What are the most pressing challenges in Alzheimer's disease? How are scientists addressing them?

In conversation with... Philip Scheltens

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Dr. Randolph: Dr. Scheltens, thank you for joining us today. Could you fill us in a little bit on your background, how you got into the Alzheimer's field, and why this is a personal interest to you?

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Dr. Scheltens: Very early in my residency in neurology, I found I was intrigued by patients who showed cognitive disturbances. At that time--and we're talking late eighties, early nineties--Alzheimer's disease and dementia were not at all a focus, especially not in neurology. Despite that, I was intrigued. I went on studying Alzheimer's disease using MR imaging. MRI was a new method of brain imaging, and I got inspired by looking at the hippocampus and hippocampal shrinkage. We did some studies on how this worked in terms of sensitivity and specificity to help the clinician diagnose Alzheimer's disease.

From that time on, I remained in the field. I was mostly interested in the use of all types of biomarkers, improving our diagnostic capabilities because the ultimate aim for me has always been to develop better treatments. It was my idea, my mission, and my vision that I think better treatments can only be developed if we understand the disease better and if we can diagnose much earlier.

So from the early nineties until today, I'm still a very much biomarker and biologically oriented clinician looking into better methods of diagnosis and using that type of information to create and conduct better clinical trials. Before I retire, there has to be a treatment, and I want to be part of that process.

I personally am sort of intrigued by dementia. I have a little bit of experience in my family but not that much. My grandfather had it and I watched that when I was a child, but I think for most of us, it comes from being inspired by the patients we see. I still run a clinic every week and I do still see patients; I think that's very important for me also to keep myself motivated. It is almost a personal sort of war

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***Philip Scheltens, MD, PhD**, 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. Scheltens is professor of cognitive neurology and director of the Alzheimer Center at the VU University Medical Center in Amsterdam.*

The interview has been edited for clarity and length.

against dementia for my team and me--a war we want to win. That's because I think this disease is the greatest challenge we've ever seen.

The whole field of neurology is full of challenges, but we are able to treat MS patients now much better than we did, Parkinson's disease patients, and some other diseases we're treating well. But Alzheimer's disease is still the biggest of the neurological challenges that we have. And I'm personally still motivated to do anything that I can do to help that process.

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Dr. Randolph: You mention becoming interested in dementia in the late '80s and early '90s as a neurologist, which was a little unusual at the time, particularly in Europe, where old-age psychiatrists were the ones primarily dealing with dementia. Did you encounter much resistance early on?

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Dr. Scheltens: Oh yes. Oh yes. Especially in the hospital where I was trained. It had a large center on peripheral neuropathy. There were people working on MS. And I said, "Well I want to do Alzheimer's." And they said, "Are you crazy? I mean we don't do this. That's not even a neurological disease!"

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Dr. Randolph: That's really interesting. You really were something of a pioneer in bringing biomarkers and neuro-imaging into the investigation of Alzheimer's disease.

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Dr. Scheltens: Yes. And now you see that because of the biomarkers, because of the imaging, because of the lumbar punctures, you see finally now neurologists getting more and more interested. And I think finally it will be seen as a more neurological sort of disease. If the therapies come around, then I'm sure that all neurologists will jump on the bandwagon and say, "Oh, I'm going to do this," but before that, there was just basically no interest.

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Dr. Randolph: In the last 10 years much has changed in the field clinical trials and Alzheimer's disease. We now have secondary prevention trials. We have early symptomatic disease trials. What do you see as the major challenges to conducting these trials?

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Dr. Scheltens: First of all, doing the right trial in the right patient with the right drugs, but I think we have taken that step now that we include all the biomarkers as a part of our inclusion criteria. I think that's a big step forward, and the definition of Alzheimer's disease as a biological construct has really advanced that.

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Next, we all have to work on recruitment. It's still astonishing that in the field of Alzheimer's disease, people are still very reluctant to participate in clinical trials. I find that very, very difficult to understand. I don't think it's an issue with the patients; I do think it's an issue with all the doctors that deal with dementia--from general practitioners to psychiatrists to neurologists. They are not yet in the mode to say, "Well, if I make this diagnosis, you immediately have to participate in a clinical trial," which is the case in oncology, for instance. We have to do much better when it comes to recruitment. Frankly, it takes too much time to finish a Phase IIa program because it just takes too much time to recruit and enroll the patients.

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Dr. Randolph: Do most of your symptomatic subjects come from your clinic pool, or do you have a network of referral sites that will help you with that?

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Dr. Scheltens: Both. When we started the brain research center--the dedicated trial center--in 2010, I had been doing trials for 10 years but only in the symptomatic stage. But I saw the landscape changing, and we decided to set up a different site, sort of apart from the hospital to be dedicated to clinical trials only.

It has been a challenge to recruit patients, but now we are sort of faced with another situation. We run, I think, 10 or 11 trials mostly in the very mild prodromal stage and hardly any symptomatic trials anymore. So now, we are looking for symptomatic trials because we can't offer trials to our symptomatic patients anymore. For the prodromal and even the preclinical trials, it is easy for us to recruit from our own patient pool because people visit us at a very early stage. But we also are connecting to other sites around our center and in the rest of the Netherlands.

We also go out and set up clinical trial centers nearer to the hospitals in the rest of the Netherlands because distance is sometimes still an issue for potential participants. We strongly believe that will help with increasing recruitment speed.

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Dr. Randolph: I did want to ask you about this because with increased focus on prevention and disease modification, particularly with respect to the anti-amyloid strategies, has sort of left the folks who have mild to moderate disease without access to many clinical trials.

Do you think that anti-tau programs might be recruiting folks with the mild to moderate stage?

