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New Horizons in Alzheimer's Disease

Announcer:
Welcome to CME on ReachMD. This activity, entitled "*New Horizons in Alzheimer's Disease*" is provided by Prova Education and is supported by an independent educational grant from Biogen and Eisai.

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Here is Dr. Alireza Atri.

Dr. Atri:
This is CME on ReachMD, and I'm Dr. Alireza Atri.

Dr. Sabbagh:
And I'm Dr. Marwan Sabbagh.

Dr. Atri:
So let's dive right in, Dr. Sabbagh. How important is it to diagnose Alzheimer's disease at an early stage in a really timely manner?

Dr. Sabbagh:
I think you and I would agree, Dr. Atri, it's very important. Specifically because an early diagnosis, particularly in the mild cognitive impairment phase, gives us more of an opportunity to intervene and alter the projection delay, postpone or prevent the emergence of dementia. It would allow us to prognosticate, allow us to set expectations, and allow us to guide our patients through the journey of Alzheimer's. The second reason is that we would also try to differentiate different kinds of dementia. Not all dementia is Alzheimer's: Lewy body dementia, Parkinson's dementia, vascular dementia, primary progressive aphasia, and the like.

So how we evaluate each of these is different. Some would be neuropsych testing, some would be FDG PET, some would include MRI, some include lumbar puncture. So a lot of the diagnosis will determine what tests we use. So not all – one diagnostic strategy applies to every patient as we evaluate them. I am selective in how I use FDG PET. And amyloid PET, of course, I'd love to use, but it's not reimbursed.

And Dr. Atri, how would you approach this?

Dr. Atri:
Well, I agree with you. I think a timely diagnosis is really, really important. You know, I think about, sort of, the pillars of diagnosis and management. And I think the first pillar, sort of like the legs to a chair, the very first one is a timely and accurate diagnosis and an appropriate disclosure. Without that, individuals can't really get the care they need. And, you know, they can go years and years without an accurate diagnosis. And this can affect really their function, their well-being; it could cause a lot of issues financially. They could be taken advantage of, for example. And once you lose a function in the brain, it's hard to gain it back. So I think for those reasons, it's really important.

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The second leg, I think about it as education and psychoeducation and teaching the patient the family about what this means. What are diseases that affect the brain, like Alzheimer's disease? What are other conditions that can exacerbate that, like sleep apnea, for example, or issues with mood or with nutrition or alcohol?

And then I think about the third leg as pharmacological, which is also taking away bad drugs, adding the drugs that are FDA-approved at the different stages, but really individualizing this care and then treating symptoms and shoring up their support systems.

And the fourth leg for me is really through their environment and their care partner. Really taking care of the care partner and shoring up supports for them.

Dr. Sabbagh:
Keeping the importance of an early diagnosis in mind, Dr. Atri, can you please discuss some of the guidelines surrounding early diagnosis, imaging biomarkers, and genotype?

Dr. Atri:
So if there's a concern from the patient or if an informant, a family member, for example, sees a change in their cognition, function, or behavior, or even the clinician notices there are some changes that are occurring, for example, in disease management and their abilities to manage their conditions. For example, if there's suddenly brittle diabetes or out-of-control hypertension or heart failure or falls or confusion, difficulties managing appointments or medications, visits to the ED, delirium, you know, things like that – hospitalizations. I think those are really main issues regarding starting a timely evaluation, which involves, certainly, listening to the history, doing a very systematic review of systems for cognition, which is attention, aspects of memory, executive function, visuospatial function, aspects of language, looking at activities of daily living – how they may have changed, are they more effortful, are they requiring – are they doing themselves or are they needing some help? Are they becoming dependent? Have they transferred some of those functions to someone else in the family, for example, or a partner? Are there changes in behavior or neuropsychiatric symptoms? Is there anxiety? Is there depression, sleep problems, impulsivity, for example, anger, irritability? All those things are important. Certainly, looking at risk factors, including family history, their medication profiles, and other exposures including what they, you know, lifestyles. What are they doing and not doing, for example. Are they drinking too much or are they not exercising, for example.

