

Zoom in on **Dementia & Alzheimer's**

Dementia Drugs Town Hall: What's New, What's Old, What's Approved, What's Covered?

July 26, 2023 | 1 p.m. EDT

Transcript of Zoom with Dr. Cynthia Lemere, Scientist at Brigham and Women's Hospital and Associate Professor of Neurology at Harvard Medical School

The information provided in this transcription is a public service of BrightFocus Foundation and is not intended to constitute medical advice. Please consult your physician for personalized medical, dietary, and/or exercise advice. Any medications or supplements should be taken only under medical supervision. BrightFocus Foundation does not endorse any medical products or therapies.

Please note: This transcript has been edited for clarity and brevity.

NANCY LYNN: Good afternoon, and welcome to the Dementia Drugs Town Hall: What's New, What's Old, What's Approved, What's Covered? I'm Nancy Lynn and I'm with BrightFocus Foundation. We fund research to understand and treat Alzheimer's disease, macular degeneration, and glaucoma. We are absolutely delighted to be with you today and have a fantastic scientist here to explain some of this very quickly changing landscape to all of you. I'm going to just let you know, you will have a chance to ask questions live, but we received 90 questions ahead of time, and I want you all to know we are reading every single question. We're going to get as many answered as we can today, but if your questions are not answered, you'll have a chance to resend them or write to us, or we'll cover them in a future episode. We're definitely going to try to cover everything except for very personal requests.

I'm going to give a sense of what we're going to try to cover today before I introduce Dr. Lemere. We have this incredible landscape now with new disease-modifying drugs. So we're going to start by trying to cover what's

happening with these new drugs that actually seem to slow progression of the disease which we've never had before in history. Then there are the others, I called the other drugs for memory and thinking like Aricept, Exelon, Namenda, Namzaric. Then we have 2 approved drugs for what we might call more mood or agitation and insomnia.

We've received a lot of questions about supplements and vitamins: "Will any vitamins and supplements help?" And then other non-drug strategies to reduce your risk; things that you can do that are not drug related to reduce the risk or slow down getting symptoms and signs. And a couple of other categories, so it's a lot to cover.

But happily, we have a wonderful speaker today, Dr. Cynthia Lemere. So I'm going to introduce now, Dr. Cynthia Lemere is an associate professor of neurology in the Anne Romney Center for Neurologic Diseases at Brigham and Women's Hospital and Harvard Medical School in Boston. Dr. Lemere's research focuses on using the immune system therapeutically for the treatment of Alzheimer's disease which is really cool. She has worked on anti-amyloid vaccines and antibodies for more than two decades and she is a member of BrightFocus Foundation's scientific review committee, which helps to rank and evaluate the grants that the foundation supports and funds.

Two last things before we start with Dr. Lemere, her disclosures, she does consult for different pharma companies and has at different times to help them as they develop their drugs. And importantly, I want you to know she is not an MD and does not see patients in the clinic. She's the real deal. She is a scientist. A lot of scientists want to make that distinction so that you know that they're not talking to patients in the clinic every day, but they do, of course, talk to people all the time and present their data and their insights.

So I'm going to start and thanks for those of you that are asking questions on Vimeo. I'm going to get to them. But I'm going to start by asking Roger to put up the first slide so that we can jump right into a discussion about the drug that's approved, and the drug that just read out at the big Alzheimer's conference; Donanemab and Leqembi. So Leqembi is the drug that was just FDA approved in June. And Donanemab (Leqembi

is an Eisai/Biogen drug) because I know some of you are kind of asking about who's drug is which, and there's a lot of confusion. Donanemab is the new Lilly drug that just announced its data. You can see here, this is what these companies have put out in their press releases in terms of what they are showing in terms of slowing down cognitive decline and then also slowing down the loss of the ability to perform activities of daily living. So, Dr. Lemere, what's the difference and what do these drugs do in terms of their efficacy or their effect?

DR. CYNTHIA LEMERE: Well, thanks, Nancy, so much. And I want to just thank BrightFocus Foundation for inviting me to participate in this webinar today. These are very, very exciting times, I think for the field of Alzheimer's in general, and last week I was at the Alzheimer's Association International Conference in Amsterdam, where Eli Lilly presented for the first time their Phase 3 data on Donanemab, and it looks really promising. It looks very, very good. So Nancy, I don't know if you want to put that slide back up or not.

NANCY LYNN: Yes let's put it back up for a second so you can refer to it.

DR. CYNTHIA LEMERE: So, there are a number of differences between these antibodies. So first of all, the anti-amyloid antibodies in general are meant to clear beta amyloid, which accrues in plaques in the brain to remove that plaque amyloid from the brain, help clear it, and hopefully that will then result in slowing of cognitive decline. There are 3 antibodies now that have shown that. Although the first one, one clinical trial showed definite efficacy. The other one did not show efficacy, and so that one's a little more controversial, that's Aduhelm from Biogen, and that one is approved by the FDA. It's called accelerated approval. So it means that it's a conditional approval. That means that if somebody wants to get that antibody, they can now, but they have to agree to be in a randomized clinical trial. So they have to be eligible for that clinical trial, they have to meet the criteria, and then they would be participating in that clinical trial, and Medicare would cover the cost of the antibody. Otherwise, you know, it can be purchased and used by clinicians or their patients.

