Good afternoon. Thanks for having me here today. So I'm going to have a quick overview of a slow disease today and going to be focusing on some updated on the clinical diagnosis and management. So as you all are aware, it's a neurodegenerative disorder. It's usually sporadic. [INAUDIBLE] unclear. About 1% to 2% risk of acquiring Parkinson's for the general population. The risk increases to 2% to 4% of people who have an immediate family member involved. It's estimated around 1 million people in the United States are affected with Parkinson's with annual incidence rate of around 60,000, and this is going to increase. The average age of onset is 62. And the risk increases above age 50. At 65, about 1% of population are affected, and this increases up to 2% at 80. The most important risk factor is actually age, which is very relevant to this audience. A maze of affected twice.

The genetic risk factors definitely play a role, but the familial classic Mandellian autosomal dominant or recessive and monogenetic familial just are a small part of Parkinson's, probably less than 5%. However, there is polygenic influence certainly. The certain genes including one that's involved in glucose [INAUDIBLE] rather gene known also to be causative of Gaucher disease that has been identified in both a sporadic and familial cases, again linking the pathophysiology of these genetic and sporadic cases together. Environmental exposures are definitely being recognized more and more in terms of increasing risk of Parkinson's. From what we can know right now, exposure to pesticides and herbicides, especially certain types, like rotenone.

And the Vietnam veterans Agent Orange exposure has been clearly recognized by VA as an increasing risk of incidence of Parkinson's. Also exposure to well water upbringing in rural areas and exposure to high doses of manganese, repeated head injury. And in terms of protective factors, exposure to nicotine, for unclear reasons, seem to reduce the risk of developing Parkinson's. Diets that are high in your rate, especially in males, can reduce the risk of developing Parkinson's. And there are some questions about exposure to NSAIDs, and that's kind of not very clear.

We are in the bicentennial anniversary of descriptions of Parkinson's this year by James Parkinson's in 1817 the publication of his monogram essay on shaking palsy. And in honor of him Shopko named this disease, Parkinson's disease. And I think this is interesting because the diagnosis was made based on clinical observation. And this still remains very true. So it's a disease that you know the diagnosis is very clinical.

At the time of James Parkinson, motor symptoms were the primary focus. But now we understand that symptoms include premotor symptoms and include non-motor symptoms. The key premotor symptoms are Parkinsons, which kind of start many years before the onset of motor symptoms, include lack of sense of smell, the dream enactment, which was referred to earlier, REM behavior sleep disorder, this is the lack of loss of normal paralysis that people have during the dreaming phase of a sleep and leads to violent dream enactment. This can start decades before developing Parkinson's or related conditions.

The other common premotor symptoms-- constipation, as well as anxiety and depression. But motor features are really the key to diagnosis. The four Cardinal features are tremor, bradykinesia, rigidity, and impairment of gait and posture and stability. The tremor, typically, is a rest tremor. It often starts asymmetrically and remains asymmetric. It can reemerge with prolonged outstretching of arms and maintaining a posture or during ambulation. So seeing somebody that walks with a tremor in their hands is suggestive of a rest tremor that re-emerges. Bradykinesia is the key clinical feature that's a requirement for diagnosis of Parkinson. It's not a tremor, but it's bradykinesia. Operationally, it's a decrementing in the amplitude and speed of repetitive movements.

Clinically translates into that sense of fatiguing and getting a slower and a weakness which is not related with loss of muscle strength but an ability to continue doing tasks, and especially with repetitive tasks. We often clinically can look at finding bradykinesia with simple like repetitive finger tapping, hand opening, foot tapping tasks. And the key with bradykinesia, is the task starts good, and it starts to become a slower and more difficult, whereas upper or lower motor neuron weakness does not start good. It's weak from beginning. There's not that kind of a decrementing. And with repetitive moments, we also have to distinguish it from when it is dysrhythmic and incoordinated, but there is no kind of a gradual decline. And that's the characteristics of ataxia cerebellar disorders. So there are good, actually, screening tasks to do repetitive movements.

