J.TIMOTHY GREENAMYRE: So what I'd like to talk about today is Parkinson's disease from the standpoint of how it's diagnosed on a day-to-day basis, how we begin treatment for Parkinson's disease. And then I want to go into the non-motor features of Parkinson's disease, which will overlap a little bit with what Dr. Leventhal just talked about.

Parkinson's disease was first described in 1817 by James Parkinson. And he really got it very close to perfect in his description when he was describing involuntary tremulous motion with lessened muscular power in parts not in action. And even when supported, with a propensity to bend the trunk forward, so the patients had poor posture, passed from a walking to a running pace, and the senses and intellect being uninjured. That last part, he got slightly wrong.

These are the cardinal features of Parkinson's disease. A rest tremor, which occurs when someone is just sitting in a chair, for example. It's not a tremor that occurs exclusively with use of that hand. If you only have a tremor that comes with use of the hand, it's not a Parkinsonian tremor. Bradykinesia, or slowness or a general paucity of movement. Rigidity, which is just resistance to passive manipulation across a joint, typically the elbow. And postural instability or balance problems.

There's a host of other motor symptoms that we often look for in history or on exam. These include changes in handwriting, changes in facial expression, a stooped posture, shuffling gait, decreased arm swing. From a practical point of view, we are asking about is it difficult to get out of a chair or the middle of a couch or your car? Difficulty rolling over in bed and drooling or speech difficulties. Now these features that I've put asterisks on were all noted by James Parkinson in 1817, so he was really very observant.

So how do we make a diagnosis on a day-to-day basis when someone is coming into clinic? We want to look for an insidious and unilateral onset. So it should begin on one side or the other. It does not typically begin on both sides simultaneously. We want to see two of three, a rest tremor, slowness or rigidity. We want to exclude secondary causes like drugs and metabolic problems. And ultimately the diagnosis is made by pathology, but we get a good idea based on response to medications and the course of the disease.

Drugs, of course, can cause Parkinsonism. And the most common culprits tend to be the anti-emetic drugs, things like compazine, Reglan, or metoclopramide. We see this very commonly. Dopamine-depleting agents, such as reserpine or tetrabenazine, neuroleptics-- and this includes the so-called atypical or newer agents-- valproic acid or Depakote, SSRIs can do this and it's often unrecognized, and many other drugs simply cause tremors of various kinds.

In the differential is vascular Parkinsonism. And this is typically caused by small vesicle ischemic disease. So we rarely get an MRI scan in the course of trying to diagnose Parkinson's disease. But if we see hints that there may be vascular problems systemically with a history of hypertension, hypercholesterolemia, diabetes, that kind of thing, and some atypical clinical signs, we may get an MRI scan.

These are extreme cases, these MRIs that I'm showing here. We often see vascular Parkinsonism with much less extensive damage on the MRI. Normal pressure hydrocephalus can cause something that looks a little bit like Parkinson's disease, but it's usually easily distinguishable from idiopathic Parkinson's. HIV usually doesn't get so far as to look like Parkinsonism any more. Years ago it did. And then there's a variety of Parkinson's plus syndromes, things like cortical basal degeneration, multiple system atrophy, progressive supranuclear palsy, and some of the spinal cerebellar atrophies. And in their early stages, these can be actually quite difficult to distinguish.

So in making a diagnosis, a variety of criteria have been put forth. And I realize this is probably too small for you to read, but on the left here, the inclusion criteria are basically the cardinal features of the disease that I mentioned earlier. There are exclusionary criteria, and I'll just talk about a couple of them. Repeated strokes or stepwise progression, neuroleptic treatment, a remission the disease, supranuclear gaze palsy or cerebellar signs, such as ataxia, bebinsky signs, so on. Things to suggest other than idiopathic Parkinson's disease.

And then the things that tend to support the diagnosis are unilateral onset, a rest tremor. And rest tremor's not always present, so seeing it is reassuring. Asymmetry at the beginning-- and that asymmetry usually persists-- an excellent response to medication, and so on. There are some non-motor features of the disease. And I'll talk about these in more detail in the last portion of this presentation. But these include a loss of sense of smell or anosmia, sleep disorders, particularly something called REM sleep behavior disorder. And this is essentially acting out your dreams in the night. So normally, we are paralyzed when we sleep. If you have REM sleep behavior disorder, you are fighting, you're battling, you're shouting in your sleep, you're hitting your bed partner, and so on. It can be very problematic.