Donanemab is the antibody that is coming soon, I believe, to the market,

but it's not there yet, and Leqembi is the one that received accelerated approval like Aduhelm. Aduhelm got accelerated approval in 2021. Leqembi got accelerated approval from the FDA this past January, so January of 2023, and then July 6th, just earlier this month Leqembi was given full FDA approval, and it will be covered by Medicare for people that are eligible. So that means people who have amyloid in their brains (and there are multiple ways to test that that we can talk about later), and people who are showing the earliest stages of clinical symptoms. So keep in mind that plaques start depositing in the brain about 15 to 20 years before the onset of clinical symptoms. So not everybody with clinical symptoms of dementia have plaques. Not everybody has Alzheimer's. So it's really important to only use these drugs in patients that actually have amyloid deposits in their brain, and are on their way to full-blown Alzheimer's disease. And so Leqembi showed reduction in clinical decline in their test. Their primary endpoint was something called the CDR Sum of boxes. It's one particular battery of cognitive tests, and the patients there that received Leqembi, the high dose, of Leqembi, did show a 27% slowing of cognitive decline over the 18 months of treatment. But even better, they showed that in another series of tests that are completed by both the patient and the caregiver, and they showed that there was a 37% slowing of decline in the abilities to perform activities of daily living. And so that could be driving a car, cooking dinner, paying bills, being able to use the internet effectively, that sort of thing. So that was pretty remarkable, and people were excited to see this go forward. It's also worth mentioning that these weren't the only 2 tests that showed positive results. All of the clinical tests showed positive improvement or slowing of cognitive decline. So that was really important.

And then Donanemab recently finished their phase 3 clinical trial. And what they showed was that 35% of patients in a different battery of cognitive tests showed slowing of cognitive decline. And then, in their measure of activity of daily living, they showed that there was a 40% slowing of cognitive decline.

Now there are multiple differences between these antibodies. So the Aduhelm antibody binds a form of beta amyloid that gets stuck in plaques, and it's fibril or amyloid. It's what I call regular amyloid. Leqembi is an

antibody that specifically binds, and when I say bind, it means that it's binding to it, and then immune cells are getting rid of it. So it forms an immune complex. It's the antibody and the beta amyloid form that it targets. So Leqembi recognizes really small aggregates of beta amyloid, and these are called beta oligomers or beta protofibrils. So they happen, they occur before the actual fibril is formed of beta amyloid, and the fibrils are found in plaques. The protofibrils can also be seen in plaques, and there's also some evidence that these A β oligomers, the really small aggregates, can be seen around the perimeter of plaques. So all of these forms are somewhat plaque associated. Donanemab is different in that it binds to a very specific form of beta amyloid, a form that I've been studying for more than 20 years now. It's called pyroglutamate 3 beta amyloid and definitely don't remember that. It's just it's a specific form of beta amyloid. So the beta amyloid protein gets shortened at one end, and then there's a chemical reaction that changes that end of the molecule, and that makes that molecule more sticky. It doesn't get degraded as quickly. It doesn't get cleared as quickly. And from our work, and now work from other labs, we've shown that this form of Pyroglutamate-3 A β is actually found in all plaques and in vascular amyloid. So it's a different antibody. It's targeting a pathogenic form of beta amyloid and that may be why it's doing such a good job at clearing plaques.

The other important thing to notice between these two, or to note between these two antibodies, Leqembi and Donanemab, is that in the Leqembi trial they did not prescreen for tau levels in the brain. So tau and phosphorylated tau in particular, are present in the Alzheimer's brain. So phosphorylated tau can be found in plaque, so the neurons...

NANCY LYNN: And I'm just going to jump in, Dr. Lemere, because we're assuming people know the terms. So these are the two different proteins. Amyloid beta and then there's all these different forms of amyloid beta and tau that accumulate in the brains for a pathological diagnosis of Alzheimer's. So just to make sure that's clear.

DR. CYNTHIA LEMERE: And the plaques are outside nerve cells. The tau, the phosphorylated tau gets stuck inside nerve cells and causes these things called tangles, and the tangles inside the neurons are not good for

the neurons. They can impair the function of the neurons and eventually kill the neurons. And so, Eli Lilly, when they did their Donanemab trial, they actually did PET scans to measure the amount of tau in people's brains; phosphorylated tau, so pathological Alzheimer's related tau in the brain in addition to also measuring the amount of amyloid in the brain. And so they separated out their data by low to moderate tau people and people with high levels of tau combined with the low to moderate. So the data that they're showing here this 35% and 40% slowing of cognitive decline is in the people that had low levels, low to intermediate levels of tau tangles and tau pathology in the brain. That means when you look at the combined, it's slightly less, and it's actually more like the Leqembi. It's almost identical actually to the Leqembi trial.

