Parkinson's Treatment: A Journey Through Time Transcript

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Introduction and Guest Background

Welcome to the Parkinson's Solutions Summit 2.0. I'm your host, Dr. Ken Sharlin Coming to you from Ozark, Missouri, at Sharlin Health and Neurology. Today's special guest is Dr. Stanley Fisher.

And I will say first that Dr. Fisher actually was a teacher of mine. And so far as he, at least was, I know he still is the president of the Kansas City Clinical Neurological Society and put on an excellent, excellent educational conference every year, as well as being involved in the Missouri, Kansas City Neurological Society, which helped to, educate me as a neurologist.

So I certainly appreciate that. And I know Dr. Fisher as an excellent teacher and excellent communicator. And let me tell you, folks, if you want to read a CV that will take you a long time, you read Dr. Fisher CV because he's got many, many accomplishments.

He is currently serving as the Vice President and head of Medical Affairs, specialty Pharma Division of Amneal Pharmaceuticals, and they make a particular version of the drug Carbidopa-Levodopa and we are going to be talking all about Carbidopa-Levodopa today.

Of course not just the one that Amneal is responsible for, but the breadth of history of this extremely important drug that is in fact the cornerstone and gold standard in the treatment of Parkinson's disease.

And yet I find and Dr. Fisher, I'll be very interested in hearing your perspective, that truly there's a lot of misunderstanding as well about this drug.

So, Dr. Fisher, thank you so much for being part of the Parkinson's Solutions Summit. And please, take it away. Thank you. Thank you. And I really appreciate that.

And so happy to be a part of this summit and reach to so many people. you know, I'm a movement of neurologist, at heart, and practiced for almost 20 years before I transitioned, to my role in industry.

And drug development. And probably if there is something I really miss from my years, it's, educational part teaching medical students, residence fellows, junior faculty, speaking at symposiums.

Levodopa as Parkinson's Gold Standard

Now, in my role and industry, I'm a bit limited and, where I speak and what I say, even though I found a way to talk about drug development and educate my fellow physicians on the complex, process of drug development that I think is so important for us to understand.

Yes, yes. Well, maybe we'll just dive right into to leave a dopa and you start where it seems right. I always think about to help folks, maybe put a little, pin in the history.

I think about the book by Oliver Sacks called awakenings and the wonderful movie, you know, with Robin Williams and the post and syphilitic parkinsonism.

And I'm sure there's much more, there. But it's a it's a great and sort of romantic, if you will, introduction to the topic of Levodopa So tell us about Levodopa for sure.

For sure. you know, this is probably the most effective, medicine in neurology in the last 100 years. And, you know, probably one of the very few medicines that continue to be a gold standard and cornerstone of treatment of this disease for more than four decades.

You know, some people think TPA was that for, stroke, but, you know, you know, if you look at that, almost 100% of patients with Parkinson's disease at some point in their journey use Lever Dopa that is definitely not the case for stroke that can be given was in very short period of time.

If you look at epileptic drugs and, you know, sanity in, in, Depakote, they was surpassed by other new, medicines and very few of them using today. And that's true for so many lever dopa remains the cornerstone, like you said, and the most effective and the most used Parkinson therapy to this day.

And it's interesting. I, just talked to, head of, and ideas, and, head of, neurological division of FDA. And there is a three lever dopa formulation on the docket for FDA.

This some it's interesting. Right? So now, 50 years later, people still innovating with the lever dopa. because leave a dopa remains the most effective compound we have for the symptomatic treatment of Parkinson's disease.

And even though you often hear people say, well, we do not have disease modifying agents for PD, they all symptomatic. And that's true in a scientific sense.

Maybe. But nobody would argue that levodopa dramatically changed the disease and life of Parkinson's patients. Right. frozen within gears of the diagnosis, unable to function.

Now, majority of Parkinson's patients live, a really productive life. There is no increase in mortality. Yes, there is increase in morbidity. And we're getting closer and closer to make it a treatable, chronic condition.

from the death sentence, it once was like class or other disorders. So definitely from semi scientific point of view, it was, medicine that dramatically modified that disease.