And hypokinesia is very much linked to the broad concept of bradykinesia again, these are kind of a delay in the onset of a spontaneous movement and we can see it in a number of features like the patients don't blink that much, they have this masked face, they just have the slowness of starting to move, and the initiation of movements become difficult. And when we talk about bradykinesia, it's really slash hypokinesia. Rigidity is an increased resistance to passive movement, which is checked by moving the joints passively. And usually an increase can be seen in extrapyramidal disorders like Parkinson's, which is independent of how quickly the limb was moved and what direction it's moved. An increase in a tone that is dependent on velocity and direction is spasticity, which is more related to cortical spinal tract, and motor cortex, and the spine. Gait impairment, again, it's kind of a characteristic feature of Parkinson's.

And it's something that develops slowly, and narrow based gait, slow pace, and length of the strides become shorter, heel clearing can be reduced. Patients tend to stand up slowly, turn slowly. Transitions, usually, are more difficult and remain more difficult. In more advanced situations, there are halting of the gate with hesitation or freezing, where they just get stuck to the ground. And partial instability, although it's a feature of Parkinson's, but is not expected as a very early feature of Parkinson's. So patients, as the disease progresses, develop problems with postural reflexes, and that can translate to falls. But if they have significant problem with their posture reflexes, they get up from the chair to fall and so forth in the early phase, that's actually a red flag with idiopathic Parkinson's.

so operationally, I think United Kingdom society brain background curious something that we know practically still rely on and basically it requires bradykinesia plus one other cardinal feature. So if you have rest tremor and bradykinesia, you have Parkinsonism. And for Parkinson's disease, there's a number of supportive features, like presence of rest tremor, unilateral and asymmetry that's persistent. Disease should be progressive over a course of 10 years and usually responds to L-dopa that lasting for more than five years. And development of the specific side effects like dyskinesia, which is involuntary, chorea for movements, as a result of side effect of levadopa is also supportive.

So within the past couple of years, there is a new criteria for diagnosis of Parkinson's that really should be used at this point by Movement Disorder Society, but this is a little more nuanced. It still requires the presence of bradykinesia plus either rigidity or rest tremor. If that is present, that's Parkinsonism. Then it requires a number of absolute exclusion criteria to be ruled out. And this absolute exclusion criteria, really, are the main features are that we can think about differential diagnosis of idiopathic Parkinson's, so the main features of a number of degenerative Parkinsonism or secondary Parkinsonism are listed in terms of this absolute criteria. And then there is a distinction between clinically established Parkinson's, when we don't have any red flags, or clinically probable, when we have red flags but the red flags are offset by presence of supportive features.

So certain presence of certain things like early cerebellar deficits, early dementia, early significant posture and instability leading to fall. These are all red flags for idiopathic Parkinson's disease. These are things that could develop along the way, and, you know. I think this is actually very kind of refined criteria to kind of make that diagnosis. Talking about non-motor features-- I'm going to go back to differential in a second. So we recognize now that this is a big part of the burden of the disease. And a lot of issues related to-- imagine the Parkinson's comes from the non-motor features. Cognitive impairment is a big one. Now we don't expect patients to develop dementia within the first year of Parkinson's disease. That would be operationally defined as likely to be Lewy body dementia. And most often other patients develop some degree of cognitive impairment.

And up to 30% may develop dementia along the way. A significant cognitive impairment in the first few years, actually, is kind of unusual. The most common profile for these patients is the pattern of so-called subcortical dementia, or subcortical cognitive impairment, which involves not the cortex, but the mechanisms that involve the subcortical area. So this includes impairments with the speed of processing. It's very typical early, even can be seen patients approximately speak slower and talk slower. Also, some impairments in executive functioning. It could be, for example, be translated into selective problems in memory, which is usually related to recall. But it's not as much problem with encoding as we expect in Alzheimer's early.