So, if you're taking everybody across the board with early-stage Alzheimer's disease, then the two antibodies work very similarly. If you're looking specifically at patients that have low to intermediate levels of tau in their brain, of phosphorylated Tau in their brain and the tau pathology in their brains, then Donanemab seems to show a better effect compared to all stages of tau pathology. That means that basically the bottom line is, the earlier we go, the better at treating disease. So it's going to be more difficult to treat people with full stage pathology, full stage cognitive decline with these antibodies. In fact, it's not recommended at all. But now you know, Lily was very smart and trying to parse this out. And by doing this they showed that treating, basically treating earlier is better and has more efficacy.

NANCY LYNN: And I'm going to jump in. And, Roger, you can take down this slide now, because I'm going to talk more about these disease-modifying drugs. But since you are just talking about how you qualify if you are in a very early stage, mild Alzheimer's disease, or what's called mild cognitive impairment. So somebody's written, do these drugs, will they work for FTD (frontotemporal dementia) or vascular dementia or Lewy body dementia? Do we know yet whether these are going to be as effective in other types of treating other types of dementias?

DR. CYNTHIA LEMERE: At this point now, we don't know. These are these are drugs that target beta amyloid. Some of these other diseases have some beta amyloid. But FTD, for example, does not typically, so tau is very important in FTD. And there are treatments being developed now for tau,

even tau antibodies, and that might be more relevant for those particular diseases. Now something like dementia with Lewy bodies, there's a mixture of pathologies there, and many people with dementia with Lewy bodies do have amyloid plaques. And so at some point it might be relevant to, or it might be useful to use an anti-amyloid antibody in that indication. But we won't know until it's tested in clinical trials, and to date that has not been done.

NANCY LYNN: I'm asking in the chat since somebody just asked, What is tau? So I'm asking Dr. Rossi. Oh, she's already done it. Dr. Sharyn Rossi from BrightFocus Foundation is also on this zoom. So she's going to answer some of the questions in the chat box while we're having a discussion. And just before we launched today, Dr. Lemere was telling me that along with Leqembi, Aduhelm, and Donanemab, Lily is actually doing trials on, I would call it like the next generation, which I'm going to ask Dr. Lemere to talk about a little bit, but Leqembi, Aduhelm, and Donanemab are all taken by infusion. Right? So tell us about Remternetug, which I'll just mention, is not approved yet, but it is in trial so but Lily is also testing a drug called Remternetug. Tell us about that.

DR. CYNTHIA LEMERE: It's hard. They make really difficult names for all these antibodies. But Remternetug is basically a modification or second generation of Donanemab. And so at the meeting last week in Amsterdam, they discussed a bit about that drug. It has been altered a little bit so that it could avoid some of the side effects. So, for example, they're hoping that by giving this antibody, instead of giving an intravenous and fusion directly into the bloodstream by giving in, they call it a subcutaneous under the skin injection similar to, for example, insulin shots, that sort of thing. By giving under the skin injections that may, they're hoping, may actually reduce the amount of side effects this ARIA, which we can get into in a bit. But that's the point they're trying to reduce the amount of side effects. They're trying to also stabilize the antibodies so they'll last longer. And to avoid what did occur with Donanemab early on, which is that, some people developed antibodies against the drug antibody, and so that can eventually neutralize the effects and not clear the amyloid anymore. And so this newer version of Donanemab, called Remternetug would be given as an under the skin injection probably every other week. And in Phase 2

clinical trials they showed really rapid clearing of beta amyloid from the brain. Even faster than Donanemab, and in Donanemab trials Phase 3 trials amyloid was clearing very quickly and by the end of the trial 78% of the people that took the Donanemab treatment had reached amyloid negative status by a PET scan. That means that there weren't enough plaques in the brain left to call that person amyloid positive anymore. This newer version of Donanemab, called Remternetug, appears to be clearing beta amyloid even faster than Donanemab. And so, you know, it'll be interesting to see. They just started a Phase 3 clinical trial with this new antibody, and I think it started in November 2022. Typically, it's at least 2 years. It's an 18-month trial, so it'll probably be 2 and a half years something like that two to two and a half years before you know, they analyze the data and we'll know what the results are.

NANCY LYNN: And before we start to move on, well, that's an interesting question. And what I want to go to after this question, Nina's question is coverage for these drugs, because we have a lot of questions about that. And of course, the side effects that have been publicized greatly, sometimes accurately, and sometimes not. But Nina asks, "If you take Leqembi, does that mean that later you can't take one of these newer iterations of the drugs?" Because I think, already all the new versions of the new drugs are being tested.