Nobody would argue. And we were so effective at treating motor symptoms that you hear again and again today that non-motor symptoms are more problematic than motor symptoms.

You wouldn't hear that 50 years ago when patients couldn't move. Nobody even talk about non-motor symptoms. It is our success in treating motor symptoms was libido by another compounds that brought other symptoms at the forefront of this, disease.

So that's by itself a tribute to how successful lever adult PA was over the last five decades. Oh, wow. You know, Dr. Fisher, you may know that, of course, I am a board certified neurologist.

I do everything that you would expect from a good neurologist, but I have a more integrative practice, and we're very interested in the role of therapeutic lifestyle medicine as well as systems biology and precision medicine, and what can be drawn from the emerging science to help our patients.

so I, I do attract a lot of folks that are interested in what might be called natural medicine. And they say, well, I'm a little skeptical about taking leave a doe, but I don't want a drug.

I want to be treated with something called naturally. Now I understand where they're coming from. But I say, look, first of all, leave a dopa is very natural.

In fact, your brain makes liver dopa in order to produce dopamine, right? So absolutely. Yeah. Could you tell us a little bit about that biochemistry?

Because I think it's it's super important that people understand that this is something, you know, there's a lot of rage and holistic medicine. I don't know if you're familiar with it about something called peptide therapy.

And, you know, some of it's pretty legitimate. Some of it's a little shady. but at any rate, and I'm not here to pick on peptides. I can't think of something.

short of maybe Vladimir acetate for, you know, M. S., which is still a drug, but it is a chain of, of amino acids. Leave a dopa. We made clear the dope we need. Like, we need food.

We need to leave a dopa. It's rather simple. Amino acid. There's nothing can be more natural than that. Right? So in the 1950s was, Abbott Clausen lab.

They work on the, resorption toxins, in, animals, specifically mice.

Levodopa Biochemistry and Brain Delivery

And they noticed that, damaging dopaminergic system caused, symptoms of parkinsonism in animals. And they suggested that the cause of parkinsonism is the, lack of dopamine as a neurotransmitter. Now, they appropriately decided that giving dopamine, would not work because it wouldn't cross blood brain barrier.

But levodopa being a simple amino acid process, easily broad blood brain barrier. So if you no longer can synthesizes an appropriate amount in the brain, having it as a supplement.

And I would say to people think about it as an oral supplement or in any other form, it is a supplement is amino acid that get absorbed through the gut like any other amino acid.

If anything, we know that although amino acid may interfere with absorption, that's why I would recommend leave it up for an hour before meals, because it send me and I acid and it gets to the brain and we try to get, appropriate amounts there, and it goes into neuron and there like natural levodopa.

It's got, turned into dopamine. Then that gets released in a very natural way. So probably nothing. Probably. This is the only truly natural therapy we have because other truly a designer drug that May Inc, decrease, libido upon metabolism like monoamine oxidase inhibitors, CMT inhibitors, or dopamine agonist, that kind of, a keys to the dopaminergic receptors.

But there is nothing in the brain like this that kind of a fool brain into accepting the stimulation. So those are designer drugs. Leave it a dopa. Is that just a replacement?

What disease steals from us? Right and. Right. it it's so interesting. I mean, this isn't, you know, we could talk about, you know. Well, aspirin. Where does it come from?

The willow, you know, the bark, the willow tree and all that. But it's still, when you take an aspirin, you know, it is modifying your physiology. It's it's blocking platelets.

Your you know, there are, of course, situations where it's entirely appropriate to do so. But on the other hand, in normal, healthy individuals, you don't want to block your platelets, whereas in normal, healthy individuals you need dopamine.

You can function without it. And I think there's a statistic and I'd like folks to hear it from you because that you're the authority and maybe they'll believe you.

But, hopefully of course. So, because I could say it myself. But here's the point. When a person is diagnosed with Parkinson's disease, even at the earliest stage when they're first diagnosed, what are the statistics and how what percentage of dopamine producing cells have already disappeared from the brain?

Yeah. Unfortunately, the diagnosis, today's criteria, which, by the way, being actively revised as we speak and probably one of the hottest topics in Parkinson therapy, redesigning the this UK brain based criteria that has been there for, you know, five decades.

