



Medical Treatment for Motor Symptoms in Parkinson's with Dr. Aaron Haug
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Davis Phinney Foundation

Melani Dizon (Director of Education, Davis Phinney Foundation):

Hello and welcome everybody. My name is Melanie Dizon and I'm the Director of Education at the Davis Phinney Foundation. And today we are here to talk about medical treatment of motor symptoms in Parkinson's with Dr. Aaron Haug. Thanks everyone for joining us. Thanks all of you for showing up again. If you did show up last week, we really apologize for the technology glitch; we tried everything to get it going, but we thought that rescheduling it was the best option. So thank you so much for hanging in with us.

We have a really, really great session today. So much information. Just at the outset, I want to make sure that I let all of you know that we have received all of your questions and there are many, many, many questions.

And since we have an hour today, I don't feel confident that we're going to get to all of the questions. So I've asked Dr. Haug if he's willing to do a second session with me, where I ask a lot of the questions that you sent in. So we're going to do that. We're going to record it next week. And so we'll send you this recording of today's presentation, and then we'll also send you the session where Dr. Haug and I go back and forth with some questions. So if you are worried at the end that your question hasn't been answered, don't worry. We're going to have another chance to do so.

Dr. Haug is going to go through his presentation and then if we do have quiet time at the end, we'll answer some of the questions. I do think a lot of the questions will be answered, though, throughout his presentation.

So we're going to get started. I'm going to do an intro, and then I'm going to let Dr. Haug take it away. So Dr. Haug was born and raised in Kansas. He attended undergraduate at Creighton University and then earned his medical degree at the University of Kansas. He completed a neurology residency as well as a fellowship in movement disorders at the University of Colorado, including a year as chief resident. His medical interests include Parkinson's tremor and other movement disorders, as well as deep brain stimulation for the treatment of neurological conditions. Outside the office he likes to spend time with his wife and kids, run, ski, and follow Colorado Rockies baseball. Thank you so much for being here and I'm going to let you take it away.

Dr. Aaron Haug (Neurologist and Movement Disorders Specialist, Blue Sky Neurology):

All right. Great. Thank you so much, Mel. Well, I'm excited to be here and talking about the medical treatment of motor symptoms and Parkinson's. I think that this is an area that can seem somewhat mysterious and hopefully I'll be able to demystify it as we go along. So I think of there as being a large number of tools in the toolbox for the treatment of the motor and non-motor symptoms of Parkinson's. And as we go through the course of this talk, I'll hopefully be able to give you a better sense of what those tools are.

So there are many symptoms that can occur in Parkinson's, and today we'll be focusing on the main physical or motor symptoms of Parkinson's, which are tremor, stiffness, and slowness. The goals of this webinar are to discuss treatment strategies and then to discuss the numerous specific medications that are used in the treatment of motor symptoms.

And Parkinson's — a bit of a caveat as we begin here — not everyone will have all symptoms. And so we'll be talking about kind of the gamut of symptoms from new diagnosis to after several years of having symptoms to later motor symptoms, and the course is different for everyone. And so I like this quote from the late great Yogi Berra: "It is tough to make predictions, especially about the future." And so I don't want this to feel like a checklist of things that are necessarily coming down the pike, but more just to be aware of what's out there and that there are tools for a variety of circumstances.

And I will do my best to answer questions that could potentially arise for you. But if you do have specific questions about exactly what to do in your case, I won't be able to speak to that. Be sure to take some of these questions back to your own medical providers.

So medications for motor symptoms. On this slide, I'm going to kind of lay out everything that we're going to be talking about over the course of the hour here. And so it will gradually fill up this entire slide.

So the first category of medications that we'll talk about are those related to levodopa, including Sinemet. The second category will be the dopamine agonists. The two most widely used of which are Pramipexole and Ropinirole, but several others mentioned there that we'll discuss. MAO-B inhibitors, monoamine oxidase type B inhibitors, several medications in that category. COMT inhibitors, another enzyme inhibitor that can be useful in the treatment of motor symptoms; several options spelled out there. Amantadine, both the long time, generic formulation and two more recent brand name formulations. A new category of medications within the last year, A2 antagonists, of which there's just one member in that medication category. And the final category will be anti-cholinergic medications.

So I lay these all out there to give you a broad overview of how many options there are. And at one person's situation, potentially, maybe any of these medications might be in play, but

depending on a number of circumstances, including symptoms, severity, age, comorbidities, and possibility of side effects, some of these may be significantly preferred over others.

So as we go through the talk today, I'll be using a sort of a general case that outlined some of the broad ways that symptoms can progress over time. And so we'll use the case of a specific individual, a theoretical individual, to see how things might transpire over time.

Okay. So Mr. Jones is a 60-year-old man, age 60, the most is the average age of diagnosis for Parkinson's. And he's had about six months of left-sided hand tremor, particularly when the hand is at rest. He has also noticed a harder time with some manual dexterity, like fastening buttons, and others have commented at times that his left arm doesn't swing, kind of like he's carrying an invisible suitcase with his left arm. So he's referred by his primary care doctor to go see a neurologist. And as is often the case based on the clinical presentation, the symptoms, and the physical examination, he is able to be diagnosed with Parkinson's disease.