And the naming could be, for example, another area. But a full blown dementia can happen after the first 5 to 10 years. And originally James Parkinson described this as a non-cognitive disorder. Anxiety and depression is pretty common, and these are actually common as in premotor symptoms of when we diagnose Parkinson's. Usually depression, and especially anxiety, is usually present. These are very responsive to the typical treatments that are used for treating these symptoms in non-Parkinsonian patients.

However, a twist is that some of these patients have response to dopamine medications, so their anxiety and depression may really correlate with the timing of the medication, especially dopamine medication, and really be dependent on supplementation of dopamine. But on the other side, serotonergic medication, or SNRs, work very well for this group. Apathy was referred to as actually one of the very common problems in Parkinson's. And in distinction to some other types of dementia, apathy is kind of a late process. Parkinson is actually very early and could be patients who are otherwise very well, no cognitive problem, no mood problem. But the family members usually complain of patients are not having any initiative or motivation to start any activities. And sometimes redirection of getting involved as a family-- because a lot of times, they can be more willing to do things if they're being engaged into it.

Fatigue is common in Parkinson's, and the multifactorial process affected by pain is sleep motor symptoms. And some of it is the central effect and effects the person in the brain. And a number of problems with sleep are common too.

In terms of differential diagnosis, secondary causes, the key ones are neuroleptic induced Parkinsonism that is reversible. Vascular Parkinsonism caused by certain types of stroke, or mini strokes, or microvascular disease that are usually affecting lower extremities much more than the upper extremities. There was a referral made earlier to normal pressure hydrocephalus, which could have lower extremity Parkinsonism. It seems to be a kind of overdiagnosed entity, especially overcalled by radiology, but something we don't want to completely overlook. And then toxics, post traumatic injuries with repetitive injury or postencephalitic Parkinson's are relatively rare. Most of the non-idiopathic Parkinson's we see clinically are related to a number of degenerative disorders. And among these, there are these four that account for usually about up to 15% of patients who come to the door to a clinic, and they may initially have Parkinsonism. And we usually say within the first couple of years the diagnosis may be revised to one of these Parkinson's plus or atypical form of Parkinsonism. Some of the key features is these processes are faster. They don't respond as well to therapy. And they may have additional features at presentation.

So quickly go over-- like, we know that this is a disease that affects a brain circuit, a key part of motor symptoms of the substantia nigra involvement. The substantia nigra-- the panel on the left side-- we see the loss of dopamine cells in substantia nigra, and this leads to accumulation of abnormally folded proteins. Alpha-synuclein now is recognized as a key to the pathology of disease. And one of the distinctions of Parkinson's is we have better modeling of the disease at multiple levels, from primates into the cell culture level. In terms of understanding this process.

So the Lewy bodies and Lewy neurites, a collection of this toxic material, is the key to the pathology, which leads to cell dysfunction and death. There's a number of processes that lead to the accumulation of pathology, including mitochondrial dysfunction, oxidative stress, also breakdown of the protein degradation system that takes out this abnormal protein from the cells. So it's, again, just a schematic to suggest as many pathways that converge on breakdown of clearance of this abnormal protein leading to folding of synuclein accumulation in terms of toxic Lewy bodies.

Some interesting insights come from pathology. Works with Braak and a number of other pathologists that helped to the suggested model of a staging of pathology in Parkinson's patient, to suggest that the staging of Parkinson's, based on autopsy results, starting at a level lower than substantia nigra, where the motor features start. And that's the stage three here. The pathology seems to start earlier in the lower majola and areas like dorsal motor nucleus of vagus as well as olfactory bulb, and that has raised some suggestion that these areas that are exposed to GI tract or olfactory system could be a connection with outside world, where toxins or other things that can start the process of Parkinson may start a process of protein degradation that can migrate rostrally, go up to the brain. When it gets to the mid-brain, substantia nigra, we see the motor symptoms. And the later stages when it spreads to the cortex, we get to that cognitive and balance and other problems. So the idea behind this model is in this case, spread of the Lewy bodies to the cortex associated with dementia.