But it that criteria requires motor symptoms. So usually by the time the diagnosis are made, anywhere from 40 to 60% of dopaminergic neurons are gone.

Right? So, and it's really would be effective for us to make the diagnosis early. Now, we don't know what quite yet to do with it because most of our therapy are symptoms.

Matic but, in a future, as new therapy is being developed, early diagnosis based on a biology of a disease will become a key. Yeah, there's quite a lot of things we need to solve before we can truly come up with, therapy and a biology level.

And there's a lot of unanswered question. What's the role of misfolded alpha synuclein is a toxic ways is misfolded alpha synuclein just decrease the amount of normal alpha synuclein?

Is the alpha synuclein apathy? Or if it's a nuclear tenia, that's a raging debate in the community. Every time you go to a debate, experts lined up on both sides.

and it's an exciting time that we can make a diagnosis of, abnormal synuclein before autopsy, either through lumbar puncture and CSF analysis or through, skin biopsy.

That will dramatically change our approach to early disease. But today we diagnose based on a modest symptoms. Today, if we would measure, dopamine transporter activity in the brain utilizing death scan spectroscopy, for example, in most of those patients, we would see an obvious deficit of dopamine transporter indicating the damage to dopaminergic neurons.

Now, we cannot restore today those neurons, but we can increase the production of dopamine in the neuron by simply dying as a supplement. And I like that word.

I never thought about it, but since you said about it as a supplement to produce more dopamine in, existing or saved neurons now and hopefully one day we can make it more continuous release, which would be more, physiological instead of pulsatile, which some people think may be a part of a problem.

instead of supplying continuous, dopaminergic stimulation as we have, we, kind of add a short acting drug to our system. At least we did for more than, for decades.

And the story of developing a libido plays the story, very quickly. People realize that live it Up works phenomenally. God knows all of our sex rather than, George.

God says so in his patients initially and, manganese madness and then in part presentation. But they quickly realized that, too much fluid, get, metabolized peripherally.

And dopamine peripherally causes side effects, especially nausea. It. Is this a brilliant, combination of levodopa and carbon Dopa which peripheral Dopa the carboxylic acid.

you know, that allowed us to block that enzyme and deliver more lever dopa into the brain and have a lot less dopamine outside, causing side effects. And at the time when doctors could name drugs anyway they wanted, they realized as specifically Victor Lotti at, Merck realized that that nausea and vomiting dramatically decreased.

The doctors used to talk Latin and speak Latin, and therefore they say, well, since emesis or without nausea. So he called a drug cinema, right? So now without nausea, that's combination of carb it up.

I leave it up. and later people say, well, can we do even better? Can we block the other enzyme that metabolized levodopa peripherally, which is that or methyl transfer.

Right.

Carbidopa, COMT Inhibitors, and Continuous Delivery

And the CMT inhibition, you know, became another way to deliver more content as dopamine to the brain, for

example, drug, you know, if you combine carb it up, I'll leave a Dopa and CMT in better, thanks to lever was developed that combined specifically was in taco upon you know, as one pill and now we over the years we developed three different CMT inhibitors.

you know, latest generation is a pick up on which is, longer acting. They, they also work on the, another enzyme. So we're constantly working on delivering more lever dope continuously to the brain.

Yeah. Unfortunately, that the same time or very quickly, they realized the short acting nature with potentially problematic as patient progresses. And if you see awakenings, you will see, Robert De Niro character becomes more and more dis kinetic when he takes levodopa.

Right? And people start working on more physiological, longer acting levodopa, both oral and delivered straight into jejunum or delivered subcutaneously.

And that work continues to this day. As I mentioned, there is three products on the docket. Was FDA all centered around long acting extended release or continuous delivery of lever Dopa, which, hopefully will further improve already and excellent chemical.

So we're not changing a chemical, we're just changing a delivery system. I like to say it's still a car, but instead of model T we now have kind of a Ferraris.

We're working on the Ferrari. Maserati. We we have an amazing thing. Can we deliver it better? but molecule itself remains to be unbeaten and still the most effective therapy we have.