So in such a visit as that where there's an initial diagnosis, there are often many questions that arise. And one of those is often, *What can we do about treatment? What can we do about this? And specifically, Should I start a medication?* And nested under that question is a whole number of other implied questions. *Well, what exactly does medication help? How much does it help? What side effects might occur? How many times a day do I have to take this? Maybe I've never really taken medication before. And what is the cost?* This is always a consideration when talking about prescription medication.

So the way that I would answer those questions is going to depend more on the specifics of the case. So in our case here, Mr. Jones is working full time is an engineer. And his tremor is embarrassing at times when he's giving presentations; his left arm is sore at times because of the amount of shakiness that he has. And he's actually found that he is not exercising as much as he used to because everything feels more difficult — kind of like moving through molasses. So we circle back to the question, *Should I start a medication?* And we'll talk about this based on his symptoms, I would recommend that he do start a medication.

But shouldn't I wait until my symptoms are worse? I heard that medications only work for five years, and can't I just increase my exercise, or what can I do besides medications? I won't talk a lot in this particular talk about complementary and alternative treatments in Parkinson's, but I will say that exercise is one of the best medicines and one that you don't exactly need me for by all means a person with Parkinson's should exercise as much as they're able. We know that exercise really, unlike prescription medications, has a wealth of scientific evidence that it can actually slow the progression of Parkinson's disease.

But again, *Shouldn't I wait until my symptoms are worse?* Now this has been studied. And the answer is, usually not. What the research shows is that postponing treatment decreases quality of life *now* without really improving the effectiveness of medications in the future.

What about this? I've kind of seen online. Maybe medication only works for five years. I would say it's true that medications work best in the early years of living with Parkinson's in a couple of specific ways. There tend to be fewer ups and downs, fewer fluctuations in the early years. And there's also less likelihood of certain side effects, especially the side effects that are dyskinesia, the wiggly, fidgety, and voluntary movements that are different than the rhythmic regular movement of tremor. However, this has as much to do with how many years a person has had Parkinson's as it does with how many years they've been on medication. Occasionally some people have kind of strived to save medication for a rainy day until they feel like they really need it. And then sometimes some of these complications, the fluctuations and the dyskinesia, sometimes begin within a much shorter period of time after starting the medication, because it has as much to do with how long you've had the Parkinson's as it does with how long you've been on medications.

Okay, well, you've talked me into it, Doc. I'm willing to try medication since the goal of medication is really to improve my quality of life. So which medicine?

Well, there are multiple reasonable places to start and preferred strategies really can vary among expert prescribers as well as among people with Parkinson's. So I'll lay out what some of their considerations are here. So the first category of medications, carbidopa/levodopa, this is really the gold standard treatment for Parkinson's. It's been around for approximately 50 years, and it remains one of the most effective medications that we have. So it's made of two ingredients, carbidopa and levodopa. Levodopa, sometimes called L-DOPA for short, is converted to dopamine in the brain. Dopamine itself is too big of a molecule to cross into the brain. So this precursor, L-DOPA, is the right size where it can cross into the brain and then be converted into dopamine.

As we talk about all seven of these categories of medication, really, increasing dopamine indirectly or directly is the goal of all of these medications. And L-DOPA is the most direct. It is converted into more dopamine in the brain. Carbidopa, by the way, is a transporter. If the levodopa is given by itself, you end up getting a lot of dopamine in the stomach, in the bloodstream, which causes some of the most common side effects: nausea and lower blood pressure that can cause lightheadedness. So by combining it with carbidopa, more of the L-dopa gets into the brain rather than in the peripheral parts of the body where we don't want it.

So, as I mentioned, we have L-dopa, the most effective medicine at improving tremor, slowness, and stiffness, the cardinal motor symptoms of Parkinson's. Possible side effects: nausea, lightheadedness, as I mentioned, those are the two most common, but I will say that those are really two of the most common side effects with all of the medications that we'll be discussing, because that's what dopamine can do when it's in your stomach or in your bloodstream. It can make you feel nauseous or lightheaded. And so nausea and lightheadedness are on the list of possible side effects, really for all of the medications as we go along.

So carbidopa/levodopa is available in several formulations. Generic carbidopa/levodopa is by far the most common. This used to be available only as a branded medication called Sinemet years and years ago, actually brand name Sinemet is not used often at all. But the words said about and the name Sinemet is still used quite often when referring to carbidopa/levodopa, 'cause it's kind of a mouthful to say carbidopa/levodopa over and over again. So another formulation is carbidopa/levodopa controlled release tablets, sometimes called Sinemet CR, or there's a dissolving tablet which used to be called Parcopa. This can be helpful if a person has trouble swallowing. And then there's also carbidopa/levodopa extended release capsules. These are kind of like the controlled release tablets, but the tablets are really absorbed somewhat erratically. Some people find that switching from the regular release or immediate release carbidopa/levodopa to the controlled release, the effect of it is less predictable. And so a lot of times we will not use Sinemet CR as part of a person's throughout-the-day medication regimen due to this erratic absorption that occurs in some people. Rytary* is a capsule filled with little pellets that are both immediate release and controlled release carbidopa/levodopa, and it has some of that more consistent, desirable effect that we would have hoped for with Sinemet CR.

