: [laughs] Stellar setup. Yeah, I was just thinking like I feel my usual dumbed down binary brain is, "Oh, it would be essential tremor or something that's Parkinson's or Parkinson adjacent." I think once I get away from essential tremor, they're probably headed towards a movement specialist direction. So, I guess, my question and maybe what Matt is asking is, is this something I should get MRI for us in anticipation of that visit? Is that helpful to me at all or should I leave that to the experts?

Albert: As far as structural imaging goes, if a person has typical idiopathic Parkinson's disease and doesn't have any other abnormal exam findings, the likelihood is that the MRI is not going to be informative. As a movement specialist, if somebody is referred to me without a brain MRI, there's a couple of things that would be red flags, again, that would lead me to order MRI. One is, is there anything atypical about this? Because some of the atypical syndromes can have particular imaging correlates that can be helpful.

If somebody has a lower body predominant form of Parkinsonism, so they don't have a lot of tremor, you look above the waist, you have them do the bradykinesia tasks, they don't look that slow and you get them up to walk and they're really slow and shuffling or they have freezing. That person I would definitely get an MRI for. You're really looking for two typical causes of lower body Parkinsonism. One is vascular disease. Somebody who's got a lot of frontal white matter disease can present with a slow shuffling gait without a lot of upper body involvement.

Then the other one is normal pressure hydrocephalus, NPH. NPH is treatable with a VP shunt. And so, again, that's a diagnosis that you wouldn't want to miss. The clinical features that would lead you to think about that as somebody who has Parkinsonism that really involves their gait and walking a lot more than it involves other symptoms. So, that's what I usually think of in terms of getting an MRI scan.

Obviously, there's no harm in getting an MRI. I don't know if your hospitals like this. Everybody comes into the emergency room for anything, they get an MRI. So, I think somebody who's got Parkinsonian symptoms, it's reasonable to think about doing an MRI, but there are some cases where it's going to be much more important than others.

Matthew: Yeah, we have these MRI machines. They like to keep them running 24/7 essentially.

Paul: [laughs] No in Kashlak, we're just doing plain films.

Albert: The other imaging study, it's good to know about for Parkinsonism are DaTscans or dopamine transporter scans.

Matthew: Yeah, that was going to be by joke. I want that.

[laughter]

Albert: [laughs] So, DaTscans are functional study. It's a SPECT scan. With these studies, the radiologist is injecting alike and that gets into the brain and binds to presynaptic dopamine transporters. For patients who have lost dopamine neurons, they're going to have decreased uptake. And so, the classic picture of Parkinson's disease is that you'll have decreased uptake, more on one side of the brain and the other corresponding to the symptoms. It's important to remember that DaTscans don't differentiate Parkinson's disease from other neurodegenerative forms of Parkinsonism. DaTscans can be good to rule out people who have an essential tremor, or vascular Parkinsonism, or drug-induced Parkinsonism. They have normal dopaminergic neurons. So, those patients will have a normal DaTscan. But patients with PD, PSP, MSA, and these other neurodegenerative conditions that we talked about, they'll have abnormal DaTscans and the scan won't be able to differentiate those.

Matthew: In a specialist's office, your office, are you getting those often? Do you find them helpful? I don't think, Paul and I are going to be ordering them. That was part of my joke to Paul that he likes to order the new fancy tests.

Albert: This is, I think, variable from physician to physician. I personally don't order them. If clinically the patient looks like somebody who has PD or another neurodegenerative form of Parkinsonism because I don't think the DaTscans are going to change what you do. I would say that the two times I order it is if there's something uncertain, a little bit of a tremor, but not clear Parkinsonism where I might get it.