So we need lever dopa to make dopamine. And dopamine cannot cross the blood brain barrier. L-dopa can. But a challenge that we have as human beings is that we produce an enzyme in our digestive tract, in the liver.

I believe, called dopa de carboxylate, which very happily will convert that L-dopa that we take into dopamine. And and it of course, we have this gut nervous system, enteric nervous system.

We have dopamine receptors in our digestive tract. And so we stimulate those. Well we get certain results like nausea as you put it, that cavi dopa is really essential in order to deliver dopamine L-dopa to the brain to become dopamine and carbide over by itself, not really being a therapeutic drug.

You you can take carby dopa for very specific reasons, which I'm sure you know, you've done probably many, many times in your career as a doctor. but we give it to patients who need a little extra, when they're taking levodopa, but they don't take it by itself.

And we also talked to folks of, just breaking this down a little bit about Comt inhibition, which is basically it's an enzyme that breaks down dopamine.

So I always tell my patients, look, if we want to fill a sink with water, we have a couple choices. We can either turn the taps on as hard as it can go, and hope that the drain is small enough that it cannot drain the water quick as quickly as the water pours into the sink.

And we want to think of that as leave a dopa. But then if we put a plug in the sink, then we can start to fill that sink with water. So they really are sort of synergistic and they're opportunities for the right patient, for the right person.

Talk to your doctor about blocking some of those enzymes that break down. Leave the dopa. Yeah. No I and this is definitely has been a very successful way to prolong the action of otherwise very short acting compound, which have a often a half life of, 90 minutes and which works beautifully early in the disease.

because, you know, there's still enough neurons in the brain that stores that and convert to dopamine and releases. But as that buffering capacity goes away, the physiological effect from a short acting drug.

So the pharmacodynamic effect started to approach its pharmacokinetic right. So earlier on pharmacokinetics are irrelevant. You give it three times a day. It works.

But as buffering capacity decreases, pharmacodynamic more and more related to pharmacokinetics and that it a lot of people identify as a potential problem.

So giving levodopa continuously through infusions, so long acting oral medications, subcutaneous or straight into the jejunum became the name of the game.

And I hope that one day somebody will come with once a day or to dopa that will, you know, really become a very easy treatment. Now, it is important to understand that, you know, the earlier we initiate that kind of therapy, the probably better patient, is, you know, not to develop those fluctuations and more complications, which include wearing off and dyskinesia that patient develops.

And now there is very difficult to prove what exactly causes it. And there is, of course, a lot of risk factors to developing those motor complications, including sex, weight, age, severity of a disease, onset of a disease.

But overall, there is still this, not fully proven hypothesis that continuous dopaminergic stimulation may be able to deal with those problem. It is not a simple hypothesis to prove a lot of people tried.

We have a limitations of our tools, right. So we are working with tools that are patient diaries. Imagine treating breast cancer. Was the diary asking you how do you feel today?

How did you feel in the last 30 minutes? Right now I say, well, it's not the way to treat cancer. Well, that's as our tool. That number one tool in evaluating Parkinson's drugs is the patient diary.

But they report how they feel every 30 minutes. And it's a binary report. You either say I am or means to my symptoms I control or I'm off. My symptoms are not controlled.

so now no other modern diseases are treated with such a tool. We need a much better tools to develop it. And we're getting there. We're getting there.

Better biomarkers of disease, progression of how to evaluate disease. Except our exam and patient report. It will be very hard to prove scientific concepts.

Yeah, I think I hope and of course, this is just for the summit, but, we're going to be talking to the folks, from Great Lakes Neuroscience about some of their, tracking tools that are being used in clinical trials.

I'm very excited about that interview, for sure. I want to I want some help. for me and for our viewers with, perhaps dispelling a myth. And I'm not sure it's entirely a myth because you've alluded to some potential issues with pulsatile, shorter acting.

Leave a dopa. But I came through training in the 1990s, and, there was a very prevalent theory, referred to as dopamine neurotoxicity.

Motor Fluctuations and Dopamine Neurotoxicity Debate

and really, in my opinion, now sort of looking back on it, perhaps a whole class of drugs was really developed out of that, argument that we should delay the use of lever dope as long as possible.

