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Meaningful Lives As We Age

Stimulating Early Neurology Referrals for People with Cognitive Impairment Who May Benefit from Anti-Amyloid Therapies

Momentum Discussions developed by the Gerontological Society of America



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Announcer:
Welcome to a Gerontological Society of America Momentum Discussion podcast, where we delve into topics that are generating great excitement and advancement in aging.

Jen Pettis:
Welcome to this GSA Momentum Discussion podcast episode, *Stimulating Early Neurology Referrals for People with Cognitive Impairment Who May Benefit from Anti-Amyloid Therapies*. Momentum Discussions highlight topics experiencing great momentum in the field of gerontology. We're grateful to Eisai for their support of today's podcast episode. My name is Jen Pettis, and I'm the Director of Strategic Alliances at the Gerontological Society of America (GSA). I'm pleased to serve as a host for today's Momentum Discussion. I'm so glad to be joined by Dr. Armen J. Moughamian, a neurologist who cares for people with neurodegenerative brain illnesses, including Alzheimer's disease and other dementias, among other conditions. He is the Medical Director of the Ray Dolby Brain Health Center and the Division Chief of Neurology and Vice Chair of Neuroscience at the California Pacific Medical Center. Dr. Moughamian has been active in clinical trials of anti-amyloid therapies for people with mild cognitive impairment (MCI) and Alzheimer's disease, as well as with their use since the US Food and Drug Administration approved the use of these medications. Welcome, Dr. Moughamian. I'm so glad you could join me.

Dr. Armen J. Moughamian:
It's nice to be here. Thanks for having me.

Jen Pettis:
What are the anti-amyloid therapies and how do they work?

Dr. Armen J. Moughamian:
I think we should start by defining who they're for and what the disease is. Anti-amyloid therapies are for treating patients in an early stage of Alzheimer's disease. An early stage of Alzheimer's disease is defined by the mild cognitive impairment stage or the early mild dementia stage. Alzheimer's disease is due to a pathology, proteins that accumulate in the brain, and there are two proteins that cause Alzheimer's disease - two pathologies. One is the amyloid pathology, which is the first change that occurs in the brains of patients with Alzheimer's disease. This leads to a second pathology accumulating in the brain called tau. And then that leads to the progressive degeneration in the brain and then the clinical symptoms of memory loss and functional declines that we see with dementia. Alzheimer's disease is this pathology of amyloid and tau, which leads to clinical symptoms of cognitive impairment. That's what Alzheimer's disease is.

When we talk about the staging of Alzheimer's disease, we talk about these early symptomatic stages. Before symptoms, you get the pathology accumulating. When enough of that pathology accumulates, you start to get the symptoms of clinical change. Often, that's memory loss, but sometimes patients have difficulty with judgment, language, or navigational symptoms. However, the most common one is short-term memory loss—difficulties remembering recent events and things like that.

In the earliest stages of symptomatic Alzheimer's disease, patients have these memory symptoms. Maybe the patient and the family recognize it, but they feel something is different. They used to do something well, but now they're having more difficulty doing something they typically do. Somebody who cooks a lot has more difficulty putting a recipe together. They're still managing it, but it feels a little bit different. That is mild cognitive impairment. Simply put, it's symptoms of cognitive change that are noticeable to the patient or the family. We can often measure those based on tests we'll do in the office, but they adapt around them. The changes have not gotten to the point of what impacts their function. They're still driving, managing medications, managing their finances, and doing everything. They may rely more on a list or a few reminders but adapt to the cognitive impairment. That's the first symptomatic stage of Alzheimer's disease, this mild cognitive impairment.

Then, as those symptoms progress, it starts to be more difficult to manage around the cognitive impairment, and that's when you get into the mild dementia stage, where there starts to be some functional impairment. This is often in what we call instrumental activities of daily living. Things like driving, financial management, paying your taxes, managing your medications, or managing your calendar. They're still taking care of themselves but may need some help with more complex activities. That's the mild dementia stage.

Anti-amyloid therapies are indicated for the early stages of cognitive impairment, from mild cognitive impairment to mild dementia. Once we determine the clinical stage of cognitive impairment, we need to confirm it is due to Alzheimer's disease. We do that by measuring that pathology. There are a few ways to do that, either through imaging tests called PET scans or sometimes through spinal fluid analysis. Those are two hallmark ways to see if you have these abnormal proteins in your brain. That's the base of what we're dealing with.

Dr. Armen J. Moughamian:
The prior treatments that we had for Alzheimer's disease boosted people a little bit, but they didn't change the trajectory of the disease because they didn't change the underlying cause. These anti-amyloid therapies are designed to clear the brain of the amyloid, and they do that very well. These are medicines that clear amyloid from the brain, and what they do is slow the progression of Alzheimer's disease and keep people in an earlier stage longer. They address the underlying pathology of the disease and slow it down. I think one of the key features is that because amyloid is an early pathology of Alzheimer's disease, treatment of patients in these earliest stages is what is most indicated because as the disease progresses, the contribution of amyloid towards making the disease worse goes down. Early intervention and early detection are key features in improving the efficacy of these medicines in patients.