The other situation where I'll get it as there are some patients who don't feel comfortable with a clinical diagnosis of Parkinson's disease. When somebody comes to see me, I spend that first visit and at the end, I say, based on these symptoms, I worry that this is early Parkinson's disease. Patients like tests and they like to have the confirmatory test. The DaTscan is not 100% either, but I think that for those patients, I may order a DaTscan because it's really important when I'm seeing a patient to have them feel like they can move forward with the diagnosis. And so, if they're continuing to question the diagnosis of DaTscan, sometimes can help that because they'll see the report from the radiologist.

Matthew: I want to bring this back to our case here. We had Mr. Robinson. This was a 68-year-old gentleman. He was having this tremor. It was asymmetric. He felt he was just slowing down. His wife was saying that she can't read his grocery list because he's writing very small. He had some of these things we talked about. We know he's had constipation for a while. Sometimes, he's lightheaded, orthostatic, having some of the non-motor and motor symptoms that we've discussed. You just mentioned a little bit of your script there. You said, "I'm worried you might have this." How do you explain to a patient at a first visit when they're starting to cope with this potential diagnosis of idiopathic Parkinson's disease?

Albert: You'd be surprised how many people when they come to the office with this particular complaint, Parkinson's is already on their mind, especially if it's rest tremor, especially if they've consulted Dr. Google. They may already be worried about Parkinson's. And so, when they hear it,

sometimes it's not that much of a surprise. I try to be careful in the way that I talk to a patient with that first diagnosis because I have to reflect with my clinical sense. In some cases where the diagnosis of idiopathic Parkinson's disease is pretty clear, I can tell people that this is something that's going to progress slowly. There's still a lot of work that we need to do in terms of trying to find medications or treatments that are going to slow this down. If it's the right person, I'll offer them opportunities to participate in research trials because this is a lot of where the research is focused.

We'll talk about lifestyle issues. The most important thing that any of us can counsel our patients with Parkinson's to do is exercise. Obviously, exercise is good because it's going to help with your mobility and help you manage your motor symptoms. But there's more and more evidence these days to suggest that exercise itself might actually have some neuroprotective effects. There's even a research trial going on now, an NIH funded trial randomizing people to moderate and vigorous levels of exercise to see whether or not that might make a difference in terms of disease progression monitored clinically and also in terms of DaTscan. So, that's the first thing I will tell patients to do is that really wants you to encourage you to get into a regular program of exercise.

My physical therapy colleagues who see patients with early Parkinson's is that we would love to see these patients very early on. They may be still quite active, but if a physical therapist with some expertise in Parkinson's can help them come up with a better exercise plan, it's something that probably is going to make more of a difference at this point than starting medication. And then I move forward from there make sure that people understand that there are treatments that can help the symptoms. What I hope when I see somebody who has typical Parkinson's, what I hope is that when they leave the office, they feel they have a place to start. They feel I'll refer them to some online resources. There're some great Parkinson's organizations, the Parkinson's Foundation, the Michael J. Fox Foundation, the American Parkinson Disease Association. These all have great material, but I want to make sure that they get to the right place and Then I hope they leave the office recognizing that they have a diagnosis that although we can't cure it yet, our goal is to do our very best to keep them at their high quality of life for as long as we can.

Matthew: Malini, do you want to move us on with the next part of the case here and I guess, start us off with whatever the next question is going to be?

Malini: Sure. Mr. Robertson's referred to movement disorder specialist. He's diagnosed with Parkinson's disease and he begins treatment with carbidopa-levodopa. So, we wanted to get your input on what your general approach to initial pharmacological treatment of Parkinson's disease is.

Albert: This is actually one of the most interesting questions as a movement disorder specialist, I have to say this is what makes trying to manage these patients interesting and fun because as a Parkinson's specialist, we have a lot of different pharmacologic options. Carbidopa-levodopa, you mentioned, Malini, it's the oldest medicine, still the best medicine for Parkinson's. Another option for early therapy are dopamine-agonist medicines like pramipexole and ropinirole. These work by binding to postsynaptic dopamine receptors, so they don't have to be converted in the same way that levodopa has to be enzymatically converted to dopamine.