And now I'm even wondering what role do those those drugs. Dopamine agonists may have a very limited role right now because it seems that this dopamine neurotoxicity theory from a clinical perspective has largely been dispelled.

Can you help me with that? Yeah. So obviously people observed that when you initiate patients that don't pass very

quickly, they develop what we call motor fluctuation.

They it works and then it doesn't work. You take a next dose, take some time. It works. And so we call it motor fluctuation. And then at a peak dose patients would develop abnormal movement called dyskinesia. Right.

So you have a peak those dyskinesia you own you're doing well. You disconnected. Then you're off and you take a pill. You want you then while you disconnect a can you.

And the longer disease lasted, the more and more that happened. And a lot of people felt that that may be due to toxicity. A lot of studies were done to see what happens.

And, there was no study that proved that lever dopa is toxic. You know, again, yes it does. As disease progresses, the, pharmacodynamic resembles pharmacokinetic for a short acting drug, but it's not a to accessory or that and the dopamine agonist were a longer acting drugs were given early.

They did not cause to some degree motor fluctuation and dyskinesia, but they were not as effective in treating symptoms and they have a plethora of side effects.

So they they they may helped especially much younger patients not to have a lot of fluctuation early, but at an expense of less control of symptoms and some side effects.

Now, today, people develop new type of dopamine agonist that would work on a specific receptors affecting motor function without causing significant side effects.

And we will see if that will, change the way we treat. But the idea that we should do, levodopa sparing therapy kind of fell out of favor. And especially with the development of extended release formulations and, better use of the drug as well as development of the medication that block the metabolism of levodopa and maybe inhibitor, CMV inhibitor that prolong the action.

I believe it of all that together made dopamine agonist less desirable. However, there are still patients who do really well, and there are certain symptoms that respond better to dopamine agonist, so they're not completely useless.

But the idea that everybody should be initiated on dopamine agonist in order to delay levodopa went out of favor and no longer consider scientific. Yeah.

And my my personal experience in clinical practice, I still like to occasionally use a little bit of retargeting. I just find that's the, of course, for the viewers, the, patch, it's a dopamine agonist patch, and it allows people to have more or less of a continuous stimulation of, dopamine like compound across the skin.

Those folks are usually still on leave a dopa carby dope. but I do find it's sort of like the rising tide raises all ships. And, you know, it's sort of helps to maintain a certain level of stimulation and maybe have a little less fluctuation even from there.

B don't believe a dopa for sure. And look, not every patient has side effects from dopamine agonist, right. However, again, you know, the some of the side effects, like impulse control problems are a quite significant, cause significant distress in patient and family.

So we got to be careful who we put on those drugs and what are we trying to accomplish? But, by by all means, I truly believe that there are significant role, as long as we do not have that perfect continuous dopaminergic stimulation, which, you know, I believe may, help to alleviate those needs.

We need, all the, weapons we have in our armamentarium. Because every Parkinson patient is unique. There is no two parts, and patients are alike. And we should treat them that way.

You mentioned that. And it's true that we don't yet have a fully FDA approved disease modifying therapy. But there

has for many years when we haven't really talked about this particular enzyme, monoamine oxidase.

As you know, there are a couple of 2 or 3 products out there. three, I think now that, block monoamine oxidase, the other enzyme responsible for metabolizing dopamine, among other neurotransmitters, which what is what makes them a little dicey at times to use.

but my question is we're talking about sledge lane rescheduling, etc.. there has been some literature suggesting these drugs may be protective. So in a sense, disease modifying.

I wonder if you can highlight just a little bit of that. Yeah. So that, that that came from years of when people discovered MPP model. Right. So, you know, you may remember that in the 80s there was an outbreak of sudden onset, advanced Parkinson's among drug users in San Francisco, Bill Langstone and Doctor Tetrault.

well, people who were there and they noticed that the local chemist laced heroin was what became known as MPP. And it, it was the, the, basal ganglia toxin.

Now, that's the most common model today. Now, once we have a model animal model, everybody start using said, what can we give to an animal to prevent Parkinson from that toxin?

so they used everything they have on a shelf. They actually did it alphabetically. Eventually they came to a drug called so Agilent, they tried it. And, if they give syllogism and then gave MPP monkeys wouldn't develop Parkinson.