Jen Pettis:
You mentioned early detection, and I imagine that's usually in the primary care provider's office. How do primary care providers and others ensure that people who may be eligible for these anti-amyloid therapies receive timely referrals to neurology so that a neurologist can determine if they are indeed candidates?

Dr. Armen J. Moughamian:
This is a big challenge; I'll be frank: there's no quick fix. Mild cognitive impairment is mild. I say that jokingly, but it's true. Mild cognitive impairment is mild. If it is overtly apparent that the patient is having trouble communicating or functional impairments, they're probably already in the dementia stage. I will say that primary care is excellent at detecting this. Primary care doctors know their patients better than anybody. When they notice a patient instructed to start a new anti-hypertensive is struggling to understand things they would have understood previously that should raise alarm bells. You should think about a referral or doing a cognitive screening assessment. There are a variety of measures that are useful for detecting mild cognitive impairment and objectively measuring the level of cognitive decline.

For mild cognitive impairment, specifically, the Montreal Cognitive Assessment (MoCA) and the Saint Louis University Mental Status (SLUMS) Examination are very sensitive for picking up mild cognitive impairment, the objective declines that we would see in mild cognitive impairment. Other tests, like the Mini-Mental State Examination (MMSE), are less sensitive. There are other briefer tools, things like the Mini-Cog, which are probably much better at picking up the dementia stage than the mild cognitive impairment stage but still a very useful tool in primary care. If a primary care doctor notices something, I think they should say, “I'm worried that was a little bit harder to understand than it was previously. I'd like to set up a meeting with you to talk about this specifically.”

This isn't something that you can do, as you're holding the door handle and trying to walk out the door. I think setting up a specific meeting to do this A) emphasizes the importance of cognition and B) gives you some time to be able to tell that patient to bring somebody else with them. Having an outsider's perspective on their memory and function is incredibly important in any neurodegenerative disease. Diseases of the brain are different because the organ that's involved in reporting is also the organ that's involved in the disease itself. If you have chest pain, your brain senses your heart, and it says, okay, it's hurting, or it's not hurting, etc. But in brain disease, that organ is the brain. It can be difficult sometimes for patients to recognize their symptoms.

Dr. Armen J. Moughamian:
Sometimes, they over-report, and sometimes, they under-report. In that follow-up visit that's geared at cognition, you bring somebody else in, and you ask them some concerns, such as what they are and if they have concerns about their memory. Assessing function is incredibly important because function is how these diseases affect people's lives—and then doing some level of objective cognitive assessment as brief as a Mini-Cog more sensitive as the MoCA or the SLUMS test. If a patient brings up, "Oh yeah, doc, I'm having some difficulties coming up with words, I'm having difficulties remembering things as well," or the family member brings it up to them; I would do the exact same thing.

Jen Pettis:
I think of primary care as probably providing dementia care, so to speak, for the lion's share of individuals with dementia. Who are the people who present to the primary care office? We've established that if they've got mild cognitive impairment and are potential candidates for these therapies, they need to go. Who else in your thoughts with Alzheimer's disease and dementias should be a priority?

Dr. Armen J. Moughamian:
Alzheimer's disease went from a diagnosis of exclusion, meaning it's probably not something else, so it's probably Alzheimer's disease, to a diagnosis of inclusion where we have tests that we can prove that they have that underlying pathology in the brain. I would say the priority for referrals is for the mild cognitive impairment stage because not everybody with a mild cognitive impairment has Alzheimer's disease. We now have the tools to say you don't have Alzheimer's disease. And I think that can be very reassuring. The appropriate referrals are for early-stage patients, where we can give them a diagnosis with more certainty and put them on the track for treatment. That's one group.

The other group are patients with significant behavioral changes that are too much for the primary care doctor to manage. Referral to a center like my own or another neurology center that can help families adjust around the memory problems and maybe some medications to help temper some of the neuropsychiatric symptoms. I think that's another place where we can be very helpful.

Another is where there are patients and families who are struggling with how to manage that patient. We don't know how much to intervene when they're living alone. Getting a more formal assessment can help families understand the significance and severity of the cognitive change to better assist that patient. We're always balancing these two forces with cognitive impairment, which, as the disease progresses, can impact their safety. On the other hand, we want to honor their autonomy and independence. Those things can be a conflict. A more in-depth evaluation can help the family better balance so that the patient maintains their autonomy while staying safe.

Jen Pettis:
When the primary care clinician determines that someone with MCI or early Alzheimer's disease might be a candidate for the anti-amyloid therapies, what steps can they take to prepare the person for their neurology appointment? What can they do for tests that gets them to you and able to have that most productive visit?

