Introduction and Speaker Background

Hello, everyone, and welcome to the Parkinson's Solution Summit 2.0. I'm your co-host, Dr. Barbara Pickut. Today I have the pleasure of speaking with Dr. Peter LeWitt Peter, welcome.

Thank you for joining us. Thank you, Barbara, for the invitation to be part of this. as you can see, I have a few bandages here. I had my session with the surgeon, to deal with all those, remnants of my long life of exposure to the sun.

Doesn't hurt. I'm glad to keep talking here. And, don't worry about the bandages. They just are there for show. Barbara invited me. thanks to the fact that I've been involved in Parkinson's, care and research for many years.

And I am glad that we have the chance to have this discussion about topics near and dear to me. I'm based here in, southeastern Michigan. I work at Henry Ford Hospital, West Bloomfield, as well as the Detroit Medical Center, and Wayne State University School of Medicine, where I have a position as a Sastry Foundation endowed chair in neurology.

I've been involved in clinical research ever since my training ended. And, in the course of this discussion, we'll have a chance to go over what's new in research.

What, promises we have for arresting the disease or getting better symptomatic treatment for the problems of it. And I'm sure we'll have a chance to, go over many different topics here.

I wish we could be talking to the audience directly, but I understand there's a lot of you out there. Yes, indeed. Thank you. Peter, a broad range of topics.

let me get us started with, things that that maybe people, could be applying. So we have this phenomenon sometimes in Parkinson's called freezing of gait.

And can you give share your perspective with us? on phrasing of gait in Parkinson's and maybe some strategies that people can use to, to help mitigate that?

Sure. So freezing is not the same thing as being under medicated. In fact, many patients have the phenomenon of their feet locking in place. occurring even when their medication is at full tilt in them.

In other words, the freezing might be an episode for a few seconds, prior to which the patient was fully mobile. Or you, the patient had no tremor or any other symptoms, but all of a sudden the feet are just not moving and it can be very situation specific.

Freezing of Gait and Coping Strategies

For example, occurring when starting out, when making a turn, when coming to a doorway, when walking in a crowd of other people, when doing two things simultaneously, like holding a conversation and walking, and why the the feet shut down and will not move momentarily, or sometimes for ten to 30s is really not well known.

It's obviously coming from the brain. It's not don't blame your feet. But this phenomenon, which is particularly common after five or more years of having Parkinson's, is a real problem because it's unpredictable.

It can lead to stumbling or even falls. It can limit somebody in terms of feeling mobile or safe in the world. And it certainly is very stigmatizing where it comes from the brain, or if all kinds of freezing of gait are the same, is a matter of great study.

There is an international group of which I'm a member, which has been studying the phenomenon and trying to get, a framework down to at least, use a uniform rating scale.

And we've had meetings on that topic, and we'll continue to do so. In addition, there's some promising ideas for freezing of gait, such as, reprograming the pattern of the way somebody walks.

And this has culminated in, a physical therapy program called LSVT big. The LSVT stands for Lee Silverman Voice Training, a program that also, has, skills to help train, the reinvigoration of the Parkinson disease voice.

But in this case, the LSVT big is a program trying to overcome using tricks that people have found to be helpful to keep the seat moving when a freeze occurs.

And these, techniques, are sometimes very successful. It can include strategies such as having a target, a light beam, or other cues such as a metronome to keep you walking.

But all of this is is sort of dancing around the fact that we don't really know where in the brain this comes from. We don't know why everybody with Parkinson's doesn't get it, or why those who have it, it just won't go away.

Despite it being such a nuisance and a disability, there have been some medication trials. I carried out one of them with a, drug that actually is on the market in Japan and also in the United States for freezing of gait, but it just doesn't work.

We our trial was, terminated only because we were not finding any responders. And yet there may be a pharmacology relevant to helping with freezing. in my experience as a, center where deep brain stimulation has been carried out, a certain number of patients, and this has been reported in the medical literature as well, with freezing of gait, have improved, although it isn't as effective that we would recommend someone freezing of gait for that reason alone to go on to have EBS.

So those are that sort of a background on it. What other things would you think we should talk about? Barbara. so that's that. I think we can round that off and I'll ask another question.

So it's, so it's a queuing strategies that we're still offering people. And my thought is oftentimes I've heard people what they experience is when there's a narrowing of space or a heightened, physiological, soup because of circumstances.