And then the last formulation of levodopa is levodopa inhalation. Here, it's packaged without the carbidopa. And this is kind of like Albuterol for asthma, except it's levodopa that can be inhaled.

As we go through the talk, you'll see these little asterisks next to some medications, which indicate they're available only as the brand name medication, meaning that in some cases cost can sometimes be an issue. We'll circle back to talking more about this.

So this is carbidopa/levodopa. It's often dosed several times per day; three times a day is probably most common. And we'll circle back to some more information about that when we talk about what we do with Mr. Jones.

So the second category of medications to discuss are the dopamine agonists, sometimes abbreviated "DA". Dopamine agonist. So likely, dopamine agonists provide benefit for tremor, stiffness, and slowness, the core motor symptoms, and dopamine agonists are generally considered to be the second most effective category of medications behind levodopa.

There are certain advantages and disadvantages when comparing dopamine agonists to other medications. Some of the advantages include that over the course of several years, the agonists are less likely than levodopa to cause motor complications, less likely to lead to the peaks and valleys of fluctuations, and less likely to lead to the dyskinesias. An additional benefit is that sometimes dopamine agonists can have a benefit for treatment of depression. Depression is a common non-motor symptom among people with Parkinson's, but the dopamine agonists are sometimes even used outside of the Parkinson's populations as an off-label treatment for depression. And what I see is that sometimes dopamine agonists can be quite helpful for treating depression if a person with Parkinson's is dealing with that symptom.

What are some of the disadvantages of dopamine agonists? While there can occasionally be other unpredictable side effects, and this includes sudden sleepiness or sleep attacks — now, sudden sleepiness is listed in the prescribing information for many of the Parkinson's medications, but it's more likely among the medications that are dopamine agonists than it is with levodopa or the other medications we'll discuss. And then this is potentially a big one to be aware of — impulse control disorders. This is the feeling of a loss of control over your ability to control how much of something that normally feels good: eating, sex, shopping, spending, gambling, but really losing control over those impulses and doing those things to the detriment of other areas of your life. And so it's not extremely common among dopamine agonists or any of the medications, but it's more likely with the dopamine agonist than it is with other categories of treatment. And so if you're taking a dopamine agonist medication, that's something to be aware of — that if you're experiencing impulse control disorder symptoms, you should immediately discuss those with your prescriber.

So the specifics of dopamine agonists: due to a lower risk of dyskinesias over several years, they are often used as part of a levodopa-sparing strategy. And there are multiple options in this category. Pramipexole or Mirapex is available both as an immediate release or regular release, usually three times a day, or as an extended release, which is needed to be dosed only once or maybe twice a day. Likewise, Ropinirole, formerly known as Requip, is also available as immediate release or as extended release. And then there are a few formulations of dopamine agonists that are available only as branded medications. This includes the Neupro patch* and then two medications that we'll talk about in a little bit for rescue treatment for so-called OFF periods. This is Apokyn injections* and a brand-new treatment just approved within the last few months — Kynmobi*, which is a sublingual strip, kind of like a Listerine strip, that has apomorphine dopamine agonist. And these can be used as rescue treatments for OFF periods.

The third category of medications among the three that might be most commonly considered as initial treatment are the monoamine oxidase type-B inhibitors. So MAO is an enzyme that's involved in normal dopamine recycling in the brain. Inhibiting the MAO enzyme leads to an increase in dopamine, and these medications slow down the breakdown. And so you end up with more dopamine. These medications on their own typically have a fairly mild, fairly modest benefit, but they tend to be well tolerated. So these medications are often used alone in early Parkinson's, or they're often used in combination with other medications for later stages (and I'll talk about that shortly). Due to fewer side effects, these medications can be used in people who are older. I will often prescribe MAO-B inhibitors to people on into their eighties due to the generally good tolerability.

Now, if you look at the prescribing information — you unfold that tiny thin piece of paper that comes with all the medications — the list of possible side effects for monoamine oxidase inhibitors will be pretty similar to the dopamine agonists and to the carbidopa/levodopa, but the frequency and severity tends to be lower with the MAO-B inhibitors.

I don't have it on the slide here, but there is a theoretical concern for these MAO-B inhibitors interacting with certain other medications or foods. Interacting with antidepressants like Prozac (fluoxetine), or interacting with tyramine-rich foods like aged meat or aged cheese or red wine in clinical practice. The likelihood of this interaction with these medications is very unlikely. There were older medications that were not MAO-B inhibitors but inhibited both the A type and B type of MAO, and those medications, like an old antidepressant called Reserpine, you really did have to watch for combination with something like Prozac or those certain types of food and drink because it could really raise your blood pressure. But with MAO-B inhibitors, this interaction is theoretically possible but in practice quite unlikely. So if someone is taking one of these medications, I will say that they can eat a normal amount of meat, cheese, red wine, and that they can still take antidepressant medications.