Another class of medicines that can be used for initial therapy are monoamine oxidase type B inhibitors, MAO-B inhibitors. So, MAO-B inhibitors are not very potent in terms of their symptomatic effects. There're a few different ones. Selegiline is the oldest. Rasagiline, a lot of people know rasagiline as Azilect. That's probably the one that's used the most. There's also a newer one, safinamide. So, there's a few different MAO-B inhibitors. These are not that strong in terms of their ability to treat motor symptoms. Fifteen years ago, there's actually some controversy about whether or not rasagiline might have some disease modifying effects. And so, some people will still use it early for that reason.

When you're deciding between levodopa and dopamine agonist, there're a few things you want to think about. You want to think about, well, which one's going to be the most effective? That's usually levodopa. Which one is less likely to cause side effects? Side effects can be both short-term and long-term side effects. This is where you have to give a little bit more thought. It's a little bit more nuanced in your decision-making. Dopamine agonists usually have more short-term side effects. Nausea, excessive daytime sleepiness. There are case reports of people taking dopamine agonists falling asleep while driving.

Here's an interesting one I heard from a pilot patient of mine once. If you're on a dopamine agonist, you're not allowed to have a commercial pilot's license. But if you're on levodopa that is allowed. Because they're not thinking about the Parkinson's, they're thinking about the daytime sleepiness that you can get with an agonist. And then the side effect that I think has swung the pendulum back to levodopa is the fact that dopamine agonists are-- they have a two-to-three-fold higher risk of causing impulse control disorders.

Matthew: This blew my mind, Paul. I had no idea.

Paul: I feel like this had rattled around in my brain at some point, I'd forgotten it, but this was a nice reminder. Nice is maybe not the right word, but a good reminder.

Matthew: Can you give an example? How does that present, the impulse control disorders?

Albert: The four types of impulse control disorders that are most often associated with Parkinson's medications, especially agonists, compulsive gambling, hypersexuality, compulsive buying, and binge eating. And so, I'm sure your patients are like mine. These are not side effects of medication that anybody is ever going to report to their doctor unless they are told about it ahead of time.

Matthew: Yeah.

Albert: If I prescribed somebody pramipexole of ropinirole or another agonist, I will tell them, "These are side effects that you should watch out for. If there's any inkling of it be sure to let me know we should find a different alternative." One of the interesting things about this impulse control disorder is that there's now this other syndrome associated with dopamine agonists called dopamine agonist withdrawal syndrome or DAWS. The highest risk factor for somebody developing dopamine agonist withdrawal syndrome is that they have impulse control.

Matthew: Oh, gosh.

Paul: You start them and then you can't get them off the medicine. And so, that's a lot of the reason why people have swung to levodopa. It's the best medicine anyway. And so, the risks of dopamine agonist, I think, in a lot of cases will outweigh the potential benefits.

Matthew: Now, I see these medicines most commonly prescribed for restless leg syndrome. I wonder if the dosing is way different or is that a risk that just people aren't aware of? Because for restless leg, I guess, give the patient some iron supplements first [Paul laughs] before you potentially give them an impulse control disorder that if you take the medicine away, they're going to have withdrawal? That sounds terrifying.

Albert: Yeah, the doses of medications of the agonist that are used for RLS are typically much lower than those that are used for Parkinson's disease. But I would think that's a good reminder that even somebody who you prescribe one of the agonists too for RLS, you should still just give them a heads up say, these are not very common and especially at the doses that people are going to use them it's not a very common side effect, but you should watch out for them anyway.

Matthew: Wow, that is just the-- Audience, maybe you knew more than Paul and I did but that is a scary side effect. So, be careful with those when you're prescribing for your restless leg or if someone has Parkinson's and ask about those symptoms. I think probably more within our wheelhouse in primary care, what do you think we can do for some of the non-motor symptoms, autonomic symptoms that patients are having? What should we look for there?