An intrinsic part of Parkinson's disease can include depression, anxiety, erectile dysfunction, cardiac sympathetic denervation is common, but probably not clinically significant, orthostasis, memory problems, and dementia and psychosis. And we'll go through those individually when I discuss some of the treatments. And as Dr. Leventhal said, some of these symptoms can precede the diagnosis of Parkinson's disease by many years. So it's very typical for somebody to come in to the clinic and we think they have early mild Parkinson's disease. And I ask about smell and they say, oh I haven't had a sense of smell for 20 years, or I've had constipation for the last 10 years or all my life. So this is a very common prodromal symptom.

And this is largely repetitive to what I've said before, just talking about how we diagnose on a daily basis with unilateral onset, rest tremor present, slowly progressive, and then the supportive history of anosmia, constipation, REM sleep behavior disorder, and so on. Red flags to the diagnosis that can help make you suspicious or exclude the diagnosis include a rapid or sudden onset. The exception being that it's not uncommon for our patients to say I, developed my tremor after I went in for a major surgery or after my husband died or at that kind of thing.

A major stress, whether its physiological or psychiatric, can precipitate the earliest symptoms, but it's not full blown disease at that point. It's just I started noticing a tremor, for example, after this event. Symmetric presentation argues against PD. Rapid progression. So if you have a patient who is going from normal to wheelchair bound or falling within a year or two, that's probably not typical Parkinson's disease. A lack of response to typical medications is a red flag. Early falls, early cognitive impairment, and very severe early autonomic dysfunction.

Just a word about the DaTscan, which was approved for diagnostic purposes in Parkinsonism a few years ago. We use it very rarely. We don't do imaging. If the cases present typically. We can occasionally use it for diagnosing something that's a little bit odd. But it's not particularly specific. So things like multiple system atrophy, one of the Parkinson's plus syndromes, can show the same defects that Parkinson's disease does.

I'll give you an example of when I did use it. I saw a 28-year-old woman who had just had a baby who had a tremor that looked exactly like Parkinson's disease. And I thought it was Parkinson's disease, but to convince ourselves, we did DaTscan and it was diagnostic for Parkinson's disease. Which brings up the point that although Parkinson's is a disease of aging, it is not rare to have it come on earlier,

The bottom line is that diagnostic accuracy increases the longer somebody has the disease. In its very earliest stages, the signs and symptoms can be quite subtle and nonspecific. So the longer somebody has it, the longer they have to accumulate and develop their symptoms. We can diagnose it with more accuracy. Accuracy also goes up by seeing a movement disorders specialist.

So a little bit about the initial treatment of Parkinson's disease. The decision of when to start treatment when somebody comes in with symptoms that are early, mild Parkinson's disease is very individual and is really a collaboration between the patient and the physician. And typically what we think about is functional impairment is the disease where their symptom's interfering with things that they want to do on a day-to-day basis. And that can be functionally, it can be socially, it can be cosmetically. Some people are very embarrassed by having a little bit of tremor and want it to go away.

But the threshold is different for everybody. Some people want treatment at the first sign of the disease. Some people will undergo or be willing to bear severe symptoms before they want to even consider medications. And these are typical discussions that we have. There's a common myth that levodopa or Sinemet's effects only last five years or only last 10 years. And we have our patients and a lot of physicians, actually, feel that. And It is a myth. There is no advantage or disadvantage to starting levodopa treatment or any other symptomatic treatment of Parkinson's disease early versus late. So we can put that one aside.

In general, the non-dopaminergic drugs, things like amantadine, selegiline, resagiline generally have minimal to mild symptomatic effects. So they're not going to have a dramatic effect on the patient. The exception is anticholinergic agents such as trihexyphenidyl or benzotropine, which we use for tremor and which are very effective.

Now the choice of which flavor of dopaminergic drug to start-- that is levodopa containing medication such as Sinemet or Stalevo versus a dopamine agonist has to be individualized. Overall, levodopa is more efficacious for the motor symptoms. It's easier to start, easier to titrate to a therapeutic dose. But it's associated with earlier development of motor fluctuations. Things like wearing off between doses or a peak dose dyskinesias, or unpredictable off periods.