So in the category of MAO-B inhibitors, there are multiple options. Selegiline (or Eldepryl) was the first of these medications. The second was Rasagiline, which was Azilect, and has been available as a generic for about five years now. And then the newest addition to this category is Safinamide, or Xadago*, which is still available just as the brand name medication. So several categories of options that we've laid out, where do we go from here?

We discussed the options of levodopa, dopamine agonists, and MAO-B inhibitors. And in his case, based on the fact that his symptoms include of prominent tremor and that he's having some interference with his (and not just his day-to-day hobbies and enjoyable activities, but also) his ability to work, I recommend in his case that we start with the most highly effective and often well tolerated medication — levodopa — and a typical starting strategy with this medication is to use the tablets that are 25/100 milligrams, where the levodopa is the hundred-milligram amount, three times a day, and usually cut cutting the tablets in half for the first week, taking it three times a day. And then after a week going up to a full tablet three times a day. Sometimes we'll titrate it even more slowly if needed, if a person is having nausea or other side effects.

So in his case, we start the medication, and he does have some mild nausea, especially when he just first starts taking it. And he's taking it on an empty stomach. I'll speak to that for a second. This medication does tend to work best on an empty stomach because some people are very sensitive to an interaction between the levodopa and dietary protein. So if you have bacon and eggs for breakfast or chicken for dinner, if you take the medication right at the same time, you may not absorb the full amount of the levodopa. You may not absorb it well at all. And so you can still eat a normal amount of protein, I typically say, but if you're going to have a protein-heavy meal, then the medication should ideally be at least half an hour before, or at least an hour afterwards. What about non-protein food? Well, those are fair game. So crackers, fruit juice, that can sometimes help to settle the stomach, and it can be taken right at the same time as the medication if needed. So he takes this medication, especially in the morning with crackers, and he no longer has that nausea. And within a week, you notice significant improvement in his tremor and his coordination; his left hand is no longer shaking when he's giving presentations. And it's easier to do buttons, easier to type, all of those sorts of things.

Melani Dizon:

Can I just chime in real quick on this? So we heard a really interesting story that I wanted to make sure to share. And since you were talking about this in terms of what to take with your medicine — we were talking to a physician who's had Parkinson's for a really long time. And she's a doctor she's read everything there is to know she's heard everything taking all the different medication. And she was recently watching a video that we had posted and the doctor had recommended to take her carbidopa/levodopa with a full glass of water. And she said that for whatever reason, she'd never heard of it, heard that sort of direction before. And she said it changed everything. She said she takes a full glass of water every time she drinks, or every time she takes her medicine. And she's been telling everybody she knows about it. And everybody's saying it's a big, big deal. So I just pass that along because it's so fascinating that she is somebody, you know, who's a doctor and has a lot of that education, has had this for a very long time, and she noticed a really big difference. So I don't know how that would impact sort of if you have nausea, but I think it's a good tip.

Dr. Aaron Haug:

Yeah. Thanks, Mel. I think that's a great tip. That's actually not one that I've heard before either, but I will add that to the toolbox. It's also helpful to drink water for a number of the non-motor symptoms like constipation and lightheadedness that can occur just as other disease symptoms. So that's a great tip.

Okay. So following up with Mr. Jones. Several years later, Mr. Jones notices that his medications are wearing off in between doses. His 7:00 AM dose used to last until noon, but now it gets to be 11:00 AM and he's starting to notice some reemergence of his tremor. And so this is what can sometimes happen in a typical day; as the years go along with Parkinson's, you take your first dose of medication in the morning. Maybe you're starting out feeling stiff and slow since you haven't had anything since the night before, and then your symptoms feel better. They are alleviated. We call that ON time.

And then the medication peaks in your system, and then it starts to dip. And then the symptoms may begin to return. And then a person may take another dose of medication and have this kind of roller coaster that they feel throughout the day. And we call these wearing-off periods or OFF time. OFF periods are an area of the renewed interest recently because there are some new medications specifically approved for the treatment of OFF time. And so you may have seen ads pertaining to OFF time, and I've had a number of patients come in and say, "I don't really feel kicking in and wearing off. I kind of feel the same all day with my medications." And I say, "Well, that's probably a good thing. We may be that these happen in the future. But if you're not feeling them, that doesn't mean that your medications not working. That may be that you're at an early enough stage that the medications continue to control your symptoms. And you're not as reliant on every dose of medication to control your symptoms.

So over the course of years, a fluctuating response to medication can occur as the underlying disease progresses. And so it's common to take medications from several categories, either the categories we've already discussed, or from ones that we're about to discuss, to try to smooth out some of these up and down fluctuations.

So some of the strategies to treat fluctuations, to try to make it so that fluctuations don't occur. A person is starting to experience fluctuations. How can we modify their everyday treatment regimen so that it's smooth again, so that we don't have these peaks and valleys and symptoms? So if a person started on carbidopa/levodopa, then adding a dopamine agonist would potentially be an option, or vice versa, changing a dopamine agonist from a short-acting one to a long-acting one, or to the Neupro patch* would be an option. These are all strategies to try to smooth out some of the ups and downs. Or adding a booster medication. What would that be? Let's talk about that.