I think at that point, what one can do is then take that and also add in. What is really important is to do at least, you know, one standardized assessment using some kind of measure, whether that is, for example, something that's freely available, like the MoCA [Montreal Cognitive Assessment] or something more expanded. But what I would say is, when you do a standardized instrument, is not to take a single cutoff as being diagnostic. I think you have to put that in the context of the patient's, you know, age, education, and other abilities. And at that point, you may be able to – and along with a physical exam, medical, neurological, etc. – but at that point, you make a decision. You know, is there something here that's different? Is there subjective kinds of decline, or is this nothing? In which case you always have the opportunity to improve their healthy activities. Or could there be mild cognitive impairment or something beyond that? So the level of functioning. And then, two, what you want to do is to do enough to delineate this syndrome. Because the syndrome, whether it's an amnestic multidomain MCI [mild cognitive impairment] involving memory and executive function or it's a multidomain dementia syndrome involving visuospatial function, that maps on probabilistically to the underlying brain diseases. But it's not a one-to-one. And so at that point, it helps guide some of your other investigations for what could be the cause. But beyond that, it helps you with symptom management.

So at that point, if one wants to delineate the kind of behavioral syndrome more, you could refer for neuropsychological evaluation, which I find very, very helpful. And then oftentimes, we will send tier one labs, which is, you know, from the blood, looking at, for example, CBC [complete blood count], a chem-20, a TSH [thyroid-stimulating hormone], a vitamin B12, maybe homocysteine, ESR [erythrocyte sedimentation rate], and a CRP [C-reactive protein]. That's a large catchall to look at conditions that may be affecting cognition. Oftentimes, they're not really the sole source, for example. But, you know, thyroid function can be optimized and is something that is in older patients, oftentimes, an issue.

And then we can do something like a structural imaging, and I think that's really, really important. Every individual requires one good structural imaging study. It should be with an MRI if they can manage an MRI. And with that, we look at both excluding other causes, but also including the possibility this could be Alzheimer's disease or another condition by looking at patterns of atrophy, let's say, in the medial temporal lobe, in the parietal lobes, other patterns of atrophy. And I know you like to use quantification there. And then there's a number of other things that we could do after that to really drill down to have high confidence regarding a definitive diagnosis.

And once you have a diagnosis, and you disclosed it – which is, I think, a really big process. I think that, you know, you and I both follow the disclosure process. What's your approach to sort of care and treatment, both pharmacological and otherwise? And, you know, what are the expectations that you give to patients and families?

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Dr. Sabbagh:
Yeah, this is a critical question, Dr. Atri, because you see quickly what the limitations of what you and I have in our toolbox on a daily basis as clinical practitioners of neurology – of behavioral and geriatric and cognitive neurology. So the fact is that in mild cognitive impairment, there is no drug approved. American Academy of Neurology does not routinely endorse the use of cholinesterase inhibitors. It is common practice to use them in mild cognitive impairment, but there is no recommended guidelines around it. Memantine has no clinical utility in mild cognitive impairment or mild dementia. In the mild cognitive impairment state, I might consider, depending on possibilities of off-label use, some cholinesterase inhibitors, but I would also direct a lot of my efforts toward lifestyle interventions, diet, exercise, cog stim. There are structured cog stim kind of programs. And that's when I would say to you that those things make sense because there's a lot of evidence that physical exercise, cog stim, lifestyle intervention, directed programs work very well in mild cognitive impairment. And so I would direct my efforts.

In mild dementia, I would use a cholinesterase inhibitor, understanding that a lot of my day job is spent managing the side effects, right? So nausea, vomiting, weight loss, loss of appetite. And I would use memantine as an adjunct to the cholinesterase inhibitors. Memantine has a very benign side effects profile. And then after that, I would talk about what are targeted symptoms: sleep disruption, agitation, anxiety, depression, paranoia. And then I might try pharmacological therapy directed to some of those target symptoms. But again, much of these are off label.

