What are the most pressing challenges in Parkinson's disease and movement disorders? How are scientists addressing them? What lies ahead?

In conversation with... Leo Verhagen Metman

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Dr. Randolph: Tell us little about your background and how you got interested in neurology, and Parkinson's and movement disorders in particular.

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Dr. Verhagen Metman: Sure, I'd be happy to. I studied in the Netherlands at the University of Leiden. And when I was done with that, I was not sure what my path was going to be, so I went to the United States and worked in the Artificial Heart Lab, under Dr. Willem Kolff, who had just implanted the first plastic heart a human. Those were exciting times.

I realized that being a heart surgeon was not going to be for me, so I went to Baylor and landed in neurophysiology research, which I really liked. Then I decided to do neurology and ultimately realized that I wanted to specialize in movement disorders. And one of the reasons was I was fascinated by the phenomenology. You make a diagnosis based on what you see without having to do much else. Maybe that means I'm a little lazy, but I was fascinated by that, just looking at the patient, talking to the patient, and figuring out what they have.

And then, also, the fact that there were already very effective treatments at that time, both medically and surgically. I did a fellowship in movement disorders at the Experimental Therapeutics branch at the NIH, where I studied on a two-year fellowship and then stayed on for another five years as a visiting scientist. And what we did there was mostly early-phase trials in Parkinson's, focusing especially on mobile fluctuations and dyskinesia. And that was also the basis for the thesis I completed to obtain my PhD from the University of Leiden in 2002.

By then, I was already working in Chicago at Rush, which I believe was one of the first movement disorder centers in the United States. It continues to be one of the country's largest clinical research centers for movement disorders. Here at Rush, I've continued to be involved in numerous trials, both pharmacological and surgical, and both early and later phases of the studies.

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Leo Verhagen Metman, *a member of WCG's Scientific Leadership Team, shared his insights during a recent conversation with Christopher Randolph, PhD, ABPP-CN, Chief Scientific Officer, WCG MedAvante-ProPhase. Dr. Verhagen is professor of neurology at Rush University Medical Center in Chicago.*

The interview has been edited for clarity and length.

To this day, I continue to be driven by the fact that we can, on the one hand, already do so much for a patient–such as biopsychosocial and trans-therapies–but, on the other hand, that we continue to learn on a daily basis. I think it will ultimately lead to better therapies–therapies that are not just symptomatic, but also change the course of the disease, ultimately leading to a cure.

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Dr. Randolph: That leads me to my next question. Could you talk a little bit about how treatment options and treatment approaches have evolved over the last 25 years or so, including deep brain stimulation and other surgical interventions?

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Dr. Verhagen Metman: It's kind of interesting to know that the most effective drug is still levodopa, the dopamine precursor, which really came to market in 1967. And since that time, many drugs have come and some have gone, but they lack the impact of levodopa. The only medication that is currently available for levodopa-induced dyskinesia (one of the side-effects of this wonderful levodopa drug) is amantadine; it also came out in 1967. So maybe not as much has been accomplished as one might think, but I think the times are changing. At this very moment, there are multiple trials that are very interesting and have different approaches to try to stimulate dopamine receptors.

As far as surgery is concerned, the '50s introduced surgery for Parkinson's disease in the form of lesional therapies: Probes were stuck in the brain and the tip of the probe was heated up, or a radio-frequency lesion was made, to destroy the small part of the tissue; this could lead to very good results. For instance, it's well known that Michael J. Fox had a lesion to control the tremor early in his career, before anybody knew he had Parkinson's disease.

We've moved away from lesional therapies: In 1987, for the first time, it was published that you could actually, instead of making a lesion, go to the same area with the probe and leave a continuously stimulating deep-brain stimulation electrode in the brain, safely, and continue to stimulate the brain to control the tremor. Since then, deep-brain simulation technology has dramatically improved; today it's a standard treatment–mostly for patients treated with levodopa who developed motor fluctuations and dyskinesias.

I think the future of this whole surgery part is also continuing to look brighter and brighter with newer equipment and newer methodologies.

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Dr. Randolph: Moving into the clinical trial landscape, you mentioned Rush is well known as a very prominent movement-disorders center, and home of the Movement Disorder Society, controlling a lot of clinical trials research in terms of managing and developing scales and endpoints. So as an active clinical trial site, what kinds of challenges to you run into in recruiting subjects with Parkinson's Disease for different types of studies?

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Dr. Verhagen Metman: I think we could talk about this for a long time because there are so many issues. It probably depends a little bit on the type of study you're doing, but overall, recruitment is always an issue. And even though this is what we do, and we are well-skilled in asking our patients to participate, they're not always willing to. And there could be very mundane reasons. For example, traveling frequently to the site is a problem for mostly all our patients. Especially when you live in a city like Chicago with its awful traffic.