So if someone is more nervous or there is a physical narrowing of space. And so of course, in my mind I'm thinking, well, you know, these are thoughts, can we interpret them differently?

So have there been any cognitive, interventions for freezing of gait? There have been a few. And it's a very important topic you brought up because, it may be that freezing is sort of a protective strategy.

it's curious that a lot of people have freezing at a doorway or hurrying to get onto an elevator. You know, the threat is as you walk out of the doorway, someone might bump into you.

Or if walking in a group of people, the trajectory of someone walking could could, bump into you and perhaps your brain is protecting you. That's sort of my interpretation of some of the phenomena, because on an open, passageway with with no obstacles out there, the freezing may be much less likely to happen than going through a crowded space.

In fact, in our clinical trial, we created, cardboard box obstacle to bring on it. Also, we found that we could trigger freezing by having someone doing a mental exercise, such as naming animals that have tails or doing some mental calculation.

So there, that clearly is something about engaging the brain, distracting, the, the walking phenomenon, in some instances. But not everyone has the same problems.

And there have been some curious ways to help against it. For example, marching in place, talking to your feet, right, left, right, left, taking one step at a time, rather than the sort of semi automatic activity of walking.

some people have found to that relaxation techniques have worked, but but nothing works perfectly yet for everybody. Fortunately, the LSVT, big program does try to, bring together all of the known strategies of sensory tricks and and changing the tasks such that freezing might be less likely to happen.

And, maybe one of these days we're going to figure it out from a patient telling us what it's all about. Yeah, okay. We look forward to that. Yeah. Very good.

I'm curious about any updates on disease modifying strategies or a. Well, it's a very active industry going on both at the academic level and, the pharmaceutical industry and other consortia such as the Parkinson's Study Group in North America and other international groups that have seized upon ideas.

Basically, we don't know what causes Parkinson's disease, but we have a lot of clues. We know that there's an abnormal accumulation of aggregated, misfolded protein called alpha synuclein.

Alpha synuclein. It has to be there. It's there all over our bodies. But in there's nerve cells in the brain. it seems to be a final common pathway for damage to nerve cells.

Why they gradually die in the regions of the brain that have to do with movement, and to some extent, even the thinking process. so preventing that aggregation from happening, is an obvious target, one that we can model in animals, one that we can show targeted engagement by giving a drug or some other therapy to try and block that.

And currently there are several studies ongoing which are using the immune system in an effort to, grab on to abnormal, alpha synuclein protein so that it doesn't go on to spread into other nerve cells that are healthy.

And this idea has, good support from animal research. the clinical trials that are ongoing have been going on for several years using what are called monoclonal antibodies.

These are engineered, immune modulators that, can be safely given to somebody. Many of our therapies for arthritis and, and, psoriasis and so on are monoclonal antibodies that are routinely used in other aspects of medicine.

And the current clinical trials that are ongoing haven't reached their conclusions yet. They're going on for several years. But, the one that's going on, supported by Roche and Genentech, so far has put out some public statements suggesting that it may be doing the right thing of slowing down disease progression.

Now, that's that's the challenge. By the time Parkinson's is diagnosed, it's already relatively advanced in the nerve cells of the brain. by the time the symptoms are there, more than 50% of the population of nerve cells that make dopamine and and have to do with the symptoms of Parkinson's have already been lost.

Disease Modification and Research Directions

So getting an earlier view of it by a biomarker or some other technique certainly would be nice to have. And so at the same time as therapies are being developed, the industry of developing biomarkers, has been growing worldwide, in a cooperative manner.

But back to some other things about neuro protection. there's also a group of compounds that are being tested that may decrease the propensity of alpha synuclein molecules to misfolded, to aggregate, to damage cells.

So besides using the immune system, there may be a particular chemical that sort of can coat the synuclein protein and protect it a little bit better from the environment tool or endogenous metabolic pathways that cause it to be damaging.

And there are other ideas out there. There have been many therapies that have been tested out more than 30 neuro protection strategies over the years, ranging from antioxidants, drugs that enhance mitochondrial function that will, powerhouses of nerve cells.

Other strategies that have been tested include the drug selection and rescheduling mob inhibitors. These are drugs that slow down the breakdown of dopamine.

And they also have the antioxidant properties. We don't know exactly how these drugs fully work. And to date, although these drugs are marketed and sometimes thought by clinicians to be effective protective agents, they really aren't.