Dopamine agonists, on the other hand, are associated with far fewer motor fluctuations but they're less efficacious. They have to be started and titrated very slowly and they're associated with more frequent side effects, including hallucinations, somnolence, edema, impulse control disorders. Things like gambling, deviant sexual activities, staying up all night to watch internet porn or internet shopping or things like that. Generally we don't start dopamine agonists in people over about age 70. If somebody is on them and reaches 70, we don't necessarily stop them unless they're having problems, but we don't start them as a new medication, in general.

And a general rule for starting all of these drugs is to start low and go slow. So when I start Sinemet, for example, which most of you have probably started with your patients, I start it extremely slowly. I start with a half a pill a day for a week. And then a week later, they go to a half pill BID. And a week later, TID, until they get to one pill three times a day, and then I sort of reassess. But this way, I almost always avoid side effects of the medication.

When we're thinking about three times a day dosing of a drug like Sinemet, we think about TID dosing rather than q8 dosing, because they need therapeutic levels during their waking hours and not so much overnight. And a convenient way to do this is to have them take their medication with meals. Now they will read from their pharmacist, and you've probably heard and maybe told your patients don't take it with meals, because protein can interfere with absorption. On a practical basis, however, for most patients, particularly in the early to mid stages of the disease, there's not a big interaction between protein and absorption of the Sinemet. It doesn't have a big functional impact. It's easy to remember to take at meal times and it's easy to forget to take it at other times and to work around your meals.

Another thing to think about is that the sustained release, levodopa preparations, are often absorbed erratically, which leads to less predictable effects and sometimes what we called dose failures. Finally, anecdotal evidence suggests that sustained release or patch formulations of the dopamine agonists tend to be a little bit better tolerated, perhaps even easier to start. We avoid those peaks in the blood and brain levels of these drugs. And it seems to be a good effect.

So that's all I'm going to say about starting medication in Parkinson's disease. I'd be happy to discuss specifics with any of you in the question period. But I want to turn to management of the non-motor symptoms, because these are often neglected in the disease. This is the list that I showed you before. And I'll go through most of these one by one. And I'm going to give you the recommendations, the practice guidelines from the American Academy of Neurology. And this is the same kind of data that Dr. Leventhal just presented with a, b, or c kinds of recommendations, indicating that the knowledge state that we have.

So first, REM sleep behavior disorder. Acting out your dreams, hitting your bed partner, falling out of bed, that kind of thing. Right now, there is insufficient evidence to support or refute any specific treatment. But I can tell you what we do in practice that seems to be effective. Melatonin over-the-counter seems to work very well, at least in the early stages. Anywhere between 3 and 10 milligrams we use, sometimes higher. And it can be very effective. And we typically dose this about a half hour before bed.

When that fails, we consider clonazepam. And again, that can be quite effective. Antidepressants, both SSRIs and tricyclics can exacerbate the REM sleep behavior disorder. But antidepressants are often used in our patients and needed in our patients. Constipation-- and I'll echo what Dr. Leventhal just said-- polyethylene glycol seems to be effective in treating the constipation in Parkinson's disease, although there haven't been any huge trials of it. We suggest increased water and dietary fiber, as he said. Stool softeners can be useful. There's no information on the oral systemic drugs in Parkinson's disease. And of course, Parkinson's drugs can exacerbate or even cause constipation.

I'll also echo one thing that Dr. Leventhal said in passing, and that is that when we use something like MiraLAX or polyethylene glycol, we suggest daily doses. And we have to find out what the right dose for an individual is, but it's much easier to keep the stool soft and passing than to chase a bout of constipation and then stop taking the polyethylene glycol and then take it again when you have a problem. It's better to find a dose that that works every day. And it's very safe and can be used long term.

Urinary incontinence is common in Parkinson's disease. And this blends in with normal aging in both men and women, but it's common in Parkinson's disease. There are no good randomized controlled trials of drugs, although we often use, or urologists will use, anticholinergic agents. And they can be clinically beneficial. But of course, the anticholinergic agents can cause confusion and cognitive impairment in the elderly and in Parkinson's disease. So we have to be careful about that.

Orthostatic hypotension occurs in Parkinson's disease. If that's one of the presenting signs or an early sign of the disease and it's very severe, it may not be idiopathic Parkinson's disease. But some degree of orthostasis is common in the disease. What I typically recommend is salt tablets as a first pass. These are typically a gram of sodium chloride. We dose it TIP to QID and increased water intake. And these can be enough to reduce the symptoms. Failing that, we go on to midodrine or droxidopa, which was recently approved for orthostatic hypotension.