Dr. Armen J. Moughamian:
I think once primary care is concerned about cognitive impairment, starting with a good medication reconciliation is probably the most important thing. Making sure they're avoiding anti-cholinergic and other sedating brain-active medications can be helpful. It may not be the entire cause, but it can exacerbate cognitive symptoms. Having a good medical reconciliation, a good history that's sent over to neurology, and that referral. Not a cognitive history, but are there other medical issues we need to know about? Are they on anti-coagulation, etc.? Knowing what they're on and their active medical issues is very helpful. And that's the knowledge that the primary care doctor has. That's number one. I think doing routine cognitive lab, a complete metabolic panel, a CBC, thyroid function, and a B-12 function are the standards you will perform for everybody. It's nice if a primary care doctor does that before referring.

Depending on your patient population, you may think about syphilis screening and HIV screening, but not necessarily in all patients. It's a risk assessment there, but it commonly needs to be done as well. Starting with the lab and medications, I would encourage structural brain imaging. This is a little bit center-to-center dependent and regionally dependent, but almost always I've ordered a brain MRI, without contrast, in all of my patients as an evaluation for their cognitive impairment. It assesses the brain's baseline structure, ensuring we don't see any tumors or large stroke. The pattern of structural changes in the brain can help me understand the diagnosis causing their cognitive impairment. At this point, I think those are the main things that I would hope primary care could do in addition to the referral. I think in the future, we may have some additional blood tests that could help stratify Alzheimer's disease. I don't think they're quite ready for primary care to be giving them yet, but I think this is an evolving landscape.

Jen Pettis:
I think our listeners would appreciate your insights into the efficacy of these anti-amyloid therapies. What are some overall patient outcomes when the doctor determines they can get the medicines? I'm interested in perhaps some individual stories if you can. Instead of sharing the overall picture, maybe some individual reflections that you have as a physician, which must be incredibly powerful and rewarding.

Dr. Armen J. Moughamian:
I'd like to start by saying these therapies are a first step. We never had a medicine that could slow the progression of Alzheimer's disease down, and these are a first step. I think that efficacy is modest, and over time, we will find the right patients or the best patients for these therapies to maximize the benefits and minimize the risks. Not every patient is eligible for these medicines, and not every eligible patient will want to go on these medicines. But I do think that we need to work patients up so that they can get to the point where they can make the best decision for themselves and their families. Opening the door, the patient has to be able to walk through it, noting both the efficacy and the safety data behind it.

These medicines' efficacy was studied in mild cognitive impairment to mild dementia stage. They slow the progression of the disease by about 30%. What does that mean? It means that it keeps people in an earlier stage longer with less functional and cognitive declines associated with Alzheimer's disease. It extends those early stages and has been shown to cause less decline in the quality of life of the patients and the family members who participate with the patient. These medicines are not a cure. They don't make anybody better, and they don't stop the progression of the disease.

Dr. Armen J. Moughamian:
I think they can have a meaningful benefit of keeping people in an earlier stage longer, so they have more time with their family, friends, grandkids, etc. It is very clear that the earlier we treat people (if you're on that earlier mild cognitive impairment stage versus that mild dementia stage), the benefit is likely more than approximately 30% in the overall population.

You asked about the individual stories, and I think here we have to be very careful about the stories of the patient. We all want the anecdote of the patient that took this medication and is doing amazingly but that is an unrealistic expectation. These medications don't make people better and we have to be very clear in the expectations of the patient and the families as they go on these medication. Jen, you asked the results in an individual patient. Here we need to be a little bit careful about setting the appropriate expectations for the patient because nobody's going to feel better on these anti-amyloid therapies, and the medicines don't even stop the progression. It's challenging to tell a patient exactly what they should expect while on these medications because the disease progresses variably. If I have a patient who's amyloid positive in the mild cognitive impairment stage, I can tell them that in the future, they will decline, but I can't tell you that in a year and a half, you will be doing X, or you won't be doing Y.

I can't predict the future. With an approximately 30% slowing of cognitive impairment, it's hard to know what that would be. However, we have well-done clinical trials that prove the efficacy of these medicines, and they show that patients stay at an earlier stage longer, especially when given these medicines at the earliest stages. We need to trust in the data that shows the efficacy of these medicines. I will say that we need to get this ball moving. We need to take what Alzheimer's disease is now into a more manageable illness where there are these disease-modifying therapies. It's always been a manageable illness, but we are opening the door for this paradigm shift towards disease modification. I think the other aspect of this is that you can't underestimate the importance of hope for patients and their family members. These therapies provide new hope for patients to keep them in this earlier stage longer. Even though the efficacy is modest at this time, I do think we will refine it and get better outcomes in patients, particularly when they're treated at an earlier stage.