So, boosters. We already mentioned one of the two categories of medications that are quite helpful as boosters, which are the MAO-B inhibitors. So as already mentioned, monoamine oxidase is an enzyme involved in normal dopamine recycling in the brain. And so by slowing down the breakdown with an MAO-B inhibitor, then we can have kind of a booster effect where each dose of carbidopa/levodopa, or potentially also a dopamine agonist, work stronger and last longer.

Another category of booster medications are the COMT inhibitors. Catechol-O-methyl transferase is another enzyme, this one involved just in the breakdown of levodopa. So not dopamine itself, but the levodopa. And as a result, COMT inhibitors are used only in combination with carbidopa/levodopa. A person taking a COMT inhibitor by itself, it wouldn't do anything, because we don't have any naturally occurring levodopa our bodies.

So there are multiple COMT inhibitor options. The most widely used by far is Entacapone (old branded name was Comtan), which is available as a separate standalone pill, or is available as a medication with a very long name — carbidopa/levodopa/entacapone — all three ingredients wrapped up in one pill, which was cleverly called Stalevo when it was a branded medication. Entacapone helps the levodopa stay around longer. And so carbidopa/levodopa, and entacapone (sometimes CLE or Stalevo) has all three ingredients available in one pill. And also unlike carbidopa/levodopa, has several different strengths, ranging from the standard hundred-milligram strength of levodopa to a lower amount or several higher amounts, which can be helpful. A couple of side effects of entacapone of which to be aware — four or five percent of people can have diarrhea as a side effect, which is notable because people with Parkinson's tend to have such a high incidence of constipation. And then the pills are kind of orange and they can turn things orange. There's a little bit of iron as an inactive ingredient and so countertops or your fingertips, and also bodily fluids, urine tends to turn kind of an orange color. If you're taking this medication, it's not a problem. It's just something to be aware of.

Tolcapone is another COMT inhibitor. It is quite effective, often dosed just three times a day. But it's used fairly infrequently due to rare but serious possible side effects on the liver that require periodic blood monitoring for liver enzymes.

And then most recently there's a new entrant into this category, which is Ongentsys, or Opicapone*. And one of the advantages of this medication is that it needs to be dosed only once a day. That is somewhat of an advantage because it can reduce the amount of pill burden as time goes along. But since this is only advantageous in combination with carbidopa/levodopa, as I mentioned, if you're already taking carbidopa/levodopa three times a day, that may or may not be that much of an additional issue to take entacapone three times a day.

So another new entrant into the booster category are the Adenosine-A(2A) Receptor Antagonists. So this is the first new category of Parkinson's treatment in over 20 years. This type of medication blocks a different chemical pathway in the brain called adenosine. And we think that how that works is it allows an increased amount of dopamine signaling to occur in the brain. So interestingly, we know that caffeine blocks adenosine, and some studies showed that people that drink coffee or other forms of caffeine have a lower risk of Parkinson's. And so this is years ago where the idea came from to try to find a medication that works on this adenosine, a chemical pathway. So Istradefylline (or Nourianz*) is the only medication that's currently available in this category in the United States. And it's currently approved only as an add-on, as a booster to carbidopa/levodopa, for the treatment of fluctuations and OFF periods. Because this is available only as a brand name medication, it's more expensive than some of the other available options. And due to that issue alone would maybe not be the first option that I would go to, but it's another tool in the toolbox.

So rescue medications. Occasionally, despite efforts of all these different strategies that we just discussed on the last couple of slides to reduce fluctuations, sometimes OFF periods may still occur. And if they do, it can be helpful to have a rescue treatment, kind of like someone with asthma might take ADVAIR twice a day, every day, to try to control their asthma, but they also have an Albuterol inhaler that they can take if they have an asthma flare-up. So there are several medications that can be helpful in the treatment of OFF periods. Perhaps the simplest would be to take a little extra carbidopa/levodopa. This could be a partial tablet or a whole tablet, depending on your symptoms, depending on your discussion with your prescriber. And a couple of tips to improve the speed of onset: potentially drinking it with a full glass of water, as Mel just mentioned. Maybe we could have three tips to improve speed of onset. Also sometimes crushing or chewing the tablet. This is permissible and can help it to be absorbed more quickly. Or taking it with an acidic or a carbonated beverage. This helps to speed the absorption of the medication. So a full glass of water, maybe a full glass of orange juice or a full glass of ginger ale, as these are other things that can help improve speed of onset.

So besides just taking a little bit more of what we already know, extra carbidopa/levodopa, there are a few other options specifically approved for the treatment of OFF periods. So I

mentioned earlier levodopa inhalation. So this is an inhaled form of levodopa. It doesn't work quite like the asthma inhaler that I just mimicked. But this is something that can be taken up to several times a day for bothersome OFF periods. Probably the longest standing medication that's available for the treatment of OFF periods, which has been available for more than 10 years, are self-administered injections of Apokyn*, which is in the family of dopamine agonists that I touched on earlier. And then as I mentioned, there's a brand-new entrant into the OFF treatment category, which is the sublingual tabs, kind of like a Listerine strip, of apomorphine called Kynmobi*. I don't have any clinical experience with that yet, but it is something that is just newly becoming available. Apomorphine, by the way, is not related to morphine. It is not an opiate. It is just something that has kind of this, like all the dopamine agonists do, it has the ability to bind dopamine receptors and stimulate them kind of from the side, the same way that dopamine stimulates dopamine receptors directly.