It has to be emphasized that Parkinson's medications, particularly the dopaminergic drugs and particularly the dopamine agonists, can cause or exacerbate orthostatic hypotension. So sometimes, we're in a very difficult position. Drooling is common in Parkinson's disease. And this isn't excessive production of saliva, it's decreased frequency of swallowing. Just as everything else slows down in Parkinson's disease, including the GI tract, swallowing slows down as well.

Botulinum toxin is very effective, and people in ENT are good at doing this. In practice, some of our Parkinson's medications cause dry mouth, which can be equally problematic. Erectile dysfunction comes with Parkinson's disease. In many cases, because of the autonomic dysfunction. The typical drugs can be used for erectile dysfunction, although they haven't been tested in great clinical trials. We have to exclude other treatable causes of erectile dysfunction, including drugs. And I guess that's all I'll say about that.

Excessive daytime sleepiness and fatigue are common complaints in Parkinson's disease. It's very common that as the day goes on, people feel that they have to take a nap. And what we typically recommend is building in a nap of 30 minutes in the afternoon if their lifestyle or occupation allows that. If they need medications, modafinil can be clinically beneficial. There is insufficient evidence, however, to show that there's a safety effect of modafinil if that person is working in a job where sleepiness poses a danger or if they have to drive. And although they have subjective improvements in their sleepiness, the objective measures don't necessarily follow that. So it's a mixed bag with modafinil.

And similarly, fatigue. So as I said, I typically recommend a 30-minute scheduled nap. But methylphenidate can be considered. I have not had great luck with methylphenidate in my practice, but there is some evidence to suggest it can work in some cases. Anxiety is a common feature of Parkinson's disease. And it is probably an intrinsic part of the disease for some patients. We don't have good evidence for specific drugs or treatments for anxiety and PD, although the typical anti-anxiety drugs are used commonly and seem to work to some extent.

It's important to recognize, again, however, that the use of these drugs, things like clonazepam or other benzodiazepines, are going to increase the risk of confusion or falls or cognitive impairment in this population. Similarly, depression is a part of the disease. It's extraordinarily common in the disease. And the only drug that has a specific recommendation in Parkinson's disease is the old tricyclic Amitriptyline, although we use SSRIs regularly and they seem reasonably effective, as they do in the general population.

Psychosis becomes problematic as the disease progresses. Hallucinations, paranoia, and so on become common. And in part, these can be exacerbated by the medications that we use, both levodopa-containing medications and the dopamine agonists can increase the risk of having psychosis and hallucinations. Clozapine is a great drug for the psychosis in Parkinson's disease. However, of course, you need weekly monitoring and CBCs, because it can cause a fatal agranulocytosis, so we don't use it very often.

Quetiapine can be considered in psychosis and PD, although quetiapine can make Parkinsonism worse, which is a general problem. With all the medications that we use to treat psychosis, they will tend to make the motor features worse. And if we have to increase medications for the motor features, it can make psychosis worse. Olanzapine is one medication that should not be considered for PD, in that it can make things much worse. You've probably heard that there's a new drug on the market that's just been approved, pimavanserin and Nuplazid. It's only available through a specialty pharmacy. It's so new, we don't have any experience with it, so I can't tell you our own experience at this point.

It's supposed to not have any deleterious effects on motor function because it acts in a different mechanism. What James Parkinson got wrong about Parkinson's disease was that there are almost invariably cognitive changes in the disease. They can be mild to severe and they are typically progressive. The degree of cholinergic denervation, the loss of the cholinergic in Parkinson's disease is actually greater than that in Alzheimer's disease. And for that reason, the cholinesterase inhibitors can be somewhat effective in treating the cognitive impairments in the disease. So donepozil and rivastigmine. Seem to work for some people.

There's a little bit of evidence for severe people with Parkinson's disease, dementia, or diffuse Lewy body disease that memantine may be helpful. It improves survival, at least. And it's also important to recognize, again, that the PD medications, especially those with anticholinergic properties, so the things that we might use for tremor control or for bladder control, can make the cognitive impairment worse. So we always have to look at the medications in this context.