DR. CYNTHIA LEMERE: Yeah. So, as a scientist, I can't really answer that question very well for you, but in theory I don't see why not. I think it's one of those things where people will eventually be switching over to the second-generation antibodies. And there are, by the way, multiple second-generation antibodies that are in testing right now. So there may be a chance to do that. But I think, you know, it may be a while later.

NANCY LYNN: I just want to show, since Dr. Lemere is talking about it, Jeffrey Cummings' chart, and for those of you, and I'm sure there are many that are discouraged and confused even at a time when we have a breakthrough in having some drugs that seem to slow the progression of the disease if you're in the early stages. This is a chart showing all the different drugs that are being tested right now. So, I find this a little overwhelming. And they're all targeting different potential causes. So I just wanted to take a second.

DR. CYNTHIA LEMERE: If you could put that back up just for a second. Yeah, I just wanted to mention and show the upper left corner because I think that's really critical to look at. So the way this circle works is the outer circle is Phase 1. So the early, mostly safety and tolerability studies. Phase 2, which are smaller trials, are in the middle. And then the inner ring, these are all Phase 3 trials that are in progress right now. And then, Nancy if you can just go down a little bit, yeah, perfect. As you can see on the left there, these different color symbols relate to different targets. So while red shows the anti-amyloid drugs, not all our antibodies. So there are a number of different drugs targeting amyloid. There's also epigenetic targeting drugs shown in light blue. And I've been studying inflammation for decades now and inflammation has become, and immunity, have become very big targets. We know that inflammation plays a role in driving the progression of Alzheimer's disease. So there are a number of different therapies under clinical investigation right now, targeting inflammation, metabolism, the metabolism in cell slows down and can sometimes get clogged in Alzheimer's disease. So there are a number of drugs trying to fix that neurogenesis. Promote more healthy neurons and promote neuronal regeneration. That's also an area. You know, as you go through this list, you can see there are a lot. There's tau there, and synaptic plasticity. So synapses are the connections between two neurons. And that's vital to transferring information, signaling information and communication between neurons. So there are drugs that are specifically trying to improve the connection between the nerve cells so that they can function better and last longer. And then, lastly, there are also drugs targeting the vasculature. And you know about 80% of patients with Alzheimer's disease have vascular amyloid and that is probably playing a role in the disease process. But there are also, you know, patients that have vascular amyloid without Alzheimer's they have what's called vascular dementia.

So there are lots and lots of new drugs being tested right now, and some of them are actually repurposed drugs from other indications. And I think what's coming next, and in the very near future, is going to be combination therapy. So once these, I know there was a question at one point in that excel file about, "Can you take something like Aricept with Leqembi?" And yes, a lot of these clinical trials, the standard of care,

including Aricept or Memantine, were used in combination with the antibodies during the clinical trial, so I think that will be possible. But there are a number of initiatives right now from NIH and other funding agencies to really start looking at how we might improve the clinical benefit of, for example, anti-amyloid antibodies by using combinations of different therapies. So I think that's going to be the new, the next frontier that we have to really conquer in order to get much better clinical benefit.

NANCY LYNN: I think that's a good segue to just maybe discuss the other class, the other drugs for memory, and thinking that we were talking about Aricept, Exelon, Namzaric, and Namenda, and whether, we have a lot of questions, so I'm going to combine them into one, what's the difference between these and the anti-amyloid or monoclonal antibody drugs? And should people keep taking them? How long should they take them? Can they take them in combination, which you just started to talk about? And then I think we should go back and discuss side effects of the drugs and Medicare coverage. And I just want to say to the team, I'm happy to keep asking questions, since we have 90 in the hopper. But if you want to ask your question directly to Dr. Lemere please raise your hand or put the question in the chat, and we'll try to get to it.

DR. CYNTHIA LEMERE: Well, up until a couple of years ago now, there has been only symptomatic relief type drugs for Alzheimer's disease. And by symptomatic, I mean these drugs might help for a while to maintain the ability to think, the ability to remember names, to speak clearly, all of that. However, these are symptomatic treatments, they don't alter the progression of the disease.

NANCY LYNN: Would they work for everybody?

DR. CYNTHIA LEMERE: They may not work for everybody. And it might be that someone might have to try more than one to see which one works best for them. They all have their own side effects. and some of these can be used in combination. So, for example: one combination might be, start somebody with Aricept (Donepezil) and that can be used at all stages, but it's really most effective at the early and at the earlier stages. And then eventually, you know, I heard actually, through personal experience within my own family that you know you can expect some symptomatic relief for

2 to 3 years, and then it won't work as well anymore after that. And you can add things at that point, such as glutamate regulators like Memantine, for example, and that might help for a bit longer. But none of these drugs will stop the disease progression, or even slow the disease progression. But they are helpful for at least some period of time in many people.