So the idea of this hypothesis being actively investigated is that the Parkinson's, along with a number of other neurodegenerative disorders, could be a prion-type disease based on the mis-folding of proteins, and you know if that's proven of course, would be a significant change in our thinking about this. In terms of how this impacts damage in the cells, including substantia nigra that are the main cells for dopamine, translates to a loss of dopamine activity in the basal ganglia.

So the green picture on the left is a normal absorption of dopamine, and the one in the middle is a patient with Parkinson's, where the posterior part of the putamen part of basal ganglia, there's lower absorption. And as you can see, that middle part is asymmetric, and that's very typical of Parkinson's. So this is a type of test called DaT scan, a dopamine transporter scan, that is now FDA approved and available. We have it in Presby. It is a test that can sometimes be used for confirming the clinical diagnosis of Parkinson's, although again, a lot of times it may not be needed, but in cases where there is some difficulty with diagnosis, it could be helpful. It doesn't distinguish from atypical forms though. So the end result of affected basal ganglia is that this is a circuit disease between basal ganglia, thalamus, and cortex. The regulation of movements gets disrupted.

This is really a simplified version of how basal ganglia work, but the main process is, in Parkinson's disease, the thickness of these arrows changes, and this translates into the movements become halted, initiation becomes more difficult. And that's what basal ganglia does. It's sequencing, initiation, and scaling of movements. So patients can move, but it's difficult. And if they continue to move, become repetitively and progressively slower. So the interest, main issue here, is that this is exactly where our current symptomatic treatments target, and we talk about Levodopa or dopamine medication, and we are getting more insight about how this system becomes disrupted.

There is more insight now. There is a lot of rhythmic activity in this part of the brain, and in Parkinson's, they seem that they have a lot more rhythmic activity. Basically, the basal ganglia key structures, like subthalamic nucleus, GPi, they become really, really noisy, and therefore you can't really get the information out. Now this is where we think that dopamine actually works, so between the left and right side. The main difference is that we are going to get improvement in this noisy activity in the basal ganglia with Levodopa or dopamine medications, and this is where we think is also the basis for modern surgical therapy based on deep brain stimulation.

So if you look at that thick arrow in the center of the left panel from GPi to thalamus, that's a normal state-- it's a state in Parkinson's where we have a lot of noisy activity, and in the right panel that center arrow is kind of much thinner because this patient has a DBS, the deep brain stimulation, basically modulates that noisy activity, and can allow the normal pattern of movements to be established.

So on the topic of treatment, as it was referred earlier, there is no disease-modifying treatment for Parkinson's. There is research suggesting that regular daily exercise may have some slowing effect, but one distinction of Parkinson's with all of these other neurodegenerative disorders is that we currently have very effective symptomatic treatment for Parkinson's, and that could make a huge difference in the quality of life for these patients. There is also a good push for developing some disease-modifying treatment with a number of targets being recognized and closely looked at. A lot of them look at, again, how the synuclein protein is mis-folded or accumulated.

But going back to what we have available, which is the symptomatic treatment, this is based on primarily dopamine replacement, but now is supplemented also by a number of non-dopamine medication and surgical treatment. So with our three dopamine agonist approved are ropinirole, pramipexole, and rotigotine, there is Levodopa, which is a dopamine substrate, and allow the brain to make its own dopamine. So that's the main distinction, and why Levodopa remains a superior medication. And a number of medication that are adjunct to Levodopa. And among the monoamine oxidase actually be inhibitors, which we have selegiline and research, and then we just had another medication, sulfanomide might approve this week and when are we going to be added to this.