Parkinson's tends to progress even of taking these medicines. So, the Michael J. Fox Foundation, and other national and international websites give a very good background on current therapies that are going on that are being supported by these foundations, in part.

And I think the important message for the audience is that, Parkinson's is actively being researched with a variety of ideas that have come from many different directions.

I'll give you a clue as to where the thinking goes. If you find a group of patients with Parkinson's who have something different in their lifestyle and their environmental exposures and their diet, something like that, well, there's a clue for a therapeutic trial.

And one of them was a finding that people who have elevated levels of uric acid in their blood seem to have a much lower risk of Parkinson's and much slower progression.

This is actually some work that I had done many years ago and part of our biomarker studies. And with this information, a clinical trial was set up by the Parkinson's Study Group, which intentionally increased uric acid levels, which is a natural metabolite of certain chemicals that come in in our diet, such as caffeine, for example, we intentionally increased uric acid.

And in one group of the patients in the study, and then it was a placebo group as well, the idea being that perhaps we could simulate nature's experiment, that people who have naturally occurring elevated levels might have less progression over a period of time.

And although uric acid can trigger gout and kidney stones, the amount given was was judged to be in a safe realm. And indeed there were very few episodes of that.

Unfortunately, this study didn't give positive results. Probably the biggest reason is that it's a two year study, and Parkinson's disease may take decades to slowly evolve or protective effect from something like this may take much longer period of time than, well that we can devote to a study.

So the signal didn't come back that this was working, but it's still interesting information. And another interesting, observation in the general population is that people who are smokers decrease their risk by a substantial amount, up to 50%.

And this has been borne out in more than 50 studies over the years. So what's that all about? But smoking but in a way of delivering nicotine. And so for many years it was thought to be nicotine is protective.

But more recently, some researchers at the Mass General Hospital have been investigating another consequence of smoking, which is low dose chronic exposure to carbon monoxide.

Now, that doesn't sound like a great idea to think of carbon monoxide as a therapeutic agent, but based on some preclinical experiments in the laboratory, some pretty interesting evidence has arisen that a low level one that won't kill you, of carbon monoxide in your bloodstream and perhaps throughout your body could in fact, turn on various biochemical mechanisms that protect your nerve cells against, degeneration.

And based on that, a safe liquid form of dissolved carbon monoxide that that clearly is at the level of what a smoker gets, is now about to be tested.

So that's another example of how epidemiology, seeing what's going on in a population who gets a disorder and who doesn't can sometimes translate into a therapeutic intervention.

And there are many other examples of where research is going. I think, we could spend a few hours covering all bases, but, it's certainly grounds to be optimistic.

Unlike so many other disorders, there are many clues about Parkinson's disease that that should make you optimistic that one of these days, the scientific community or the pharmaceutical industry, or just some bolt of lightning of insight will will lead to the therapy that will make a big difference.

Very good. Thank you. That's very interesting. Yeah. The epidemiological studies are fascinating in Parkinson's and have been going on for for many, many years. So, we're certainly not recommending smoking or exposure to carbon monoxide, but, we'll wait for the liquid form in clinical trial. Yes.

So speaking of clinical trials, are there certain trials that you're very excited about? Things are and that are in the pipeline close to or, in the next?

Well, I'll tell you, as a researcher, I both enthusiastic about research and I encourage all people to look into the possibility that they could participate in a clinical trial.

It's it's a satisfying experience, in part because you're not only potentially helping yourself, but other people as well. I also try to remain sort of, neutral in terms of enthusiasm for a particular study, because I really don't know if if we knew the answer, we wouldn't be doing research on people.

there is no perfect animal model of of Parkinson's disease. So we have to experiment with the patient population. And there is no uniform kind of Parkinson's.

Some, forms of Parkinson's probably are driven by genetic factors. Certain mutations are well known to cause pretty rare forms of Parkinson's disease.

But the average person doesn't have these gene mutations. So it may be that, for certain people who have it, a targeted therapy working on the gene mutation and trying to correct the biochemistry of that problem will be the therapy of the future, whereas for the next person doesn't have that problem, a different therapy might need it.

In short, there may be many forms, many diseases that are lumped together right now as Parkinson's disease, but actually will turn out to be some variants or, versions that have their own specific therapeutics.

Understood. Yeah. Very interesting. leave it. Dopa remains the mainstay of our in our therapeutic, toolbox. any updates there as to, how to augment the delivery of, leave a dopa into the body safely?