And there are combination therapies. There's one that's Namzaric, which is the Donepezil and Memantine together. So Aricept and Memantine together. There are also you know, drugs that are, there's only one FDA-approved drug right now for this psychotic type symptoms and behavioral symptoms. So sleep, disturbances, hallucinations, and agitation as well as delusions, are not uncommon in Alzheimer's, and so there is a drug called Suvorexant. I'm not sure I'm pronouncing that correctly, but it's an orexin receptor antagonist. It's basically blocking the hormone, a hormone in the brain that helps regulate sleep and it allows people to sleep better. And that's considered appropriate for people with mild to moderate Alzheimer's disease.

And then there are some antipsychotic type drugs, of which there's only one FDA-approved drug, which is called Rexulti, and this again is supposed to treat agitation. And so you know, when Nancy put up that round circle with the 141 drugs that are now in clinical trials for Alzheimer's, many of those are meant to address other symptoms other than just cognition, but some of the sleep and hallucinations, delusions that sort of effect.

So the difference, then, between those types of drugs and between those types of drugs and the antibodies, anti-amyloid antibodies at least, is that the anti-amyloid antibodies actually do modify disease progression. They reduce the amyloid level in some of these trials. Now they've looked and they've seen that it actually impacts the tau levels in the brain. So tau is a really important protein in the nerve, it helps transport molecules up and down neurons so that they can signal properly and talk to each other, and when it becomes hyperphosphorylated or phosphorylated, it's a chemical change in the protein, it can't do its job as well and eventually the machinery that transfers molecules back and forth and the neurons can't work anymore, it gets all tangled up and that's why they call them neuro-

fibrillary tangles.

And so there's evidence now, at least with the Donanemab and Lecanemab, that when you modify, when you reduce the amount of plaques in the brain, you also change the tau levels in the brain. But the tau is also not accumulating as fast. So it doesn't necessarily make it go away from baseline, but it's not a creeping as fast. And so, tau, is very closely related to the cognitive status of a person and so the goal is, you want to modify the whole disease process. So you want to modify amyloid and tau, which is considered to be downstream of the amyloid.

NANCY LYNN: And Thomas has asked a couple of questions about amyloid plaque. And sort of when should you test for it, which will lead us maybe well into coverage and participation in trials, and separately, what causes the plaque and how to avoid it? Which would be a good segue into things you can do to lower your risk and things your children can do during their lifetimes to lower their risk of building up of the plaque or the tau.

DR. CYNTHIA LEMERE: Okay, so I may need you to remind me of that part later. But at the beginning, what is a plaque? So plaque is when beta amyloid instead of, we all make beta amyloid, it's in all of us, and it's something that happens throughout your lifetime. Your nerve cells are making amyloid. There are other cells that make it to, but the in the brain the nerve cells make amyloid. It gets secreted from the nerve cell, and it gets cleared. And part of that process happens through the blood brain barrier, which is basically where the blood vessels line up along the brain tissue. And so it gets cleared that way. And it's thought that with aging, and in Alzheimer's disease in particular, that the clearance of beta amyloid slows down. Why that happens, we don't know exactly. There are a number of theories about it. But we know that the that the clearance of beta amyloid tends to slow down, and eventually these proteins accumulate in the brain tissue around the nerves. So it's extracellular, it's outside the nerves and it accumulates, it gets stuck. This protein is really sticky. It gets stuck in these plaques, and then that activates immune cells that are right near the plaques, and it recruits immune cells to that area. And these immune cells, they're called glia, those immune cells then start secreting molecules that can produce inflammation in the brain. And around that same time you start seeing the changes in tau in the

brain. And all of this stuff happens very, very gradually over a period of 15 to 20 years, maybe even more than 20 years and then eventually the nerve cells can't keep up anymore. And that's when you start seeing the clinical symptoms. So some of the nerve cells actually end up dying. And when you have enough of the neurons dying, then you start seeing the clinical symptoms, and they tend to die in an area of the brain that's really important for memory and learning called the hippocampus.

NANCY LYNN: Let's talk about the test for amyloid. To take one of the new drugs. Leqembi, Donanemab or Aduhelm, you need to have amyloid in your brain, right? Because that's what those drugs do. They clear those proteins out of the brain in different ways. So if you wanted to, if you either have mild, cognitive impairment or early Alzheimer's disease, and you're wanting to take the drug or enter into a trial, how do you test to see if you have amyloid in the brain and might qualify to take one of these drugs?

DR. CYNTHIA LEMERE: Yeah, well, first of all it's something you should discuss with your primary care doctor, and they may send you to a neurologist who specializes in memory and if they think that you're a suitable candidate, then they will probably order either an amyloid PET scan or they may suggest that you, if you don't want a PET scan, or they don't have access to a PET scan nearby, they can also do a small spinal tap where they (a lumbar puncture it's called) where they take a small amount of cerebral spinal fluid you know, with a needle in the back and that gets sent off to measure the beta amyloid proteins.