For younger patients, and for Parkinson we consider 65 to 70 as younger, we often advocate to start dopamine, replacement with dopamine agonist. The idea is we may be able to delay some of the complications of Levodopa. However, if there is complication of it's not enough, we don't advocate to delay, because keeping the quality of life is very important. Impulse control disorder, which is about 10% of patients may have this kind of rare but very distinct side effects of it, out of character impulsive behavior that patient develop, including excessive shopping, gambling, hypersexual activity, patients should be warned, and it's those independent. The rest of side effects are similar with dopamine medications.

Levodopa remains the key to treatment of Parkinson's. All patients at some point need to go on that. Levodopa is broken down peripherally, so the use of carbidopa is important to block the peripheral side effects, especially GI and cardiovascular side effects like orthostasis or nausea, and sometimes it's a very common problem that with additional carbidopa supplementation, those side effects can be prevented, and it's one of the reasons patients cannot tolerate Levodopa. There's also target like COMT or MAO, which we target with other medications like rasagiline, entacapone, to increase this synaptic availability of Levodopa.

So this schematic is very simplified, and this is not uniform for everybody. But the idea is you have a honeymoon period, but the Levodopa part is working well, then you have a period of complication, especially motor complication, involuntary movement like dyskinesia, happening. And at the end it makes what's called failure, which is usually not failure of the dopamine medication, but progression of symptoms, like cognitive problem, posture instability, swallowing problem, that does not respond very well to medication. But overall this is a slow disease and we tell patients most of the time the cause of death for patients of Parkinson's something other than Parkinson's. Although to some extent, an advanced stage, things like fall or dysphagia can contribute to morbidity and mortality.

So downside of levodopa is that it doesn't work with certain symptoms. A number of side effects that need to be addressed. The issue of sensitivity to food is very important. Some patients are very sensitive to this. A high protein content in the food can disrupt the absorption of the Levodopa, and therefore they get a very inconsistent benefit from medication, so usually ask them to take medication 30 minutes, 45 minutes before food, and if they are very sensitive, have to even distance it further.

Then patients get to the stage that they may develop sensitivity to Levodopa. That's when we get some major problems in the motor fluctuations with on and off response to medication when they have a good time, and then they don't have a good time. And they may also develop this involuntary movement, dyskinesia, which is not actually dangerous. Many patients don't actually have major problem with it, but the subset, if it's a lot of involuntary movement, and these involuntary movements go away as soon as they don't take their medications. Up to 50% of patients may develop this pattern of motor fluctuation and dyskinesia, so it's not universal.

The high doses of Levodopa, pulsatile exposure to Levodopa, could increase their, accelerate the progression to motor fluctuations, but at the same time, disease progression itself can cause it too. So it's not that you don't treat a patient 10 years because of fear of developing dyskinesia, the next day you put them on medication, that's going to come. And it's a focus of a lot of advanced symptomatic trouble, because right now, we have better tools to control these problems.

So this is a good depiction that, in the beginning of the treatment, the upper panel. The patients, as a result of a dose of Levodopa, they don't get to that dyskinesia threshold. As they come to that middle panel, the duration that the medication works is shorter. And as going to the lowest panel, the duration becomes even shorter, so patients, after two or three hours of taking medication, they turn off. All of their symptoms become severe. As soon as they take medication, it turns on again, and that's become a big difference for patients. But since they crossed the threshold of dyskinesia, they're also going to have that involuntary movements.

So there's a number of strategies, including some of newer medical strategies developed to address this problem. So there are certain common-sense measures that we use, including increasing the dose per administration, the change in dosing frequency, or total number of dosing, adding dopamine agonists, or MAO-B inhibitor, or COMT inhibitor like entacapone, or combined with Sinemet, like Stalevo can be helpful. But there's also a situation where consider use of a longer-acting formulation of Levodopa or surgical treatment can be helpful.

Now a couple of points I want to make at the end. One is that the advanced medical therapy has, we have seen a couple of new products that can help to improve the longer-acting release of the Levodopa. One is this extended-release Levodopa, Rytary. On average, it allows a four-hour sustained level of Levodopa, versus regular Levodopa or even the current CR formulation, which is not having a good pharmacodynamic. So this can translate into, on average, one or two hours good on time being added for patients.