So what to do in our case. So Mr. Jones continues to take carbidopa/levodopa three times a day. He adds rasagiline 1 milligram daily, and as intended, he notes improvement of his ON time and less early wearing off. So about a year later, Mr. Jones returns with a new issue. He's not having much tremor, but about 60 minutes after he takes his morning medication in particular, he notes some bothersome, fidgeting movements of his head, neck, and shoulders. He doesn't have it, it doesn't happen while he's in his appointment. But quite helpfully, he has taken a video of them when they are occurring at home. And this is a tip that can be helpful, is to bring a video in of what you're experiencing in your daily life, because it's important to distinguish between tremor and dyskinesia. The movements in this case are kind of these fidgety, squirming dance-like movements, dyskinesia, which can affect the upper body or the arms or legs.

And this is a really critical distinction between, well, is it tremor or is it dyskinesia? Because dyskinesias are actually a side effect of treatment rather than part of Parkinson's itself. And so if a person is having more tremor, they need more medicine. But if they're having dyskinesias, we maybe need to handle the medication in a different way, like maybe a lower dose more often, or the addition of something that can treat dyskinesia, which brings us to amantadine. So amantadine is unique among Parkinson's medications. It does provide benefit directly for motor symptoms of tremor, stiffness, and slowness, as the other medications we've discussed. It also sometimes is even used early as monotherapy, as first therapy. Although due to some of the possible side effects, we'll touch on that, is maybe not the first choice for a lot of people. But what makes amantadine unique is that it is the only medication that is used to treat dyskinesias. It's the only way to get more treatment for the motor symptoms while also potentially putting a lid on or dampening dyskinesias. The exact mechanism by which this occurs is not fully understood.

There are several options. By far, the most widely used is amantadine, which what used to be known as brand named Symmetrel. And within the past couple of years, there've been a couple of extended release formulations, one that's a capsule; one that's a tablet. These are

called GOCOVRI* and Osmolex*. These have the convenience of being just dosed once a day. They unfortunately haven't been studied directly against amantadine. Maybe they would have fewer side effects than amantadine due to having a lower peak level in the system, but that hasn't been well studied. So one of the problems with amantadine is that side effects can potentially limit its use, particularly over age 65. And some of those side effects are what we call anticholinergic side effects: dry eyes, leaving the blurry vision, dry mouth, worsening or causing constipation, and even causing hallucinations.

So one more category of medications to discuss anticholinergics. So it's worth noting that these two medications help really only with tremor; they do not help with stiffness and slowness. Acetylcholine is a brain chemical, a brain neurotransmitter, that's in balance with dopamine. And so these anticholinergic medications can help tremor. The two options here: the more broadly widely used one is trihexyphenidyl, also known as Artane. And then the other option is benztropine, which is Cogentin. And so side effects, again, unfortunately may limit the usefulness of these medications over age 65, and "anticholinergic side effects," as you may have just heard me say from amantadine, is actually the term used to describe some of the possible side effects that these medications can cause — dry eyes, dry mouth, constipation, and hallucinations, but for tremor in particular, and in younger patient populations, this can be a helpful tool.

Just a brief mention of some of the surgical therapies that are available for Parkinson's. These are sometimes considered when motor fluctuations or dyskinesias cannot be fully optimized with medication adjustments alone. And this can be either DBS, deep brain stimulation surgery, or the Duopa pump, which is a sort of Sinemet gel, carbidopa/levodopa that's continuously infused directly into the small intestine through a surgically placed tube. So these are more advanced treatments that can sometimes be helpful, and more information about those is available through other places on the Davis Phinney site.

So for Mr. Jones, he adds amantadine to his regimen of carbidopa/levodopa and rasagiline. His tremor remains controlled and his dyskinesias improved to the point that they are no longer bothersome. And as time goes along, he continues to work with his neurologist when new symptoms arise.

So we have covered all of the medications that are used for the motor symptoms of Parkinson's and optimal medication treatment. As you can tell, it depends on symptoms, severity, possible side effects, and other factors including age. And for this reason, it can be beneficial to work with a neurologist experienced in the treatment of Parkinson's, often a movement disorder specialist. So thank you very much for your attention throughout this presentation. We'll address some questions now, and then there will be a second part of this forthcoming in the next weeks.

Melani Dizon:

Great. Thank you so much for this, Dr. Haug. You can stop your sharing so that maybe people will be able to see us. Some people couldn't see us; they could just see the slides, which is all that was needed right now. So that was great. So this is really excellent. One of the things, just because you just recently touched on it, is I want to talk a little bit about DBS. A couple of people have asked about medication — how you, how you're able to get rid of medication with DBS, or is it just less medication, or what is typically working? And then also, you know, what is it about the medications effectiveness that determines whether or not you would be a good candidate for DBS?