And the newest, though, is that there are a number of assays or platforms now to measure beta amyloid in the blood in plasma. And so there, I'm not sure if, I know it's approved for clinical trials, I'm not sure if it's approved for the doctor's office yet, but there is a blood test that's coming soon, if it's not already available. And so they can measure beta amyloid levels in the blood, and they've shown that if they compare that to PET scans or lumbar punctures, that they're getting the same amount, the same levels generally speaking, So it looks like the blood test will be coming soon, and will be useful for determining if someone might be eligible for antibody treatment.

NANCY LYNN: We've been talking about doing an episode about the upcoming new blood tests and I would ask you to just put "yes" in the chat box, if that's something that would be of interest to you in the future for us to do an episode about. Yeah, one blood test is available now.

I'm going to jump here because we're getting a lot of questions which is fantastic. So somebody asked about Metformin. Can you talk a little bit about metformin? And I'm trying to put in the chat, in case everybody is looking at it, what the categories are and what the names of the drugs are. And if you're hearing different names for things, one may be the actual scientific name, for example, Donepezil, but its brand name is Aricept. So I've tried to put those into the chat, and we can also send you resources afterwards that spell out which drugs are, you know, get the antibodies, go for the amyloid or in the brain and which ones are what I showed in the chat are Cholinesterase inhibitors, which are which and what they do, very basically. We will send that information to you with a copy of this recording after this episode.

DR. CYNTHIA LEMERE: I saw a question about MRIs. An MRI test by itself would perhaps show that the brain might be shrinking a little in some areas, but it wouldn't be by itself a diagnostic test for Alzheimer's. But it's often included in diagnoses, and it's also good to see if there's some other cause. So, for example, if there's a vascular cause, a stroke or mini strokes, or something like that instead. So it's very important for distinguishing what's going on in the brain. And with these different anti amyloid antibodies, it's critically important because it is what's used to detect this side effect called ARIA. I don't know. Do you want me to talk about ARIA now? Okay, so ARIA is, I'm sure everybody has heard about ARIA, it's been in the news a lot. It is the prominent side effect with all of these anti-amyloid antibodies. Although it's lower in Leqembi than in Donanemab. But it's something that it's called ARIA, which means amyloid related imaging abnormality. And the reason is because it's detected by MRI scans, And ARIA typically occurs within the first three to four infusions. So these, again, are infusions through the bloodstream of the antibody. Typically, it's about the first within the first three to four doses of the antibody. And in most people it does resolve. It's transient this effect and it resolves typically within three months. So it's something that can

occur. It did occur in the clinical trials, but in the vast majority of patients, it was completely asymptomatic, and so people didn't know that they had it. They were being monitored by MRI's, and that's what showed. You know they were able to see that oh, this person is actually showing some brain swelling. Brain swelling means that in a particular area or two of the brain, there's water accumulating right outside the blood vessel in the brain tissue. And so that's how that's generally when there's inflammation, there's some accumulation of fluid, and that is what's happening with this. But it does, for the vast majority of people, tend to resolve and go away.

The other type of ARIA which more frequently occurs after the edema, or swelling, is called ARIA-H for hemorrhage. And most of these are micro hemorrhages, or some other sort of vascular lesion in the brain. These are very small micro bleeds in the brain. And it's important that patients who are thinking about going on these amyloid drugs actually first get checked with an MRI to make sure that they don't already have a lot of micro bleeds, because it's something that occurs in many people and occurs with aging. So if people have four or more of these micro bleeds, then they may not be eligible. They won't be eligible for the drug because there, and the reason is for safety, they're at higher risk of developing these side effects if they have it.

Now, there are some people, a small number of people in each of the clinical trials that did experience symptoms. They tended to have more severe, you can rate on the MRI, how severe the ARIA is, they tended to have the more severe ARIA, and with the more severe ARIA the main symptom was headache, but in some people with very severe ARIA, they also had a tendency to fall more, had more confusion, brain fog, that sort of thing.

And there is also some with Leqembi. There were several deaths, three deaths of people that developed ARIA. One was a patient that had a stroke and was given tissue plasmin activator, TPA, which is a drug give to open up blood vessels during a stroke, and that person unfortunately succumbed to you know, having TPA is not recommended in somebody taking these antibodies. And the other two patients who died were both on anticoagulants to prevent stroke. And so with Leqembi. There's some

talk now about limiting the dosing to, or the availability of the drug, the eligibility to people on anticoagulants. And with Donanemab, however, in their Phase 3 clinical trial, they saw no difference in the incidence of ARIA on in people on anticoagulants versus not on anticoagulants. So I'm not exactly sure what they're going to recommend at this point on a label for the Donanemab, but certainly the primary care docs are all being warned to be very careful about, you know, discussing the benefits and the risks in patients that are on anticoagulants.

NANCY LYNN: So a couple of things about ARIA and amyloid and the testing. The initial test can be a PET scan. And how much do they cost? And is getting that PET scan covered by Medicare?