Albert: Again, when you're thinking about autonomic dysfunction in Parkinson's, it can start early and it generally progresses throughout the course. The other thing that's important to remember is that a lot of the non-motor symptoms are actually exacerbated by dopamine replacement. So, you start somebody on carbidopa-levodopa, you can make constipation worse, you can make orthostatic hypotension worse.

Especially in the more advanced Parkinson's patient, oftentimes, you have to think about balance and you have to think about what are the symptoms that are most limiting to a patient. If they're having problems with orthostatic hypotension, the first thing I would do is review their Parkinson's medications and taper off the dopamine agonist because that generally is more of a problem than levodopa. I would say in general, as you get to more advanced Parkinson's disease rather than adding more and more medicines, one of the ways to think about it is to try to simplify more and more to just the levodopa-based regimen, that's likely to be what's most effective.

To your point, Matt, I think oftentimes patients with PD will have constipation can be quite severe. I think you can use your arsenal of bowel meds to try to help. If there's a question specifically about what's causing the GI symptoms, you might have a low threshold to refer it to a gastroenterologist, make sure that there's not something else that's causing severe constipation, or gastroparesis, or something like that. Same thing with orthostatic hypotension. I think you have to pay attention to it and monitor for it

before a person has their syncopal episode and hits their head. If somebody is on a higher dose of Parkinson's medicines and you get even a slight hint of a little bit of dizziness or lightheadedness standing, we want to make sure we check those orthostatic signs in the office and make sure that we're aware of it upfront, so that we can encourage them to drink more fluid or eat more salt assuming they don't have reasons that they shouldn't do that and you can think about medicines to help support the blood pressure like fludrocortisone or midodrine if you need it.

Matthew: Yeah. And then you're trying to boost this standing blood pressure, but then you have to worry about supine hypertension is what I was reading about. So, I usually try not to mess around with those. Is it a large percentage of your patients where you're having to start those medicines for the orthostatic hypotension?

Albert: For idiopathic Parkinson's disease, it's usually not that early. Again, significant dysautonomia for PD usually comes later. If you have a lot of early autonomic dysfunction, you might think about MSA.

Matthew: Yeah.

Albert: But you do have to pay attention to these things. Again, I think that trying to take care of somebody with Parkinson's, I think really involves a lot of teamwork between the movement disorder specialist, primary care doctor, other specialists like urologists, or gastroenterologist, or psychiatrists because there are so many different systems that can be involved in PD. If our goal is to help people live well, we have to take care of all of these.

Paul: It feels like awareness is half the fight. We're talking a little bit. It just seems so much of the non-motor stuff is well within the primary care wheelhouse into knowing to ask like, be really diligent. Your depression screening maybe even more so, because we can do depression. I guess, we'll talk a bit about what medications might be more efficacious. It seems like SSRIs are one for, or erectile dysfunction, or constipation, or low back pain, like these are all things that we see day in and day out. So, just being mindful and knowing to ask about them because I think there's a lot that we can address specifically in a primary care setting that's just outside of the stuff we feel less comfortable with.

Matthew: Paul, you're America's primary care doctor. I wanted to pull you about this. Are you starting people on levodopa-carbidopa and sending them off to neurology? I haven't had the guts to do that myself, but I just wanted to know your practice and how you think about that.

Paul: No, I always appreciate when you call it my personal practice on this broad podcast platform. But in my own practice, I do not start medications. I will defer to the experts. I'm like you, I don't have quite the courage [unintelligible [00:53:26] incompetence to try them.

Matthew: Let's say, Paul and I were braver or more confident in our practice, would sending someone to you already on carbidopa-levodopa, does that make it harder for you to make the diagnosis of idiopathic Parkinson's? Could we mess anything up by starting the medication if we have the wrong diagnosis?