Dr. Aaron Haug:

Great questions. So DBS in general: it's important to know that however your medications work for you when they're working at their very best, that's typically how DBS will work for you, with a couple of caveats. Tremor can sometimes be refractory to medication and yet responsive to DBS. I guess that's really the main caveat. Maybe I'll come back to what the other part of my train of thought was. And so when a person is going through DBS evaluation, we'll have them come into clinic with their medications in their system and then come into the clinic with their medications *not* in their system — off medication for 12 or 24 hours. And we want to see that there's at least a 30% improvement in symptoms that a person is experiencing on an objective Parkinson disease rating scale, to make sure that DBS is potentially a good idea for them.

And then after surgery: there are two main targets in DBS — either the STN, the subthalamic nucleus, or the GPI, the globus pallidus, and what the research shows is that with STN DBS, people often lower their medication by about a third. With the GPI DBS, medication doses usually remain stable after surgery. There is something to be said for not aggressively taking away medication after DBS, because that can occasionally lead to onset or reemergence of non-motor symptoms, including depression. As I mentioned, dopamine agonists can have sometimes a profound antidepressant effect, and what sometimes happens in our eagerness to remove medication after surgery is that if a person has a fantastic effect surgery and they go from quite a bit of medicine to very little, or in some cases, not at all, they can occasionally develop a pretty profound depression by not being on any of their dopaminergic medications anymore. So those are my thoughts about that.

Melani Dizon:

Oh, good. That's great to know. I hadn't heard that about just stopping them altogether. Somebody asked about, so actually many questions came in, about they're taking carbidopa/levodopa. It's not working. They're feeling like it's maybe not having any effect, and their doctor just wants to keep adding and upping the dosage. Is there such thing as, "Well, it's not working here, but it's gonna work if we just keep adding it"? Or is there such a thing as just, there's just too much? You know, law of diminishing returns, like you can't take that much Sinemet, your body can't process it.

Dr. Aaron Haug:

Right, right. Another great question. So I would say that for most people with Parkinson's, the reason that levodopa might not work for their symptoms is that they're not taking enough. So I mentioned that 25/100 pill three times a day is kind of the starter dose. Well, before we kind of throw up our hands and say, levodopa doesn't seem to be working here, we go to a much higher dose than that. And this is sometimes limited by nausea or other side effects. But in order to evaluate for whether a person can truly have a levodopa response, we titrate up to as much as five tablets, three times a day. So 1500 milligrams per day. And if a person isn't having nausea then, yet their symptoms, motor symptoms, remain bothersome or have been disabling, then I would want to titrate all the way to 15 tablets a day before we say that there's no potential for improvement there.

Melani Dizon:

Great. You talked a tiny bit about caffeine and you know, there's been a lot of media and the papers — if you drink caffeine, it might help you not get Parkinson's. What about if you already have it? What are the sort of the contraindications for drinking a bunch of caffeine if you have Parkinson's and you're on medications?

Dr. Aaron Haug:

I would say the main thing — I would say three things. Because we know that coffee seems to decrease the likelihood of Parkinson's, by the same token, it maybe also can slow progression some. There's not really evidence of that, but it stands to reason. So then on a more practical level, what else can caffeine help with? Well, sometimes it can help with energy and fatigue and alertness. That's what billions of us use it for. But it can make tremor worse. And so what you see is what you get. If you drink caffeine, you feel more alert, you feel better, than maybe it's going to slow symptom progression over time. But if it makes you really shaky, then it's probably not worth it.

Melani Dizon:

A couple of questions came in about blood pressure. So is there any evidence that carbidopa/levodopa can cause blood pressure to drop? Is this related to nOH? Why people with Parkinson's, or is that sort of a pre-symptom? What is the link there? And if so, what can be done? Is it a timing of medication?

Dr. Aaron Haug:

So I mentioned that lightheadedness is a possible effect of levodopa, and really most Parkinson's medications, and that is because it has a blood pressure lowering effect. So the answer is “both-and.” People with Parkinson's tend to have blood pressure lability or instability, where they can have nOH (neurogenic orthostatic hypotension), meaning that they feel faint when they stand up or get up because their blood pressure temporarily drops. And medications have the potential to exacerbate that. The same way that taking the medication with crackers or some sort of carbs can help with nausea, it can also help some with the lightheadedness. What's happening there is

that the carbs cause the absorption of L-dopa to be slower, but they don't impair the extent of absorption. So if it makes you feel really lightheaded to take your carbidopa/levodopa on an empty stomach, then taking it with crackers, toast, a bagel, some sort of fruit or juice, some sort of a high-carb, low-protein food can be helpful.

Melani Dizon:

Great. Let's see. Another one that has come in a lot. Is there any help for, that people can take medication for constipation? Let's say they've had it for very long, you know, like that was the pre-symptom, and they have it, and now they're taking all their meds. Is there anything that will work for constipation that's not going to interfere with (aside from the sort of the lifestyle things that they can do, which is drink a lot of water, make sure you exercise, cause it's going to get things moving), what about medications?