So they said we have a neuroprotective agent. Well, little did we know that MPP by itself is not that toxic. It's an MPP plus. And to turn MPP into MPP plus, you need to block monoamine oxidase type B inhibitor.

Right. So so in addition. So Agilent blocking them metabolism delivered up I had a symptomatic effect. So multiple studies were done and none of them were truly conclusive.

They were neither protective. But then symptomatic effect. How do you separate symptomatic effect from protection that had a washout. But how long can you keep some.

All the Dopa. so the washouts were limited by nature, so nothing was proven. And then Teva was developing rescheduling and they did it in multiple models, including MPP and others.

And again, it shows that it may decrease the damage done from the chemical they tried at multiple times. They had some success in early studies, but, and a lot of us believe that it's doing something of that sort in addition to symptomatic benefit.

MAO-B Inhibitors and Disease Modification Questions

The study called a Dodger, you know, had two dose, one milligram reached every end point, two milligrams didn't agency did not agree with us that it's disease modifying.

And, up to this day, we did not prove convincingly that it is and really cannot make that claim. and it may be worth thinking about, perhaps for some folks, maybe the younger the early onset young onset mild, very mild symptoms. Yes.

You have Parkinson's. do you need a drug right now? You, you know, function at a very high level. you know, making sure. I mean, it's a once a day drug.

It has very few side effects. And in the early study, side effects were similar to placebo. It does have symptomatic benefit because you still have your own, dopamine.

Right. So, that definitely should be considered. Most patients, need more than that. Or if they do well on maybe inhibitor for a short period of time.

But it we know that maybe inhibitors work synergistically with dopamine agonist. We proved that in a study as well as Levi dopa. Right. So definitely should be one of the drugs that we should consider, both for naive patients as an add on therapy for some patients.

Now, more and more, we are seeing the integration of biotechnology into the management of Parkinson's. We talked a little bit about delivery systems delivering leave a dopa right into the digestive tract, into the jejunum.

and there has for many years now been the availability of deep brain stimulation, the ability to, put a wire, into a specific region of the brain. and I wonder and by the way, when I was in training, and and rea what was my was at Emory.

he, of course, later became the, I think the president of University of Alabama, so went a long way. But anyway, he, they were, they were just doing, pallet armies and things like that even before the DBS.

But, I wonder because I think folks will, you know, have questions about DBS. where do you see it fitting into the toolbox? And what what do people get?

what what could someone expect from. Right, right. As you mentioning, Emory program, at that time was probably one of the best training programs, in the country.

And partly due to this brilliant scientist, Mellon DeLong. But just recently passed. And I would like to give a tribute to the man who contributed so much, to all understanding of the physiology of Parkinson's disease, anatomy of basal ganglia, and role of deep brain stimulation in treating, symptoms.

So, no, I mean, DBS, was, in the 90s was one of those revolutionary therapies that really helped us to deal with advanced patients who developed, who continue to respond to live a Dopa, which is still a requirement for the treatment but fluctuate it significantly.

And remember that time the short acting levodopa was the only leave it up available over the time we now have. Like you said, the direct delivery to jejunum wherever extended release oral medication.

And we have two subcutaneous medications on a doc and in front of FDA so that it really change changing our paradigm. But DBS remains a significant and important therapy for those patients who fluctuate and have significant dyskinesia.

It would allow to. So what it does, it will allow you to have the best response you can have from the Dopa, but for longer duration of the time and hopefully without the complications of dyskinesia.

So DBS does not do better than leave a dopa you. Except maybe if your main symptom is tremor. DBS is still the best treatment for Parkinsonian tremor, but for other symptoms.

Rigidity, bradykinin what you can expect that you will be as good as your best, both for much longer time and hopefully without dyskinesia. And we now have more than two decades of data that DBS continues to act, and we can adjust and technology advance dramatically.

And we have now multiple devices made by multiple companies. We have a visualization of where we stimulate. We can guide current away from problematic area.

We can visualize it in real time. surgery can be now done asleep.