Albert: I would think a little bit for our audience, think about how ready access you have to neurologists. I think that if it's going to take six months or longer and it's hard to get them in to see a neurologist, and especially a movement disorder specialist. If a person is really experiencing significant limitation, they're really changing the way they live, they're having trouble doing their day-to-day routine, I think you can start a little bit of carbidopa-levodopa. I think that one of the issues we alluded to earlier is that sometimes a trial of carbidopa-levodopa can help you diagnostically. Somebody who's got idiopathic PD should get better in terms of their motor symptoms with some levodopa. Some of the other atypical forms of Parkinsonism that we discussed tend to be more refractory or less responsive to levodopa.

You really can't do harm in the sense that if the diagnosis is in doubt by the time that they show up in the neurologist's office, one, either their symptoms are very mild or they don't have Parkinson's. If their symptoms are very mild, we can always taper off the levodopa and see how they do and they should be okay. What I would say is if you see a patient, you're suspicious for idiopathic Parkinson's disease based on some of the things we've talked about today, I don't think you should be afraid to start levodopa. The one thing I would say is start at a low dose and gradually increase.

We all hear in medical school, carbidopa-levodopa 25/100 one tablet TID. That's what we all hear. What I usually start, start at a low dose, gradually work the dose up because the one thing you don't want is you don't want your patient with Parkinson's to develop nausea from the medication and say, "You know what, I'm not going back there again." Because as a Parkinson's specialist, levodopa is our friend. If a person doesn't tolerate levodopa, the treatment is going to be a lot harder.

Matthew: So, one tablet three times a day, is that's considered a low dose or do you start it at once a day and then gradually go up to the three times a day?

Albert: Yeah, every movement disorder specialist you ask is going to have a slightly different way of doing this. What I normally do is I might give them half a tablet twice a day first thing in the morning, another one shortly before lunch and do that for a week. If they're doing okay with that then maybe go up to a half a tablet three times a day adding a dose before supper and then the third week, I might go up to one tablet three times a day. The reason I say before meals is because levodopa gets absorbed through the gut, through the same transporters as amino acids. So, sometimes, if you take levodopa with a lot of food, especially protein-containing foods, the medicine doesn't get absorbed quite as well.

Malini: We're now fast forwarding six years. So, still with Mr. Robinson. Fast forward six years later, he comes back to your office with his wife. He'd initially, when you'd first started him on levodopa-carbidopa, experienced a really profound improvement in his motor symptoms. More recently has felt the effects of levodopa wear off after a couple of hours, which has required adjustment of the levodopa dosing. He's also been experiencing increasing effects on his gait, worsening slow shuffling stride and increasing unsteadiness, particularly in the off periods of the levodopa has worn off.

His wife also tells you that she's noticed some changes in his cognition over the past year or so. She tells you that he'd always planned their vacations in the past, but lately he hasn't been able to figure out how to book their flights or plan their trips to the airport and she's had to do this for him. She also

mentions too that he seems more withdrawn and subdued lately. The most concerning thing to her that she tells you has been that over the past month, he's mentioned to her multiple times that he thinks they're good friends and neighbors, the hawthorns are spying on them and trying to steal money from them. He's told her he had seen them wandering around their house at night. So, this is clearly a case of more advanced Parkinson's six years down the line with Mr. Robinson.

Starting with these motor symptoms that have progressed now with this wearing off with the levodopa, how do you approach motor symptoms in more advanced Parkinson's disease where you're seeing these wearing off phenomena or dyskinesias?

Albert: Yeah, so this is one of the aspects of Parkinson's that I think, if you see this as a primary care doctor, it's time to refer them to a neurologist or movement disorder specialist just because the treatment options are different. Levodopa is a great medication, but the half-life of levodopa is really short. If you measure levodopa in the bloodstream, half-life is couple of hours. And so, in earlier stages of Parkinson's, your body can accommodate that because the levodopa gets converted to dopamine and you don't get the wearing off even if the blood levels drop off quickly. But as Parkinson's advances, people will have a shorter window of time that the medication's working. They'll experience on/off fluctuations. They'll know when the medicine is working and when the medicines wearing off, or even when they're taking it on schedule, they may find that the wearing off is occurring at the end of the dose. That's one of the things that Malini was describing. People take it on time and the medicines not lasting long enough.