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Dr. Scheltens: Yes and no. I think looking at CSF tau for instance, we already see it changed in a very early stage, so I'm not sure whether tau is sort of particularly associated with a more advanced stage. And second, I'm not sure whether in that particular stage even changing anything in tau would actually matter cognitively or

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functionally. I would prefer to go very early on to rescue as much as you can. Because synaptic changes and neuronal death has already taken place so much in that mild to moderate state that I would fear that our endpoints are just not good enough to measure anything at that stage. So I'm not sure.

So for real symptomatic treatment, I still think there is room for that sort of trial, because people are asking us to do more.

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Dr. Randolph: To go on somewhat of a tangent: Agitation in Alzheimer's disease has been a target for a number of trials that didn't produce much in the way of spectacular results. Do you think that's a viable pharmacologic target?

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Dr. Scheltens: That's a good question. I have two issues. First of all, our patient population and the pool we use doesn't have a lot of agitation because they're so early in the disease. And second, I don't think the measurements of the agitation are that great to actually measure a good result or good efficacy of the intervention. I just basically don't have enough experience to, and I don't have enough patients to say that this is a viable endpoint.

There are behavioral disturbances around memory that are very important to the family and predictive of when people can stay at home, but there they are not only agitation; they're very subtle. There may be depression, there may be a little of psychosis, a little bit of anxiety. It's a whole array of changes and not only agitation.

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Dr. Randolph: What recent developments in the science of Alzheimer's disease are you most excited about? How do you think those might translate into new therapies or new approaches to treatment?

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Dr. Scheltens: From my perspective, all three of the changes that are happening in early Alzheimer's disease: amyloid-beta and tau and synaptic dysfunction. I see a lot of activity, of course, in the amyloid fields, both with antibodies, but also with amyloid-beta vaccines.

I see increasing activity around tau. I'm the PI of the AC Immune's antibody to tau, and I know that they have in the pipeline some other stuff as well against tau.

I'm pleasantly surprised to see that smaller companies are actively pursuing leads trying to protect synaptic function to ameliorate synaptic disfunction, and otherwise protect synapses from the damage from amyloid beta. A few companies I work with target this specific endpoint. I like that, because that's the endpoint most

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tightly related to cognition. It's also measurable using CSF measurements of neurogranin, for instance, and other markers--and also EEG and, of course, cognition.

I like the fact that there is a lot of activity in all these three areas. This is important because, ultimately, we probably need a cocktail of drugs targeting all three main issues in AD. We need to keep a broad focus and keep our eyes open for all the other aspects in AD outside of amyloid as well, and I'm seeing that happening. I'm very intrigued by some of the antisense approaches by Ionis Pharmaceuticals. And, of course, the huge success in spinal muscular atrophy is really inspiring our field.

So on the one hand people say, "Well, it's a gloomy field. We have a lot of trials that fail." But I actually see it positively: I've never seen so much activity from smaller and medium-sized biotech companies before. I'm still optimistic that we'll find something. We'll probably find a lot more than only amyloid-beta therapies and, in the end, we'll probably need them all.

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Dr. Randolph: That's an interesting perspective, and I think a lot of people share your viewpoint that ultimately an effective treatment is going to be multimodal in nature.

I want to get your perspective on another topic: The news over the last few months has focused in on some adverse effects of the BACE inhibitor, some of the basic programs that are out there in terms of cognitive toxicity. I just want to get your perspective on what you think which anti-amyloid strategy is likely to be most successful, and what the BACE toxicity from Janssen and from Merck and Lilly tells us about that particular strategy.

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Dr. Scheltens: It's a very challenging question. To be very honest, I was actually surprised. I was on the verge of starting with the Janssen BACE inhibitor, and I was shocked to hear that program stopped. We knew of the liver toxicity, but I had never expected that it would also be a negative in terms of cognitive deterioration, as the Merck trials showed.

I still can't really understand why this is, whether it's a matter of the dose because the idea of inhibiting BACE seems to be theoretically very appropriate. I'm think it may be not just a class effect but perhaps a specific effect of these specific BACE inhibitors because in the Novartis study, I haven't heard that they've encountered the same issues. There are one or two other BACE inhibitors that still seem to work well. So, I haven't lost faith completely. Perhaps we should tweak the dose into sort of getting a better hold on how to influence that process better.

On the other hand, I'm really quite positive about the Aducanumab and the BAN-2401, and in fact also Gantenerumab approaches. Removing the fibrillary amyloid and also the proto-fibrillary amyloid seems to have

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a positive effect on cognition over a longer period of time. So that is still my bet for 2020 or 2019--that we'll hear some positive results from one of the two or both. That will be the start of a whole lot of trials targeting amyloid and perhaps targeting amyloid even earlier than the proto-fibrillary stage.

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Dr. Randolph: You anticipated my final question. What are your predictions for 2019? What are you most looking forward to in 2019 in terms of results read out?

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Dr. Scheltens: I think everybody is focused on the Aducanumab data and I've heard that they will present the top-line results at the end of 2019. So that will be a major thing to look forward to. And I think BAN-2401 will read out in 2020.

The thing I most look forward to is that we have the AAIC 2020 in Amsterdam, and I think Amsterdam is the place where it all comes together. It will be exciting at that time of the year where we have all the data and all the analysis of these two big programs. It will either be a very gloomy and depressive conference, or it will be a nice conference, depending on the results.

Interviewee

Dr. Scheltens is Professor of Cognitive Neurology and Director of the Alzheimer Center at the VU University Medical Center in Amsterdam. His main clinical and research interests are Alzheimer's disease, vascular dementia, frontotemporal dementia, magnetic resonance imaging, PET imaging and biomarkers.

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.