Deep Brain Stimulation and Future Therapies

the imaging. So patient wouldn't have to be awake during surgery. there's still debate of, it's as good as, electrode monitoring, but, you know, more and more younger surgeons do it.

And result seems to be, at least as good as, and so the technology also we improved with sensing technology. We're now debating should we continue to stimulate the brain or should it be in response, kind of like we measure, oh, now we need to do a little stimulation.

Are we stimulating all the time? Only when needed. So lot of things are changing. Technology advancing. the surgery become easier, the electrodes become much better.

And I think all that will contribute. I hope to see one day that we will have the really, really easy to use, long acting, preferably oral, the dopa that, and then patients would take it for the duration of a disease.

That's kind of my hope. And that's what I would like to see in my lifetime. And then the subgroup of people will later need, DBS surgery. that was done quickly.

Image guidance was a tiny electrodes, very small battery that last a lifetime, not requiring secondary surgery and can be visualized so, can be programed from the distance, which, by the way, we already can, especially for people with tremor, dominant disease.

and then the only challenge will remain, we address this multiple non-motor symptoms and, treatment of motor symptoms will be easy thing that, people can do quite well for the duration of a disease.

I think we will see it in our lifetime. That's my believe. You know, and I have to admit, that's where I've been a little bit skeptical. I think the FDA just gave clearance for, an advancement in clinical trial stage to accompany implanting, stem cells, into the, I believe, into the region substantia nigra to replace dopaminergic cells back in the days of memory.

And they don't do this anymore. Of course. they were doing, embryonic stem cells. But my point is that may address a piece of the puzzle, but it doesn't really address the programed cell death.

Why are we losing these cells? Because if we implant viable cells, what's going to happen to them? And then, of course, it doesn't address any of the non-motor symptoms as well.

So it's probably going to have to have a multi multimodal approach maybe. I mean, you know, if you talk to the people who develop Stem cells, they believe that early replacement of dopamine cell may delay the onset of complications, including some non-motor complications, remains to be seen.

they obviously trying to go beyond constant dopamine replacement. They also think that one time replacement of cells may, obviate the need for continuous stimulation.

You know, deep brain stimulation. Not without problem. It is a surgery. It can cause side effects. You're not always hit the goal, right? Right. you know, stimulating some areas can cause side effects.

So it's not completely without issues. And, you know, it requires continuous adjustment. It requires new batteries. It's a device. There's a risk of infection.

So they hope that one time delivery of cells, may solve it and will continue to control symptoms for much longer time without the need of constant medication that disrupt your life.

That's a very interesting idea. I think it's deserved to be tried. like you, I'm a bit skeptical of previous attempts. And that up if either failure or in disaster.

but, we learned a lot from it, and I definitely think that we should continue to study that and see what we can achieve. Was the replacement of dopaminergic therapy straight into the brain.

So, I'm skeptical, but I also like to see what happens. And there are more and more people, looking for a gene therapy, as well, both surgical and non-surgical, that we also look to see if we can have a precision medicine.

Do we do a genetic analysis and treat each type of parkinsonism separately? You know, there's like two mutation therapies for that. And GBA mutation and there's therapy for that.

I believe in a future we may have a very different approach to a hundred different diseases that cause parkinsonism. It may not be 1 or 2 or even 50 diseases, maybe 100 different diseases, and each one will have a very some will have gene therapy, some will have cell therapy, some will have straighter DBS, some will have their, medication.

we definitely try not to that direction. Levodopa Still works for every type of parkinsonism. at least primary, parkinsonism. So that makes, very difficult to come up with.

Therapy that beats Levodopa which what has to happen. Right. but I think we need to continue to develop that precision medicine that, revolutionized oncology and bring it to, Parkinson's disease as well.

Well, that's that's amazing. Dr. Stanley Fisher, thank you so much for teaching all of us. you've been an amazing mentor and teacher for so many neurologists.

So many medical students. And it's truly an honor to have you on the Parkinson's Solutions Summit. So I really, really do appreciate it. Thank you. It was a pleasure to be there.

and any time I'm I'm looking forward to working with you in the future. Thank you.