Dr. Atri:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Alireza Atri, and with me today is Dr. Marwan Sabbagh. We're just about to discuss the clinical pipeline for Alzheimer's disease and the role of amyloid-beta-targeted antibodies and the plethora of other experimental approaches to AD, which are very, very exciting.

Dr. Sabbagh:
Moving on from the limitations of current treatment options, let's transition into some of the important aspects of the clinical pipeline. Dr. Atri, can you discuss the pipeline and the most recent clinical trial data?

Dr. Atri:
I'd be glad to. As far as the amyloid goes, there are a few things you can do with it. You can decrease the production. So what they've done is to try to take this precursor protein and take away somehow the enzyme to do the back cuts for it. And that's been done by a number of different secretase inhibitors. The issues with those over the years have been they've actually produced some toxicity, unfortunately. There is maybe some ongoing activity there. But a lot of the approach has been on the amyloid once it's produced, in getting rid of it. So early on, it was through vaccines, but the vaccines – and some people were – it was causing too much inflammation. So one of the other ways it was shifted is either you can try to stop them from aggregating or you can sort of draw them out. And so passive antibodies have been a great approach. And there are a number of them that are now in phase 3 trials or some have ended. You've probably heard about aducanumab. That's the main one that was looked at in the EMERGE and ENGAGE trials, and, I think, is under consideration by the FDA for potential availability. There are a number of other trials that have gone by. Solanezumab has been one; gantenerumab is still going; BAN2401 under the CLARITY AD trials is another one. As I mentioned, gantenerumab, that's the GRADUATE trial. And again, all these are targeting different aspects of amyloid and try to take them out. But there are other targets. However, they're sort of not maybe as mature in some ways. So targeting the tau and the phosphor-tau, both in aggregation form and also antibodies to it, that's under study.

Well, this has certainly been a fascinating conversation, but before we wrap up, Dr. Sabbagh, can you share with our audience one of your take-home messages?

Dr. Sabbagh:
Yeah, I think this is, Dr. Atri, a very exciting time in our field. We're in a transformational moment in time. We're about to transform Alzheimer's disease from a terminal disease, as a chronic disease, with the advent of DMTs [disease-modifying treatments]. We hope they'll make it into the clinic and that 2021 will be that year. And the other thing, of course, that we're seeing is that we're moving from a diagnosis of exclusion to a diagnosis of inclusion using biomarkers, including plasma, CSF [cerebrospinal fluid], and PET to inform us in a much more definitive way, increasing diagnostic confidence from about 70% to 75% up to 90% and above. Again, a transformative time, very exciting.

Dr. Atri:
I agree with you, Dr. Sabbagh. I think there is very, very exciting times for us right now. Over the last decade, we've made incredible advances in biomarkers that have made their way into clinic. And I want my colleagues to know that Alzheimer's disease is a disease that can be diagnosed accurately now during life and that while we eagerly await disease-modifying treatments to come into the clinic,

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hopefully in the next several years, I think it's really, really important to give the patients and families the ability and the autonomy to make decisions very early on by providing an accurate diagnosis and appropriate disclosure, and that this really does provide a foundation for great care and meaningful changes in their life to face these illnesses. And to be able to learn about these exciting opportunities that are occurring in our field right now.

Okay, unfortunately, that's all the time we have today. So I want to thank our audience for listening in and to thank you, Dr. Sabbagh, for joining me and for sharing all your valuable insights. It's great to talk to you today. And take care and be well.

Dr. Sabbagh:
Thank you, Dr. Atri. Thank you for including me. It was a great talk. I hope we'll have a chance to do it again in the future.

Dr. Atri:
Absolutely.

Announcer:
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