So very mundane reasons may prohibit them from participating. One of the things that's frequently heard is that they're not willing to take a chance of having a placebo. Being in a placebo arm is not what they want. Fortunately, there are some studies that either have an active comparator or have a very small chance of the placebo arm presentation. A lot of studies now require some hospital stays or staying in the clinical research center for long periods of time. That's very difficult for patients.

I also think staffing issues for each site is a big problem. There's a tremendous turnover in for coordinators, and each time you have to train staff again. I think there's some work to do for all of us to improve that. The same thing applies to the CROs' ever-changing staff. During one study, you probably have five people who replace each other in rapid succession. That often leads to ineffective communication, making the studies longer. I think that the whole process should be a lot smoother.

In terms of disease-modifying versus symptomatic therapies, my experience thus far is that recruitment is very easy. Many patients are interested in signing up for a study that actually changes, or potentially changes, the course of their disease, as opposed to testing a medication that may be just as good as one already on the market. So, I think the interest is high, even if there are certain things involved—biomarkers we want to test, there will be spinal taps involved, and other more complicated tests. I think they're willing to do that, as long as there's a chance that they actually will be able to change the course of the disease that's otherwise inevitably leading to deterioration over time.

In terms of dyskinesia trials, it's hard to take them off a drug that is effective—amantadine—to enroll them in a study of another anti-dyskinesia agent. If there's an effective treatment, and you're testing another drug that may be also effective, but not necessarily better, patients are very reluctant to come off the drugs that they need to relinquish in order to qualify for the study.

Another problem is the Parkinson's psychosis trials. Psychosis is a disturbing issue for the patient and the family and requires treatment right away. Although there are not a lot of effective treatments, there are some that work to some degree. It's difficult when patients suddenly become psychotic, which is usually induced by some of the medications that we use. They are not in the right place, and certainly their family members and caregivers are not in the right place to think about an investigational study. They think about the resolution of the problem right then and there. That would be reduction of the current medications, and perhaps adding one of the drugs that we currently have available to target the psychosis.

So, the nature of the specific problem that you want to address may also be interfering with your ability to recruit quickly.

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Dr. Randolph: There's been a lot of change in the trial roles in the last several years, predominantly moving towards the use of electronic clinical outcome assessments, using tablets, PCs to collect clinical data, and increasing reliance on biomarker and wearable technology collectors. Where do you see the field going? What do you think has been the biggest change for you as an investigator, and how do you think these technological advances have been helpful or not helpful?

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Dr. Verhagen Metman: I think that's an excellent point because it's indeed interesting that still, after all this time, our gold standard outcome measure is the modified UPDRS, the Unified Parkinson's Disease Rating Scale, that has been changed into the MDS-UPDRS, the Movement Disorders Society Parkinson's Disease Rating Scale. That is a cumbersome instrument; it takes a lot of time. Even though the anchors for the scale have been much improved, it still remains such a subjective thing to do. You sit across from the patient, you ask them to tap their fingers, and you give it a score. And the patient may not be at their best. You may not be; you may be in a bad mood and give the patient a bad score. I think it's time we move on to something that is a little bit more objective. Digital technology can help us a great deal. So far, I think the FDA has not really accepted it, but there are several technologies that are validated, published extensively, and could be very useful.

In terms of biomarkers—collecting spinal fluids has become, basically, something we do for a lot of trials now. In the past, we thought patients would object, but it seems that they're able to tolerate it and are willing to do it. But I think that will teach us a lot more about the disease processes, as well as potentially giving us a way to look at outcomes. So, certainly, there are more objective outcomes necessary and available. The fact is we need to still convince the regulatory agency to accept them.

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Dr. Randolph: That's an interesting situation. Historically, collecting CSF was a whole lot easier, in for example, Western Europe than in the United States. Do you think these days it's pretty easy to convince a Parkinson's patient to enter a trial that requires a lumbar puncture?

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Dr. Verhagen Metman: Yeah, I think they perhaps will not like it as much, but it is usually not a reason for them to say no. A good way to approach this—as we have in most trials I've been involved in—is giving the patient an option, such as, "some of you will, if you agree, have the sample taken from your spinal fluid." That's a non-demanding way to ask the patient to participate, and most will agree. But they still have the option to say no, if they really had a bad experience in the past with a spinal tap, which can be horrific, of course. But if they've never had it before, they are usually open to doing it.