Jen Pettis:
You've mentioned risk a few times so I wondered if you could share your thoughts about the safety of the anti-amyloid therapies, including what those risks are and what steps the clinical team can take to minimize or address them at least.

Dr. Armen J. Moughamian:
It's not just about the efficacy of these medicines but also about the delivery of these medicines. Because they're quite complex, both medicines are IV treatments, so they require going to an infusion center every two weeks to every month. And that's a significant inconvenience to the patient. I think that's not a side effect but a complication of these treatments requiring coordination. There are two main side effects to these medicines. One is an infusion-related reaction. Just like when people get a flu shot or a COVID shot, they can sometimes feel a little feverish, some flu-like symptoms. That typically happens in the first one to three infusions, often mild to moderate. The typical thing a patient will say is, I felt fatigued after the first infusion. They go home, sleep, get up the next day, and return to normal. These are not chemotherapies that wipe people out. But in those first few infusions, people can get fatigue, chills, and malaise. They can respond well to Tylenol and sometimes an antihistamine like Zyrtec.

Dr. Armen J. Moughamian:
The other side effect is a little bit scarier. It's a side effect called ARIA, which stands for amyloid-related imaging abnormalities. As these medicines work, they stimulate the immune system to clear amyloids from the brain. As they stimulate the immune system, they can overstimulate the immune system, which leads to ARIA-E, which is ARIA edema. It's a swelling that can happen in the brain, or ARIA-H, which is hemosiderin or hemorrhage, which are often very small bleeds that can happen in the brains of patients, either in the brain or on the covering of the brain.

The majority of patients that develop ARIA-E are asymptomatic, meaning they don't even notice that it's happening. However, they do require monitoring because we want to catch it before it becomes symptomatic. We have to schedule MRIs to monitor patients while they're on therapy. It adds to the burden of the treatment. If it becomes symptomatic, often there are mild symptoms. There are six symptoms that can happen: headache, nausea, dizziness, vision changes, walking changes, or more confusion. If that happens, patients should contact their doctor immediately. They'll need to get an MRI before their next infusion to make sure that they don't have this ARIA side effect, and you can hold the medicine, and those symptoms recover.

There is a risk, though, that these small bleeds can become large bleeds, and that can cause more permanent disability. On average, the risk of that is less than 1% with these medications. But it is a serious concern because we don't want to make people worse. One thing to note is that patients on blood thinners are typically not eligible for these treatments. Patients who have what looks like a stroke shouldn't receive any medicines to break up blood clots because we don't want to exacerbate any bleeding that happens in the brain.

As you had asked, there are some ways to stratify the risk for patients based on their baseline MRI, which can be very helpful for looking for evidence of a propensity for developing bleeding or swelling in the brain. There's a baseline characteristic of the MRI. The other test that we do is called the APOE gene test. And that gene test puts you at a low, medium, or high risk for developing this ARIA-E or ARIA-H side effect. For some patients in the lower-risk group, they feel it's more to their benefit, and in the higher-risk group, there’s more counseling involved. I still would treat people in that higher-risk group, but it's a different conversation. It’s very important to have that risk stratification so the patient goes in with their eyes open about the risk and benefit for the most individualized assessment that we can give for their risk.

Jen Pettis:
We are just about out of time, and I appreciate all that you've shared with our listeners today. But I do want to ask if you have final thoughts that you want to leave us with on this topic.

Dr. Armen J. Moughamian:
I'd reiterate some of the things that I've said already. For your primary care listeners, starting to change the conversation around cognitive impairment is incredibly important. Early detection facilitates options. Our job is not to get everybody onto these therapies. Our job is to open the door so that the families can understand what fits best with their lifestyle. What are their goals as they’re getting older and have cognitive impairment? I want to ensure that patients have all the options for these treatments. Some of the harder conversations are to say you’ve presented too late and you're not going to benefit from these therapies. We want to have less of those types of conversations.

Dr. Armen J. Moughamian:
I would reiterate the need for early detection and that these treatments are not cures but steps in the right direction and can slow the progression of the disease down, particularly when caught in that early stage of disease. There are risks to these medicines, including swelling and bleeding. However, they are manageable side effects, and there are ways to stratify the patients so that they understand their risk of developing these side effects as well as the complexity of these therapies. They're not for everybody. Again, we want to give patients their options so that they can understand what's best for themselves.

Jen Pettis:
I appreciate how many times I've heard you say the words autonomy, choice, and options. It's so important that individuals are able to determine their own care path. I appreciate that perspective. Again, thanks so much for your time and insights today, and thanks to those listening to this episode of the GSA Momentum Discussions podcast. We hope you find it informative and enjoyable. Thanks again, Dr. Moughamian.

Dr. Armen J. Moughamian:
It's a pleasure to be with you. Thanks for having me.

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