DR. CYNTHIA LEMERE: A PET scan, at least at my hospital, is about \$3,000, between \$3,000 and \$4,000. At this point my understanding and don't take my word for this, but my understanding is right now a PET scan is not covered unless you're in a clinical trial. So if you're in a clinical trial, it's covered. But if you're not in a clinical trial, it's not covered. So it would have to be covered by insurance, you know, or a copay something like that. With ARIA, there are going to be follow up MRI scans, and it's really critically important. Those, as far as I know, are also not covered by Medicare, and would be, you know, around \$900 to \$1,000 each. And they would also you know, hopefully, be covered by insurance, but I'm sure there would be a copay. And just so, you know, right now, Aduhelm is the drug itself, if you're not in a clinical trial, is \$28,000 per year. Leqembi is now \$26,500 per year, so they're really very close together. Leqembi, you know, will be covered by Medicare. The actual drug will be covered by Medicare, and the only stipulation is that the enrolling physicians have to, or the prescribing physicians have to enroll the patients in a registry and that registry is run by the centers for Medicare and Medicaid. And what they're trying, it's a very, I've seen the form, it's a very simple form that the doctor has to fill out about the patient and the dosing, and did they develop ARIA, yes or no? Was it severe? Yes or no? that sort of thing. And that's meant to collect more data on these drugs as they're being rolled out but it's not a clinical trial like Aduhelm.

NANCY LYNN: I'm just going to say, sort of as an overall, that there's a lot

that's not covered right now. There are a lot of us, I see some nods there, a lot of us who are very actively advocating to get better coverage, more coverage and everyone in our field will continue to do so. This is kind of the Wild Wild West right now in terms of getting all of this covered. Dr. Lemere I'm going to ask one of my favorite questions of the 90 that came in: "Realistically will any new drugs be affordable in my lifetime? I am 78, fixed income, \$45,000." Is there going to be something in our lifetimes that's affordable for somebody? And another problem with access is that someone may not be near an academic center that's running a trial, or they may not be near a doctor who can participate in the required registry to get one of these drugs. So those are two different issues, really the affordability and the proximity of a place that is running a registry to you. But let's start with the affordability problem.

DR. CYNTHIA LEMERE: Yeah, I think affordability is a huge issue. And there, as you mentioned, there are a number of different groups advocating for better coverage of these costs from Medicare and Medicaid. And so I think you know, I don't even know if the advantage plans will cover these extra costs. I don't know. I don't think they know yet. So I think it's there's going to be a lot of movement in this area in the next, especially in the next six months. As these drugs really start rolling out, especially Leqembi. But at this point, right now, these drugs are expensive, and they do require a lot of additional care. If they're given by IV infusion, they require going to an IV infusion center at a hospital or a clinic once a month and you know and they're going to require repeated MRI scans more frequently at the beginning, but then, after a while, it'll be more like every three months, and then every six months something like that. And right now, we don't know how long people need to be treated. These trials were for 18 months. You know, in the people that reached amyloid negative in the Donanemab trial they stop treatment. They still did very well at the end of the trial, even if they were off drug for six months. So we don't know how long they can stay off drugs. And Lily's looking at that now. But we don't know. So you know, it might be that somebody needs to be treated for a year, 18 months, something like that, and then they can go off drug for a while. The other thing is, I think they're going to be combination therapies that you know, you clear the amyloid, and then you maintain lower levels with other drugs. That might be a pill

that affects how amyloid is produced, or how, or enhance the clearance of amyloid. And so I think eventually it will be less expensive, less costly to do this, but we're not there yet. I don't know that it's coming anytime within the next two or three years.

NANCY LYNN: We only have about 5 minutes left. So we are not going to get to everything we wanted to get to today. But trust me, we're going to do more. And I'm thinking about how to how to cover all of this. So I know there have been questions about APOE-4, and early onset, and Metformin. So we're reading all the questions, I want everyone to know that. And I'll actually ask you while we're talking for these last 5 minutes, I put down four big buckets that have come up, and I'd like you to type the name of it in if you're it's your most what you're most interested in our next covering.

One is about reducing the risk. So those we've someone asked about diet. And there are other lifestyle things that you can do to try to reduce your risk of getting Alzheimer's or having these proteins building up in your brain, because these proteins start building up in your brain 15 to 20 years before you might even have any symptoms reduction. So this is good for you and this is good for your kids and your grandkids to know. So that would be the one subject matter we can start to try to dive into, which would be risk reduction. The other was blood tests, which I know a lot of people are very interested in.

In a former episode, we covered clinical trials. How do you find out what you could participate in? How do you find out what you're eligible for? And we could even, I'm thinking, maybe, start another series that, not promoting any particular trial, but just describing what trials are available to you. How do you know if you qualify or not? How do you find them, and what is participation in them really like? So clinical trials would be another subject.