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Dr. Randolph: In neurodegenerative diseases in general over the last decade or so, the advent of biomarkers (either the spinal fluid or via imaging, PET imaging) has really changed the field. And the development of antibodies from proteinopathies has sparked a lot of excitement, first in the Alzheimer's field, and I think more recently in Parkinson's disease, with the development of, obviously, anti-nucleic antibodies and other approaches that are really targeted to the pathogenesis of the disease. Where do you see this going? What are you most excited about in the near future with respect to Parkinson's therapies?

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Dr. Verhagen Metman: The imaging you mentioned—specifically looking for alpha-synuclein—may turn out to be a very good way to look at the course of the disease and the worsening or improving of the pathology. But also, on the therapeutic side, clearly, we can use any kind of pharmaceutical that will help the patient from a symptomatic point of view. I would welcome all, but what I hope is that the current ongoing trials with antibodies or small molecules that target alpha-synuclein will really pan out. I mean, obviously, what we want to do is figure out if removing an abnormal protein leads to an improved alpha-synuclein condition. We don't know that for sure, but it intuitively makes so much sense that I think it's the most exciting development we currently have.

Several trials are ongoing with slightly different approaches. Passive versus active immunization, small molecules that work slightly differently. There will be abilities to open up the blood-brain barrier with some other new techniques, such as focused ultrasound, so we will be able to deliver drugs that normally couldn't be delivered to the CNS. There's a lot of potential to deliver drugs to the brain that will change the way we treat the disease, and then I think we can actually change the course of the disease in the near future. I'm very positive about that.

I think we also need to make sure that we realize, as far as Parkinson's and probably every other disease is concerned, that there are many different forms, based on many different genetic abnormalities, for instance. So as part of all kind of clinical trials, I think that in the future we will see that gene testing will become mandatory. And it may very well be that we see big improvements with a certain drug, but only in a group that has the specific gene abnormality.

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Dr. Randolph: That takes me to my final question: With all these exciting new trials, do you have any predictions? Is there anything in particular you're keeping an eye on for 2019 in terms of trials that may read out? Where are your hopes for current trials?

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Dr. Verhagen Metman: Well, one of my hopes for Parkinson's disease, I don't think that we'll get a read-out in 2019, but I'm very keen on the alpha-synuclein antibodies. I think that it's such a novel therapy: It makes sense, and it has shown efficacy in animal models. I'm just hoping that, over 2019, the protocols will be shown to be safe so that perhaps when we get ready to see all the outcomes in 2019/2020, we don't have to worry about safety issues, and we can look at the efficacy. That's my hope in the short term.

In the long term, I think there will be more therapies that are really aiming to address small, specific, recognized problems, mechanistic problems, in Parkinson's Disease. So, we will be able to perhaps intervene at the level of the mitochondrial damage, or anywhere else at the cell membrane where a specific problem occurs as a result of a genetic mutation. That's a little bit longer-term. For now, my hope is on the alpha-synuclein trials.

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Dr. Randolph: The subjects that are in these trials—are they fairly motivated to stay in trial? Or do you have any issues with retaining people for longer periods of time for these kinds of disease-modifying trials?

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Dr. Verhagen Metman: If you have a drug that's not doing anything, and patients notice that they're going to get worse by the day, then at some point they will drop out and require symptomatic treatment. But in general, patients are very tough. Once they sign up, they sign up, and they want to be part of it. I think that retention is very high, and I think it's a compliment to the Parkinsonian patient, at least the ones that participate in trials. They're motivated, and they really want to help science move forward.

It's an issue if you have long trials. Think about it: If you remove alpha-synuclein, let's say that is effective, you need to continue to do that. At some point it goes probably from research into clinical, but for the first five years, I would think you need to follow the patients. The outcomes maybe after two years, but you need to follow patients as part of research for at least five years. Outcomes are really long-term projects.

Interviewee

Dr. Verhagen Metman is a Professor at Rush Medical College and the Medical Director of the Neurosurgery Program for Movement Disorders at Rush University Medical Center. He specializes in the medical and surgical management of patients with Parkinson's Disease and other movement disorders such as Essential Tremor and Dystonia.

Interviewer

Dr. Chris Randolph is a board-certified clinical neuropsychologist and clinical professor of neurology at Loyola University Medical Center in Chicago. Dr. Randolph obtained his undergraduate degree from Vanderbilt University and his MS and PhD degrees in clinical neuropsychology from Rutgers University and The University of Medicine and Dentistry of New Jersey.

He completed a fellowship at the Clinical Brain Disorders Branch of the National Institute of Mental Health, and subsequently held the position of staff fellow, and then senior staff fellow in the Experimental Therapeutics Branch of the National Institute of Neurological Disorders and Stroke.