Dr. Aaron Haug:

Yes. So constipation occurs, according to some studies, in 98% of people with Parkinson's. And that's just as a symptom of Parkinson's, not as a side effect of medication, but some people feel pretty clearly that their Parkinson's medication exacerbates or causes constipation. So there's a whole toolbox for the treatment of constipation. And most of it is available over the counter. So starting with a stool softener, which is usually a little red pill called Docusate or Colace, taking that up to three per day. And then the use of laxatives, whether it's the powder, a MIRALax, which is polyethylene glycol, or a number of others. And then even more advanced, there are a couple of prescription medications specifically for constipation. And so it is usually just a matter, the fight against constipation is one that we can usually win. It's just a question of how many tools we need to pull out of the toolbox. And so hydration and exercise, daily stool softener, and then potentially a daily laxative. That's something that you would need to discuss with your prescriber, but laxatives will often say don't take for longer than a week or whatever without talking with your healthcare professional. Well, some people with Parkinson's need to take a laxative once or more than once every day, long term. And so that is something to consider.

Melani Dizon:

So questions around that. People are asking if vigorous exercise would deplete their carbidopa/levodopa. Is this something that they need to think about the timing and, or upping the dose if they're, you know, real vigorous exercises at least once a day, if not more?

Dr. Aaron Haug:

Yeah, that's a good question. I haven't ever seen any evidence that vigorous exercise depletes carbidopa/levodopa or your own natural dopamine, but I have a lot of people that feel like it does. And so if that is the case, we will often tweak the regimen in some way, maybe to have an extra dose or a slightly increased dose of medication around the time of exercise.

Melani Dizon:

Okay. A lot of questions have come in before this presentation and some during the day about the Neupro patch*. Can you talk about your clinical experience with that? And some people are saying, you know, "I want to get off; it's too expensive," or, "I took it and it's great." Can you talk a little bit about that?

Dr. Aaron Haug:

Sure. Yeah. So the Neupro patch* (rotigotine). It's a dopamine agonist and has a couple of pretty clear advantages — that it's not a pill, so it's less likely to make you nauseous. It doesn't have to go through your stomach. And it's truly long acting. You put one on you, leave it there for 24 hours, and it's continuously delivering a steady amount of medication. Then you take that one off and put another one on the next day. So those are real advantages. The disadvantages include the category effects of dopamine agonists, which is that they can cause impulse control disorders. Some people have leg edema or sleep attacks. And then there's the issue that can often be present with any of the medications that have an asterisk by them, which is that they're branded medications. That cost can be an issue. So I would say that in my experience, I tend to use ropinirole and pramipexole more than the Neupro patch* for that reason. But those are the pros and cons.

Melani Dizon:

Okay, great. We have a couple of minutes left. I want to end on one question about — and as I said, don't worry, everyone. We're going to get through all of the questions in a second, recorded interview. People have questions about sleep and how their Parkinson's medications are interfering with their sleep. Are there medications that you recommend for people who are really dealing with trouble with insomnia? I wouldn't say so much RBD at this point, but just real issues with getting to sleep, staying asleep to the point where they actually can feel well enough and high enough energy to exercise, which they know is going to be critical for their wellbeing,

Dr. Aaron Haug:

Right. Insomnia and sleep issues are highly prevalent among people with Parkinson's. And I would say a couple of things. There are certain Parkinson's medications that should not be taken very late in the day. Selegiline, one of the MAO-B inhibitors, can cause insomnia. And so it shouldn't be taken really any later than lunch time. And the same thing probably goes for amantadine. It can sometimes have some activating properties. And so taking amantadine later in the day can worsen or cause insomnia. So not much after 2:00 PM is what I recommend, with really both of those medications. And some people find that their carbidopa/levodopa or their dopamine agonists can cause nightmares if they take them too close to bedtime. So that can be tricky to work around. Sometimes it needs to be dosed earlier, or use controlled release instead of immediate release. But in terms of what to take to treat sleep, there are several tools in that toolbox over the counter. Melatonin can be very helpful for a lot of people with Parkinson's. And then there are some



prescription sleeping medications, probably clonazepam, or Klonopin*, is the most widely used because it can help insomnia, REM behavior disorder, periodic leg movements of sleep, several of the movement difficulties that can occur in people with Parkinson's or sleep related difficulties.

Melani Dizon:

Okay, great. We had a few questions about sleep and marijuana and CBD. We'll actually address those on the next session. So don't worry about that. If that was your question, we will definitely get to it. I'm gonna put up this email. If you've already sent in the question, you don't have to resend it to me. I have a whole list of them, and we will ask during the during the next session. If you haven't had a chance to ask a question, you can send it to blog@dpf.org. I will definitely see that and we will get to it. Right now, I just want to thank Dr. Aaron Haug for being here. This was excellent. I don't know if you saw it in the chat, but we had an amazing amount of people saying this was the best webinar they've ever heard on medication. And I would have to agree. I learned so much. So thanks for being so clear and calm and, you know, laying it out for everybody. It was really, really great. I will be sending the slides, the video recording, audio recording, and transcript to everybody. So you don't have to request it. We'll send it to you as soon as they're available. And we'll also out the recording of next question-and-answer session. So thank you so much, Dr. Haug. It was really great having you.

Dr. Aaron Haug:

Well, thank you very much. I think that the Davis Phinney Foundation does great work and it's a privilege to participate.

Melani Dizon:

Thank you. Thank you, everybody. We will see you very soon.

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