Yes. Well, various, you know, there's a number of delivery systems that have been developed in recent years. There's an inhaled form of the Dopa as sort of a rapid on demand rescue therapy.

There's, leave a dopa and more sustained release forms. And, in fact, just last week, a new form of sustained release, Cavi don't believe a dopa. The combination pill that, used to be marketed as a brand name product sentiment, but is now more or less a generic product for the vast majority of people who use it.

So that's called immediate release. That goes to work within 20 or 30 minutes and usually is out of the bloodstream within three hours. And it's clinical effects can also wear off on that very short time scale, requiring patients to take it frequently during the day to get a consistent effect.

The long acting forms, right, tarry and then the one correction I believe it's it's name. Our branded products, they,

are longer acting.

Levodopa Delivery and Continuous Therapies

They have a higher price tag on them and maybe a higher copay for, those who have partial payment of their prescription plans, but, they can help. There are other ways to extend the duration of action of, leave it open.

Such as, inhibitors of a particular enzyme called Comt or another enzyme called Mob. But in general, a lot of people who are taking leave it open chronically are experiencing dose by dose fluctuations, irregularity in uptake of medication, sort of a chaotic roller coaster experience of taking this drug, which is so effective, which is the platinum standard of therapeutics, which is nature's way of making dopamine.

By the way, sometimes when we prescribe the drug and someone tells me that they don't want to be on a medication, I tell them that this is already in their body, that they've been making dopamine with their only the Dopa for many years, and this is just a way to help the process and leave it open, by the way, is present in our diet in small amounts, so it's even a natural substance.

If you need further ammunition, why you should take it there's no evidence that's accrued over the years that you should hold off on the use of lead, the Dopa, nor, really strong evidence that you should even necessarily keep the dose lower than what gives a patient maximal benefit.

Recently, though, some, some new developments have occurred in the delivery process, namely putting, carby don't believe a dopa in a soluble ized liquid form under the skin in a continuous pumping system that, is very similar to the way that some people take insulin for diabetes.

These many pumps, have been under testing for many years now, and they're very close, I think, to being marketed. There are two products that have been studied in the United States and elsewhere.

In at least one of them, I predict, will be on the market, with FDA approval in the next year or so. Another drug that similar in action, of course, is apomorphine, the drug that's been used around the world in similar fashion, subcutaneously, administered through a mini pump.

And that, too, is under review by the FDA for release, in the US. So we're going to have some new options for more continuous delivery, adjusting the effects of the drug to minimize motor fluctuation, minimize involuntary movements, and give a patient much more control of their optimal dosing.

Yeah, thank you for that. Would then suggest that people contact their, their, movement disorder specialist or their primary care provider to discuss, some of the things you've brought up today.

Peter, thank you so much for your time. I we're freezing up. Are we? I'm not. We froze up. Yeah. Did you hear me? Yes. Chad. Thank you for your time. Theater.

Thank you for that. Yeah. So you were sitting there? I thought you were, I thought the screen was frozen and on my end. Yeah, yeah. So we're we're good.

Is there anything else you wanted to add? I think I think it's a take. I think that, it's very helpful for people to hear. Well, I think I talked fast enough to get it all in there.

let me think. What else would be. you know that the, the, subcutaneous is on the market in Europe already. I have a patient that I used to follow there who has it.

you. Know, it's the AbbVie product, and unfortunately, it's it's not looking so good for getting to the US. It the third time, it was rejected by the FDA for not so much.

chemical. Well, I think it made. By, wasn't it something with the pump. Yeah. And, and yet the manufacturing

process of it was the reason for the problems in the past.

So in neuro derm, the other company is getting, close, I think, to approval. Although that's not public information. Okay. There's also, you know, morphine literally could be available tomorrow or next week or next month because, you know, there really weren't any major concerns that the FDA rose with, okay, rate rose about that.

And of course, it's a drug that Europeans. And that's a topic of great interest not only in Parkinson's disease but throughout medicine, because so many disorders have to do with a gene mutation or an absence of something that could be a protective factor that the body could be making.

These are some examples of where gene modification, either up regulating or blocking the effects of genes, could be a therapeutic value in Parkinson's disease.

Has had a number of, investigations so far over the past 15 years in which essentially disease modifying therapies as well as symptomatic therapies have been looked at.

one that I'm currently involved in is looking at whether we can create a transformation of the nerve cells in the circuitry of the brain in Parkinson's to better deal with the kinds of problems like freezing of gates and dyskinesias and tremors and so on, just by increasing a chemical called, Gaba or glutamic acid.

butyrate. And. Isn't that right? I'm sorry. Froze up on that thing. Yes, Gaba we'll leave it at that. Okay. And that study actually had positive results.