We also now have enteral Levodopa suspension. That is DUOPA, which is based on a surgical treatment, placing an intraduodenal feeding tube, a tube basically. It's a little bit messy to use, though, because these patients have to carry it all the time. They need to change a cartridge every day, and it needs to be stored in a fridge, and for a lot of patients who have a motor and cognitive problem, I mean, you need a good support system to use this system. It can allow them to have a sustained control of Levodopa. For some patients who have a lot of ups and downs and are not a candidate, for example, for surgical therapy, that could be an option.

And then the surgical therapy for Parkinson's, which as I showed, really replicates the effect of Levodopa, initially were based on ablative lesions, but the modern therapies are really based on deep brain stimulation, because in these methods, you don't need to cause a permanent, irreversible lesion. It's based on placement of permanent implanted leads in the brain. But these leads give a stimulation that can be programmed in a clinic, and can always be turned off, and any side effects that comes from these goes away, so you're not going to end up with a lesion in the brain with permanent side effects. And even patients are usually given programmers and a range of limited range that they can change things, so you can actually modulate the response that they get from it. So some of the major benefit from it is you're kind of avoiding high dose of medication, but you can sustain the benefit. For patients who have a lot of ups and downs, it can maintain that good on time on a 24-hour basis.

So who are good candidates? I think this is important because this is the treatment that I think is underutilized when we look at the general population of patients with Parkinson's. It really is not a treatment to think about the most advanced or worst patients of Parkinson's, patients who do not respond to Levodopa. Actually, none of those patients would benefit much. It is actually a treatment that's good for patients in a moderate stage of Parkinson's. They have response to Levodopa, but they have complications from it, or don't get the optimal control, or have a lot of ups and downs. So they should clearly be Parkinson's and on Parkinson's differential diagnosis that I mentioned, like MSA or PSP, that are not good candidates.

The presence of medication side effects other than dyskinesia could be important also. Patients who have hallucinations related to dopamine medication, excessive sedation, and that limits how much dosing they can get, they could be good candidates. And in that, one of the issues, think about what's a good time for treatment. So typically up to 75 patients are considered, and between 75 to 80 is a gray zone that patients can individually be still appropriate if they're, from medical standpoint or cognitive standpoint, they're OK. It can be still offered.

They should have, there should be absence of marked cognitive deficit or unstable mood problem, and cognitive screening is part of a standard protocol, but it's important to recognize. The patient should have mild or expected level of cognitive problems. They will not have any evidence of increased risk from this type of surgery, and that's part of a routine screening. So this is how it looks, and again, this is based on normalization of that noisy transmission.

So mechanism of DBS is not exactly known, but you know there are several mechanism, including normalization of dysrhythmic activity, oscillatory, abnormal activity, that is known. So one of the main points is, patients can go with lower amount of medications. It's also an important consideration that patients who are in their 75, for example, they have a lot of fluctuations. We may manage them for two or three more years with medications, but when these patients get to 80 or 82 years old, they are going to have a lot of problems that are worse, and then you have to cut back the medications.

Now we see that side of patients who are in their 80s, for example. And then you can't do the surgery. You have to cut back medications, because right now they develop psychosis because of high doses of medication, or you have to put them on anti-psychotic with all the risk it has. So these patients, if they're advised at 75, that this options can be looked at, it could be helpful for some of them.

And there is some updates in terms of the FDA criteria. The FDA actually updated their recommendations for clinical criteria for DBS, and they now added, in addition to fluctuations, in addition to refractory tremor, which, independent of any other feature, could respond well, they also added any patients with four years' duration of Parkinson's, DBS, can improve their quality of life independent of their symptoms. This is still not the population that we see typically in the clinic, but it's an important consideration that there is a proven improvement in just general quality of life, even for patients who are not having a lot of these complications.