Then, when they take enough medicine to help them achieve an odd state, they may have too much movement, what we call levodopa-induced dyskinesias. These are kind of writhing, swaying, bobbing and sometimes, the mouth and face. And so, trying to find the balance between wearing off which is a sign of not enough medication and levodopa-induced dyskinesias, which means that the medicine at some points during the day may be too high. This is a real challenge.

There're a few different ways to do it. The way to think about it is about the pharmacokinetics. What can we do to help stretch out the duration of action of the medicine without so much highs and lows. This is where some of the enzyme inhibitors, a COMT inhibitor like entacapone. We talked about MAO-B inhibitors before. You can sometimes add those to levodopa to help them stretch it out a little bit. There're also some extended-release forms, not the CR form. So, sometimes, people hear about carbidopa-levodopa ER, Sinemet CR. This medicine actually only lasts a little bit longer than regular carbidopa-levodopa, but there are newer forms that have a more extended half-life. These can all be helpful in terms of addressing the wearing off.

Then if a person is really dyskinetic but they can't tolerate a lower dose of levodopa, the one medicine that's available to treat levodopa-induced dyskinesias is a medicine called amantadine. Amantadine, it's an older generation medicine, used to be used for the flu. But in Parkinson's, it can be really helpful to try to help levodopa-induced dyskinesias.

Then thinking about fluctuations, the last treatment option that this particular scenario of arrays is a person a good candidate for deep brain stimulation surgery, DBS. So, patients who have a good

response to levodopa, but are experiencing motor fluctuations or finding that they're not able to optimize their motor response with oral medicines alone might be a good candidate for DBS. Interesting thing, I had patients who have other forms of Parkinsonism, which don't respond to medicine and they say, "Well, can I be referred for surgery?" Unfortunately, the answer is no. Patients with the other forms of neurodegenerative Parkinsonism that don't respond to levodopa also aren't going to respond to DBS. So, one of the requirements for a DBS referral is to show that they have a good levodopa response.

Matthew: What about this enteral gel? I had not heard of this and I was shocked that sounds like you're putting in a jejunal tube or some sort of a gastrostomy tube to deliver this. It seemed wild.

Albert: It's not something we use a lot, but it's nice to have options. I think the problem with levodopa is the variability and ups and downs in terms of the blood levels, the best way that you can guarantee a steady level is to deliver the medication in a steady way. So, there is an intestinal gel form that you mentioned, Matt, that's given through a GJ tube. It's not for everybody, but for patients who have significant fluctuations and aren't a candidate for DBS surgery, that is an option.

There's actually a newer form that is currently being reviewed by the FDA, which is a subcutaneous form. And so, if you think about your patients who have a subcutaneous, like an insulin pump. There's a levodopa pump that's in development. It's going to deliver it under the skin. I think that's going to change the way we take care of some of these patients, because one, it's obviously less invasive than a GJ tube. The fact that you bypass the gut is actually also a good thing. You might get more reliable levels than people who are having variable degrees of absorption through the gut, which the GJ tube still requires.

Matthew: Yeah. We mentioned earlier, we're still talking about just mitigating symptoms like we still don't have a disease-modifying therapy available other than exercise, maybe it sounds like.

Albert: Yeah, that's right. There's a lot of research going on in that area. If we did this podcast again in 5 years, 10 years, hopefully, we have something to talk about in terms of the disease modification area, but we're not quite there yet.

Matthew: Paul just looked terrified that he might still be doing this podcast in 5 or 10 years.

[laughter]

Matthew: Malini, what else should we ask about here? I know we have a little bit of time left and a little bit more to get through.