The publication, showed that it had results comparable to those achieved by deep brain stimulation, and expectedly so, because that target zone where, this transformation of turning glutamate into Gaba, that was the biochemical transformation, actually simulates what deep brain stimulation does by putting in electrical wire and electrical stimulation into that circuit of the brain.

So this study is being replicated currently, around the United States, and we hope that there will be good results from that. Gene therapy has also been looked at as a way to put trophic factors.

These are chemicals that encourage nerve cells to stay healthy, almost, like, fertilizer in the soil for your plants. And GDF is the abbreviation for glial derived neurotrophic factor.

This has been studied in the past, in a, trial where the gene was actually placed in the area of the brain where nerve cells are lost, the study wasn't reported out as being positive, but there's a lot of interest in to coming back to, again, trying this out, perhaps in different target zones, perhaps creating more of the GDNF product to improve the kind of effect that might occur.

Because in animal models of this disorder, it works beautifully. why not in people? Well, sometimes you have to repeat experiments, modify them, give a little bit more.

So keep your eye on that. And then finally we talked a little bit about something analogous, which is stem cell therapy. And there's great excitement in, the medical community in general for what stem cells can do.

They can turn into organs or cellular elements or, functional units of circuits in the brain to restore what's missing, what's been lost by neurodegeneration or normal aging or active disease process.

In the case of Parkinson's, this has not been successfully carried out. Years ago, cell based therapies use fetal tissue, which transformed into adult, dopamine generating cells.

Clinical Trials, Gene Therapy, and Stem Cells

And in a few patients, remarkably effective outcomes were reported, but not for everybody. There were huge risks with this. There were even ethical issues raised for using human fetal tissue for transplantation purposes.

But, in the revolution that accompanied the development of of stem cell science, it's now well recognized that one can take their own stem cells from a, biopsy of your skin, for example, and turn them into the precursors of nerve cells.

And so it may well be that in the future, Parkinson's disease and possibly other neurological disorders like Alzheimer's disease can be helped by putting in one's own cells transformed into nerve cells, and then take over functions that have been lost as a neurological disease like Parkinson's develops.

And currently there are some early phase studies that are investigating the possibilities of this. It's not without risks. Stem cells can do miraculous things.

so the optimists say, but they also can turn into tumors and to transplant something into the brain, is not a minor issue. It carries its own risks. So, I hope it's a small chemical that can fit in a pill that you can take every day and have no side effects from.

That will be the secret of how to get, protection of your nerve cells rather than to have to go to a surgical procedure. Right. Very fascinating. one last question.

if people are not in our geographic area, Michigan, how where would could we advise them to go if they're interested in being in a clinical trial? Are there websites, are there foundations?

Yeah. Excuse me? Well, the Michael J. Fox Foundation, certainly, publishes a lot of information about ongoing clinical trials. And, and there are other sources of information, as well.

the Fox Finder is a website that's run by the Michael J. Fox Foundation so that somebody could register their interest and some background about their experience with Parkinson's, so that a site like ours doing a clinical trial could get in touch.

And, possibly describe and arrange for consultation in order to consider participating in the studies we have and our region here in Michigan, people coming from far away to participate in certain studies, even crossing the border from Canada, which is perfectly legal, by the way, to be in a clinical trial.

it's nice to keep up with us, because not all centers around the United States or Canada have ongoing clinical trials. Sometimes a trial comes and goes based on, the whims of the pharmaceutical industry or how enrollment is going.

So it's it's something to keep up with quite actively if you have a, a mind then to want to be part of research and, it can be a very gratifying experience.

Even people who've been on placebo arms of treatment often walk away from a clinical trial feeling like they've made a useful contribution. And for research to proceed.

By the way, all, clinical trials need to have a placebo arm. But many of them, after their placebo arm is finished in a blinded way, can actively participate in the experimental drugs. So, many of the studies will be very satisfying to those who want to be on the active treatment and not just the sugar pill.

Okay, no doubt on it. Peter, thank you very much for your generous time and all the information you shared with us today. Thank you. It's great pleasure to be invited back.

Thank you, Barbara, for running this series. And, please drop in, some other time. I love to talk about anything else that's new. Thank you.