And the other would be early onset, or APOE4 conditions, and other types of dementia and what works for other types of dementias. If you want to cast your vote, so to speak, you can add: reducing risk, blood tests, clinical trials, or early onset and other dementia. Eventually we will be covering all of these for sure as best we can, but if you have a burning desire, you can put it in the chat, and you can also send us independently, send us the

questions and we'll respond to you.

DR. CYNTHIA LEMERE: Nancy, Before we close, I just wanted to make one more quick statement about APOE, because APOE is very important in this ARIA side effect. So the vast majority of people that have had this ARIA side effect, and again, it's been shown with all three antibodies, just with lower levels in the Lecanemab trial, but APOE is a cholesterol transporter, and it comes in three versions, APOE, 2, 3, or 4, and everybody receives one copy of the gene from your mother and one from your father. And so people could be a 2, 4; 3, 3; 2, 2; 4, 4; 4, 3. And so one copy of an APOE 4 gene increases your risk about threefold of getting Alzheimer's disease. Two copies of an APOE 4 gene increases your risk about 12 to 15 fold for getting Alzheimer's disease. And it turns out that people with APOE 4 have more amyloid, and especially more amyloid in their blood vessels in the brain. Now these are the same people who are more prone to get this vascular side effect, or vascular inflammation with the anti-amyloid antibodies. And so now the FDA is recommending, they're not requiring, but they're recommending that people get an APOE 4 test to see whether or not, so it's called genotyping, it's a blood test, to see if indeed they carry one or two APOE 4 alleles.

Many people with one APOE 4 allele did okay, did fine without didn't get ARIA. But the people with two APOE 4 alleles are at very high risk. And so, you know, that's something that should also be discussed with the doctor.

NANCY LYNN: Thank you so much. I can't believe an hour has gone by, because there's so much more to discuss. So we will continue to do to do these episodes, and perhaps we can do more of them more quickly knowing that there's this much interest. I just want to make a comment to Sonja, who's been writing in on in the chat box and has been diagnosed with FTD, that I can see just in the chat box, your extreme concern. You're only 57 years old, diagnosed with FTD, I want to note that two episodes ago we did an hour about FTD, and its symptoms and treatments. But you can write to us independently, oh, there's Sonja hi, I'm now seeing your image. You can write to us. We can put you in touch with some experts who are specifically covering FTD, because I can just feel your, I'm not going to say panic, but maybe it's not panic, but you're smiling, and I'm

happy to see you're smiling. So we will try to cover more on that. But we can also send you the episode that we did on frontal temporal dementia.

So first, I want to thank Dr. Lemere so much. I know it's hard as a scientist to try to put all of this in regular English, so thank you so much. And I know we didn't get to Dr. Steinbusch's question about the immune system. And so we're we'll get to these in further episodes. First of all, thank you all so much for attending. I see that there have been over 100 people on the entire time on the live Zoom, and then we have probably a few 100 more watching on Vimeo. Thank you all so much for participating. If your question was not answered today, if you have suggestions for future topics, we already have a lot of those, you can email us at reply@brightfocus.org. And to the next slide, please.

We also are very, very happy to send you free publications about Alzheimer's. These are pretty basic, but they're really helpful. Especially if you're, because we get a lot of questions about people who say my mother had it, my sister had it, I'm afraid of getting it. So if you want some basic information, please, email info@brightfocus.org, or call the number on your screen, we'll send you those publications. Next slide and we'll be emailing everybody who's attending all of these resources.

We talked a lot today about Leqembi, Donanemab, and Aduhelm, two are approved, and one may be approved before the end of the year. These are the numbers and websites that you can go to directly to these companies if you want further information. And I did note, since Donanemab is not approved yet, but that has had positive data read out that there are 2 trials that are continuing in the US on Donanemab, so because we've gotten questions about, how do I participate and from some people who are participating, I've just noted them here. There is an additional trial, but it's in China so I didn't include it. And then I'm sure there are trials about what Dr. Lemere mentioned of the subcutaneous next generation of Donanemab. You can go directly to these company's websites to try to get information. Or you can email us.

NANCY LYNN: We haven't selected our next topic for September 21st, which coincidentally is World Alzheimer's Day. But we're going to look at what you all the questions that have come in and everything you've put

in the chat to make a decision on that. Again, I really deeply apologize if we didn't get to your question today, we will get to it. We are happy to respond if you email us directly and thank you again, Dr. Lemere. So much for your time and preparation for doing this for our donors and the general public, and thanks again to all of you for attending. I hope you enjoy the rest of the summer. And again, please feel free to email us and have a great day.

DR. CYNTHIA LEMERE: Thank you. It's my pleasure. Bye, bye.

Useful Resources and Key Terms

BrightFocus Foundation: (800) 437-2423 or visit us at BrightFocus.org. Available resources include—

- [Presentation](#)
- [Fact Sheet: Treatments for Alzheimer's Disease](#)
- [2023 Alzheimer's Drug Development Pipeline](#)