Malini: Yeah, I think one other major feature of this later stage in Mr. Robinson's presentation has been some of the cognitive effects, and some of the psychiatric effects, and definitely would, in terms of this developing executive dysfunction what seems with the [unintelligible [01:04:33] flights. I would definitely love your thoughts on how you think about cognitive impairment and dementia in Parkinson's disease and what features you typically look for there?

Albert: Yeah, so the cognitive and the behavioral aspects of more advanced Parkinson's disease are often the ones that are hardest to manage. If there is one risk factor for somebody with advanced Parkinson's ending up in a nursing facility, it's actually PD psychosis. It's not that surprising when you think about it. When people start to develop some paranoia or mistrust of their family, their care partner, they become really difficult to manage.

Malini, you brought up two interesting points of this case. One is the cognitive component and then the other one is the more neuropsychiatric component or the PD psychosis. When we think about cognitive impairment in Parkinson's, there are some features that differentiate it from Alzheimer's. Somebody with Alzheimer's may have significant issues primarily with short-term memory with encoding and recall. The deficits in PD dementia tend to be more executive function or visual spatial, maybe less involvement of recall at the beginning. And so, this is good to know because sometimes people can have Parkinson's and have Alzheimer's and the flavor of their cognitive deficits may be a little bit different.

The one FDA-approved medication to treat cognitive issues associated with Parkinson's disease is rivastigmine. This is based on a randomized trial looking at people with Parkinsonism with cognitive issues and showing a benefit for rivastigmine. It doesn't mean that other cholinesterase inhibitors like donepezil, which a lot of us use aren't effective, but they just haven't been studied specifically in this patient population, so they're not FDA approved for that indication.

I think that if I have a patient who's starting to exhibit cognitive issues that are impairing their quality of life, I usually start them on rivastigmine or if needed another cholinesterase inhibitor. But the response is going to be more modest in general than it is for using dopamine medications to treat the motor symptoms. So, that's unfortunately all of our experience with some of these neurodegenerative dementias, the donepezils and the rivastigmines of the world, they're not that great medications but they're what we have and I think that they're worth trying.

Matthew: Yeah, it seems like the effect size with the Alzheimer's trials, the effect size wasn't super large in the rivastigmine trial as well from what I was--

Albert: Yeah, it's not very strong, but I think that there was a benefit, statistically significant and looking at clinical global impression of change, there was a shift in the curve where those on rivastigmine had better cognitive function than those not. So, I think again, it's worth trying, but with a relatively low threshold to stop the medicine if the patient's not tolerating it.

Matthew: Yeah.

Albert: Oh, and you mentioned, so the psychosis. One of the biggest challenges in terms of managing psychosis in Parkinson's is that the typical medicines that we usually use as antipsychotics we don't want to use. The dopamine antagonists that we would use for somebody who has psychosis in another context are going to make their Parkinsonism worse. And so, one thing that's good for all of us to think about is whether we're seeing patients in the clinic or seeing patients in an inpatient setting really try to avoid medicines like olanzapine and risperidone for people with Parkinsonism, even if they're agitated

in the hospital if you can. Because when you treat patients with those medicines, you'll tend to make their motor symptoms worse to the point that they may have trouble walking to point that they may have trouble getting out of the hospital if that's the setting that you're doing it.

We really have three choices really. Quetiapine, the newest medicine which is called pimavanserin, which is branded as Nuplazid and the other medicine is clozapine. So, quetiapine is the easiest one to use and so, one we often use first, but the randomized trials don't actually show benefit of quetiapine over placebo, but in real life, they do work. And so, I think that if somebody's developing some mild hallucinations, some mild agitation, quetiapine is the easiest medicine to try first.

Pimavanserin is FDA approved for the treatment of PD psychosis. It's easy to dose because it's only one dose 34 mg, everybody gets the same dose. One caveat to pimavanserin is it takes a few weeks to reach a steady state and oftentimes a whole month before you really see a clinical benefit when you do see a clinical benefit. So, using pimavanserin in an acute setting isn't something that really makes sense, you're not going to see an immediate benefit.

Then one medicine that we probably underuse is clozapine. Clozapine is probably the best medicine to treat PD psychosis, but because of that need to check the CBC, specifically the white count to make sure that they're not developing agranular cytosis that becomes a nuisance in terms of treating. And so, we don't use clozapine as much as we should even though it's the best medicine for PD psychosis.

Matthew: Yeah, I think you have to be on a special registry to even be able to prescribe it as well as a clinician. So, it seems there's just barriers to that. Well, maybe the last thing we'll ask you to comment on-- I know depression, anxiety, apathy are things that I see I guess, apathy, maybe that doesn't belong in the same bucket, but can you just comment on those things? I promise, we'll let you go soon. But this has been fantastic and we just want to soak up as much knowledge as we can.

Albert: Sure. No, it's actually I think that anxiety, depression, mood, it's interesting, Matt, you downplay the apathy because the apathy oftentimes is the most common symptom of depression with Parkinson's disease. People with depression in association of Parkinson's may present primarily with lack of motivation, anhedonia, lack of pleasure. That may be their primary symptom rather than typically what we think of is depression. But the medicines that we use to treat anxiety, and depression, and apathy in the context to Parkinson's is not different than what is used for people without Parkinson's. When you think about medicines like SSRIs or SNRIs, bupropion, these are the same types of medicines. Sometimes tricyclics, the same types of medicines that we would use for patients with Parkinson's. I think that something like bupropion which has some dopaminergic activity may be a little bit more-- may help with apathy or help with somebody who has significant fatigue or lack of motivation, where an SSRI may be more helpful for somebody who has more typical anxious depression. And we see both of those types of symptoms in people with PD.

Paul: Can you see worsening of tremor with bupropion? That'd be the concern I would have with that, because I feel of all the antidepressants, that's the one that I actually see medication-induced tremor with probably the most.

Albert: Yeah, I think both bupropion, even the SSRIs and SNRIs, I think that any of the medications that you're using for psychiatric symptoms, you can see worsening tremor. But the thing is that they're all reversible. And so, I think that you can try and address the mood issue in the way that you feel is appropriate. Like everything else, you weigh the pros and the cons. Sometimes, if you can actually help the anxiety, reducing the anxiety will also reduce the tremor. So, you can cut both ways. You just have to see how your patient responds.

I would say that the take home points are one, when you're seeing a patient with a tremor, be sure to take a careful history, careful exam, look for features that raise suspicion for Parkinsonism in general, in Parkinson's disease in specific. As primary care doctors, pay attention to those non-motor symptoms because your friendly neighborhood neurologists may be prescribing the levodopa, but depending on that person's practice patterns, they may not necessarily address the constipation, or the orthostatic hypotension, or the anxiety, or the depression.

US primary care doctors often know these patients best. And so, especially if you have somebody who has a Parkinson's that's really progressed over time, be proactive and make sure that patients doing okay, ask for subtle signs of cognitive change or subtle signs of PD psychosis. You and your team can be there to support the patient and their care partner. I think if we all do that then that's-- Until that day when we've got a cure for Parkinson's, I think this is what our focus should be.

Paul: This has been another episode of the Curbsiders bringing you a little knowledge food for your brain whole.

Malini: Yummy.

Paul: Strong work. Get your show notes at *thecurbsiders.com* and while you're there, sign up for our mailing list to get our weekly show notes in your inbox, plus twice each month, you'll get our Curbsiders Digest recapping the latest practice changing articles, guidelines, and news in Internal Medicine.

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I wanted to give a special thanks to our writer and producer for this episode, Malini Gandhi and to our whole team. The Curbsiders is produced and edited by the team at Pod Paste, Elizabeth Proto runs our social media, and Stuart Brigham composed our theme music. And with all that, until next time, I've been Dr. Matthew Frank Watto.

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